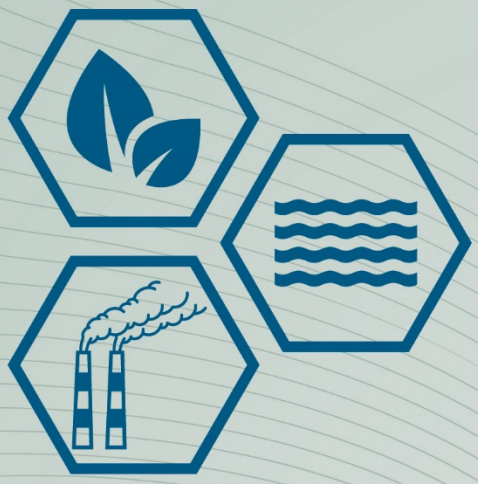

Toxicological Profile for Mercury

Draft for Public Comment

April 2022

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

DISCLAIMER

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Office of Innovation and Analytics
Toxicology Section
1600 Clifton Road, N.E.
Mail Stop S102-1
Atlanta, Georgia 30329-4027

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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VERSION HISTORY

Date	Description
	Final toxicological profile released
April 2022	Draft for public comment toxicological profile released
March 2013	Addendum to the toxicological profile released
March 1999	Final toxicological profile released
May 1994	Final toxicological profile released
December 1989	Final toxicological profile released

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Additional reviews for science and/or policy:

ATSDR, Office of Community Health and Hazard Assessment; ATSDR, Office of Capacity Development and Applied Prevention Science; ATSDR, Office of Science; EPA Office of Air and Radiation, Office of Air Quality and Planning Standards (Air Toxics Program); NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice.

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Mercury occurs naturally as a mineral and is distributed throughout the environment by both natural and anthropogenic processes. The environmental fate of mercury has been well-characterized. The natural global bio-geochemical cycling of mercury involves degassing of the element from soils and surface waters, followed by atmospheric transport, deposition of mercury back to land and surface water, and sorption of the compound to soil or sediment particulates. Mercury deposited on land and open water is, in part, revolatilized back into the atmosphere. This emission, deposition, and revolatilization creates difficulties in tracing the movement of mercury to its sources. Anthropogenic emissions of mercury have typically been to the atmosphere; although these emissions have been declining for the past several decades in North America, global emissions continue to rise due to activities such as artisanal gold mining and fossil fuel burning.

Mercury exists in different valence states and as several types of compounds (Section 4.1). For this profile, mercury compounds are classified into three general categories: (1) elemental mercury; (2) inorganic mercury compounds (e.g., mercuric chloride); and (3) organic mercury compounds (e.g., methylmercury). Each mercury class has distinct chemical properties that contribute to different toxicokinetics and toxicodynamics (Section 2.1). A complete list of the mercury compounds evaluated in this profile can be found in Table 4-1.

Atmospheric mercury is primarily in the form of Hg^0 (gaseous elemental mercury), which is subject to long-range transport. Therefore, mercury is ubiquitous in the environment and is found in locations far removed from its release site. When deposited into water bodies, mercury can be methylated by anaerobic bacteria producing a highly bioaccumulative form of organic mercury (methylmercury) that biomagnifies up the aquatic food web. For this reason, mercury can often be detected at high levels in fish and other aquatic organisms, rice, and other vegetation.

Mercury has many uses due to its unique properties. However, several of these uses have been eliminated or reduced drastically, such as use in alkaline batteries; electronic switches and lighting applications; fungicides and pesticides; paints and pigments; and thermometers and other scientific and medical devices. Historically, mercury compounds were also used in a variety of industrial processes and products (e.g., felting, explosives) and as pharmaceutical agents (e.g., antibiotics, mercurial diuretics)

(Clarkson and Magos 2006). The most important domestic end users of mercury in 2019 were in the production of chlorine-caustic soda (chloralkali), dental products, electronics, and fluorescent-lighting manufacturing industries. In 2020, the use of mercury in the production of chloralkali was reduced when one of the two operating facilities in the United States converted to a non-mercury process.

The general population is exposed to all forms of mercury. However, exposure of the general population is primarily to organic mercury from dietary exposure to methylmercury (e.g., fish, seafood, rice) and elemental mercury from dental amalgams. Relative to organic and elemental mercury, exposure of the general population to inorganic mercury compounds is minimal. Occupational exposures are primarily to elemental mercury (e.g., dentistry, chloralkali process). Predominant sources of exposure to the general population and occupational exposures are described in greater detail in Sections 5.6 and 5.7.

Mercury levels in blood and urine are measured as part of the National Health and Nutrition Examination Survey (NHANES) (CDC 2019). Based on survey data for the period 2015–2016 (the latest reported data), the geometric mean total blood mercury level in the adult U.S. population was estimated to be 0.810 µg/L (95% confidence interval [CI] 0.740, 0.886). The geometric mean methylmercury level was 0.518 µg/L (95% CI 0.456, 0.588). Total and methylmercury blood levels in young children were lower than in adults. The 50th percentiles for total blood level in children 1–5 years of age were less than the detection limit (0.28 µg/L) in 2015–2016. For the 2011–2012 period, the detection limits for total mercury were lower, reporting a geometric mean total blood mercury level of 0.262 µg/L (95% CI 0.237, 0.291) in children 1–5 years of age. The 50th percentiles for methylmercury blood levels in children 1–5 years of age were less than the detection limit (0.12 µg/L) during both time periods. For the 2015–2016 period, the 50th percentiles of total urinary mercury were 0.140 µg/L (95% CI 0.130, 0.150) in adults and below the detection limit (0.13 µg/L) in children 3–5 years of age.

1.2 SUMMARY OF HEALTH EFFECTS

The toxicity of mercury compounds has been recognized since ancient times and is not in dispute (Clarkson 2006; Genchi et al. 2017). Despite the long-established recognition of mercury-induced toxicity, toxicity associated with environmental exposure to mercury compounds has only been recognized since the 1950s (Ekino et al. 2007). Since that time, the relationship between mercury exposure and health outcomes has been extensively studied in epidemiological and animal studies. The focus of this profile is to summarize toxicological effects relevant to occupational and environmental (e.g., diet, water, soil, air) exposures. Therefore, other than mentioning past or current uses of mercury in

consumer products (e.g., cosmetics, herbal remedies, tattooing pigments, paints) or for medicinal, preservative, ritual, or spiritual purposes (Section 5.5.4), the profile does not include in-depth discussion of these topics.

The mechanisms of toxicity for mercury compounds are diverse and include targets that are common to all cells. The targets include intracellular calcium homeostasis, cytoskeleton, mitochondrial function, oxidative stress, neurotransmitter release, and deoxyribonucleic acid (DNA) methylation. A contributor to the diversity of mercury effects on biological systems is the high affinity of Hg^{2+} and CH_3Hg^{2+} for the thiolate anion and formation of Hg^{2+} and CH_3Hg^{2+} S-conjugates. This enables mercury to bind to and disrupt the structure and activity of enzymes, transporters, and other proteins that depend on functional thiol groups for activity. Given these diverse mechanisms, mercury compounds have the potential to adversely affect numerous targets.

As noted in Section 1.1, this profile classifies mercury compounds into three categories: (1) elemental mercury; (2) inorganic mercury compounds (primarily inorganic mercury salts); and (3) organic mercury compounds. Each mercury class exhibits different chemical properties that contribute to different toxicokinetics and toxicodynamics. The relevant routes of exposure for environmental exposure to the three mercury classes are: elemental mercury—inhalation; inorganic mercury salts—oral; and organic mercury compounds—oral. The following provides an overview of available studies in the epidemiological and animal databases.

Epidemiological Studies. All populations are exposed to a combination of elemental, inorganic, and organic mercury compounds; thus, no population is exposed to only one mercury category. In this profile, epidemiological study populations are classified as follows: (1) predominant exposure to elemental mercury; (2) predominant exposure to methylmercury; and (3) general population in which exposures are not defined by mercury class. Information on exposure of humans to inorganic mercury salts is limited to reports of acute accidental or intentional exposure to near-fatal or fatal levels. With few exceptions, exposure duration for epidemiological populations is considered to be chronic exposure.

For elemental mercury, populations are exposed predominantly to elemental mercury vapor in occupational settings and exposures to amalgams in dental restorations. Studies of associations between health outcomes and exposure to methylmercury have focused on populations in which methylmercury was the dominant contributor to total mercury exposure. These studies fall into two general categories: studies of outbreaks of mercury poisoning related to exposure to methylmercury (Minamata, Japan; and

Iraq) and studies of populations that consume large amounts of fish and/or marine mammals (Faroe Islands, Seychelles Islands, and others).

Numerous epidemiological studies have examined associations between mercury biomarkers and health effects in general populations in children and adults, although many studies do not identify the predominant form of mercury. In general, populations without mercury amalgam dental restorations are assumed to primarily be exposed through the diet. In people who have amalgams, mercury vapor released from the amalgams will contribute to inhalation exposure. The use of mercury amalgam in dental restorations is being phased out in the United States. This will decrease exposure of the general population to elemental mercury. Exposure to atmospheric mercury also occurs, particularly in populations near mining or fuel combustion facilities.

To quantify mercury exposure in epidemiological populations, mercury levels are generally measured in blood (BHg), urine (UHg), hair (HHg), or nails (NHg). Measurements of total mercury in blood and urine are biomarkers of total mercury exposure. In populations predominantly exposed to elemental mercury vapor, total mercury in urine serves as a reliable biomarker of exposure. For populations predominantly exposed to methylmercury from consumption of high fish diets, total BHg or HHg serves as a reliable biomarker of exposure. In studies of general population, BHg and HHg are the biomarkers most commonly used to assess exposure, although as noted above, this does not allow for confidence in distinction between methylmercury or elemental mercury.

Animal Studies. Animal studies generally focus on similar exposure routes as epidemiological studies. For elemental mercury vapor, the animal database consists of acute- and intermediate-duration inhalation studies. No studies were identified for chronic-duration inhalation of elemental mercury vapor or for oral or dermal exposure to elemental mercury. The animal database for inorganic mercury salts includes acute-, intermediate-, and chronic-duration oral studies on mercuric chloride, with a few acute-duration oral studies conducted on mercuric sulfide and mercuric acetate. In addition, a few intermediate-duration inhalation studies were conducted on mercuric oxide. For organic mercury compounds, acute-, intermediate-, and chronic-duration oral studies were conducted in animals.

Health Effects of Mercury. The health effects of mercury identified from studies in humans and animals are summarized below for the three chemical classes of mercury. For all forms of mercury, neurological and renal effects have been consistently observed in epidemiological and/or animal studies. More detailed information, including reference citations, is provided in Chapter 2.

Elemental Mercury. Neurological and renal effects have been observed in humans and animals exposed to elemental mercury vapor. Case reports of exposure to elemental mercury at fatal or near-fatal levels have observed severe adverse respiratory effects, including lung inflammation, pneumonitis, and respiratory failure due to pulmonary edema. Other targets of elemental mercury have not been well-studied in epidemiological or animal studies.

Neurological Effects. Neurological effects of occupational exposure to mercury have been recognized since the mid-19th century, referred to as "mad hatter's syndrome" due to severe neurological and psychological symptoms in hatters exposed to metallic mercury vapor during the felt-making process. Additionally, epidemiological studies provide consistent evidence of neurological effects in adults, including tremor, vision, nerve conduction, motor speed and fine motor coordination, cognitive performance (memory, and integrative function), and subjective physiological symptoms (mood swings, irritability, nervousness, timidity, loss of confidence). Animal studies provide additional evidence of neurodevelopmental effects (altered learning and behavior, altered motor activity, impaired habituation) and impaired motor function and damage to the central nervous system in adult animals.

Renal Effects. Epidemiological studies provide some evidence of renal toxicity, such as decrements in glomerular function and tubular injury. Results of animal studies show dose- and duration-dependent increases in severity of nephrotoxicity characterized by damage to proximal tubules, distal tubules, and glomerular membrane, loss of brush border membranes, and renal necrosis.

Inorganic Mercury Salts. Information on health effects is primarily from oral studies in laboratory animals, with supporting data from acute poisoning case reports in humans. No epidemiological studies specific for exposure to inorganic mercury salts were identified. In addition to neurological and renal effects, studies provide some evidence of cardiovascular, hematological, immunological, and reproductive effects.

Neurological and Neurodevelopmental Effects. Animal studies provide consistent evidence that the neurological system is an important target of inorganic mercury salts. Neurodevelopmental findings include hyperactivity, impaired motor coordination, impaired memory, and decreased sociability. In adult animals, neurological effects (hyperactivity, impaired coordination, impaired

learning and memory), and overt signs of neurotoxicity in adults (hindlimb crossing, ataxia, tremor, partial paralysis) and neuropathological changes to sensorimotor regions in the central nervous system (dorsal spinal route, cerebellum) have been observed.

Renal Effects. Nephrotoxicity of inorganic mercury salts has long been established and is not in dispute. Impaired renal function and damage in humans has been reported following acute inorganic mercury poisoning (Cappelletti et al. 2019; Park and Zheng 2012). Animal studies provide consistent evidence of dose- and duration-dependent increases in severity of renal toxicity, including damage to proximal tubules, distal tubules, and glomerular membrane, loss of brush border membranes, and necrosis.

Cardiovascular Effects. Results of animal studies provide evidence of cardiovascular effects, including blood pressure, altered cardiac function, positive inotropic effects, and altered baroreceptor reflex sensitivity.

Hematological Effects. Animal studies provide some evidence of hematological effects of inorganic mercury salts. Findings include impaired clotting, mild decreases in red blood cell (RBC) parameters (count, hemoglobin, hematocrit), and increases in white blood cell (WBC) counts. However, findings are of uncertain biological relevance due to limited evidence, small magnitude of effect, and/or inconsistency of observations.

Immunological Effects. Studies in genetically susceptible strains of mice indicate that inorganic mercury salts stimulate the immune system and induce immune complex disease.

Reproductive Effects. Dose-dependent impairment of fertility and decreased sperm motility and number have been observed in animal studies.

Organic Mercury. Neurological and neurodevelopmental effects are established as the most sensitive effects of oral exposure to organic mercury compounds. In addition, oral studies in humans and/or animals provide some evidence of renal, cardiovascular, immune, reproductive and developmental effects.

Neurological and Neurodevelopmental Effects. Epidemiological studies provide evidence of cognitive, neuromotor, and neurosensory effects associated with prenatal exposure to

methylmercury. In adults, studies show decreased performance on tests of fine motor coordination and speed, muscle strength, tactile sensation, color vision and visual contrast sensitivity, and memory and learning. Neurological effects in animals include sensorimotor dysfunction, vision and hearing deficits, impaired learning and memory, and overt signs of neurotoxicity (clumsiness, gross and fine motor incoordination, lethargy, hindlimb crossing, tremor, ataxia, partial paralysis). Developing humans and animals are more sensitive to methylmercury-induced neurotoxic effects than adult humans and animals.

Renal Effects. Studies in animals show consistent evidence of dose- and duration-dependent increases in severity of nephrotoxicity (damage to proximal tubules, distal tubules, and glomerular membrane, loss of brush border membranes, necrosis).

Cardiovascular Effects. Some epidemiological studies show associations between mercury biomarkers and small increases in blood pressure, clinical hypertension, and altered cardiac function. In animals exposed to methylmercury, increased blood pressure, positive inotropism (strengthening of heart contraction), and decreased baroreflex sensitivity (maintenance of constant blood pressure) have been observed.

Immunological Effects. Epidemiological studies have shown associations between mercury biomarkers and markers of immune function (serum cytokine levels, immunoglobulins, and immune cell counts); however, it is unknown if immune system function is altered. Studies in animals observed immune stimulation and immune complex disease in genetically susceptible strains of mice and some evidence of immune suppression in non-susceptible animals.

*Reproductive Effects. A*nimal studies provide consistent evidence of impairment in fertility.

Developmental Effects. Developmental effects, including polydactyly (extra fingers or toes), syndactyly (fused or webbed fingers or toes), craniofacial malformations, microcornea (cornea less than 10 mm in diameter), undescended testicles, enlarged colon, and protrusion of the coccyx, were observed in the Minamata poisoning population. Animal studies show consistent evidence of dose- and duration-dependent decreases in offspring survival, increased fetal malformations and variations (cleft palate, skeletal malformations [ribs, sternebrae], and hydronephrosis [swelling of kidney]), and decreased fetal weight.

Cancer. Carcinogenicity has been assessed in rats and mice following chronic oral exposure to mercuric chloride, methylmercury, and phenylmercuric acetate. Mercuric chloride induced forestomach and thyroid tumors in male rats and methylmercury induced renal tumors in male mice. There is limited evidence of renal tumors in male rats exposed to phenylmercuric acetate.

The Department of Health and Human Services has not classified the potential for elemental mercury, inorganic mercury compounds, or methylmercury compounds to cause cancer in humans (NTP 2016). The International Agency for Research on Cancer (IARC 1993) concluded that elemental mercury and inorganic mercury compounds are not classifiable as to their carcinogenicity to humans (Group 3) and methylmercury compounds are possibly carcinogenic to humans (Group 2B) based on inadequate evidence in humans for mercury and mercury compounds, inadequate evidence in experimental animals for elemental mercury, limited evidence for carcinogenicity of mercuric chloride in experimental animals (forestomach tumors in rats), and sufficient evidence for carcinogenicity of methylmercuric chloride in experimental animals (kidney tumors in male mice). The U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS 1995a) concluded that elemental mercury is not classifiable as to human carcinogenicity (Group D) based on inadequate human and animal data. IRIS (1995b) concluded that mercuric chloride is a possible human carcinogen (Group C) based on no human data and limited evidence of carcinogenicity in animals (forestomach and thyroid tumors in male rats). IRIS (2001) also concluded that methylmercury is a possible human carcinogen (Group C) based on inadequate data in humans and limited evidence of carcinogenicity in animals (kidney tumors in male mice).

Health effects of mercury compounds observed in animals at various inhalation exposure levels or oral doses are summarized in the following figures: Figure 1-1, inhaled elemental mercury; Figure 1-2, oral inorganic mercury salts; and Figure 1-3, organic mercury. Note that for all studies, exposure is expressed in terms of mercury, and not in terms of specific mercury compounds. Epidemiological studies do not typically report exposure levels (mg Hg/m^3) or doses (mg/kg/day) and are summarized in separate tables throughout the profile. The MRLs shown in Figures 1-1 and 1-3 are based on human data with exposure levels predicted from reported biomarkers (see Appendix A).

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Elemental Mercury

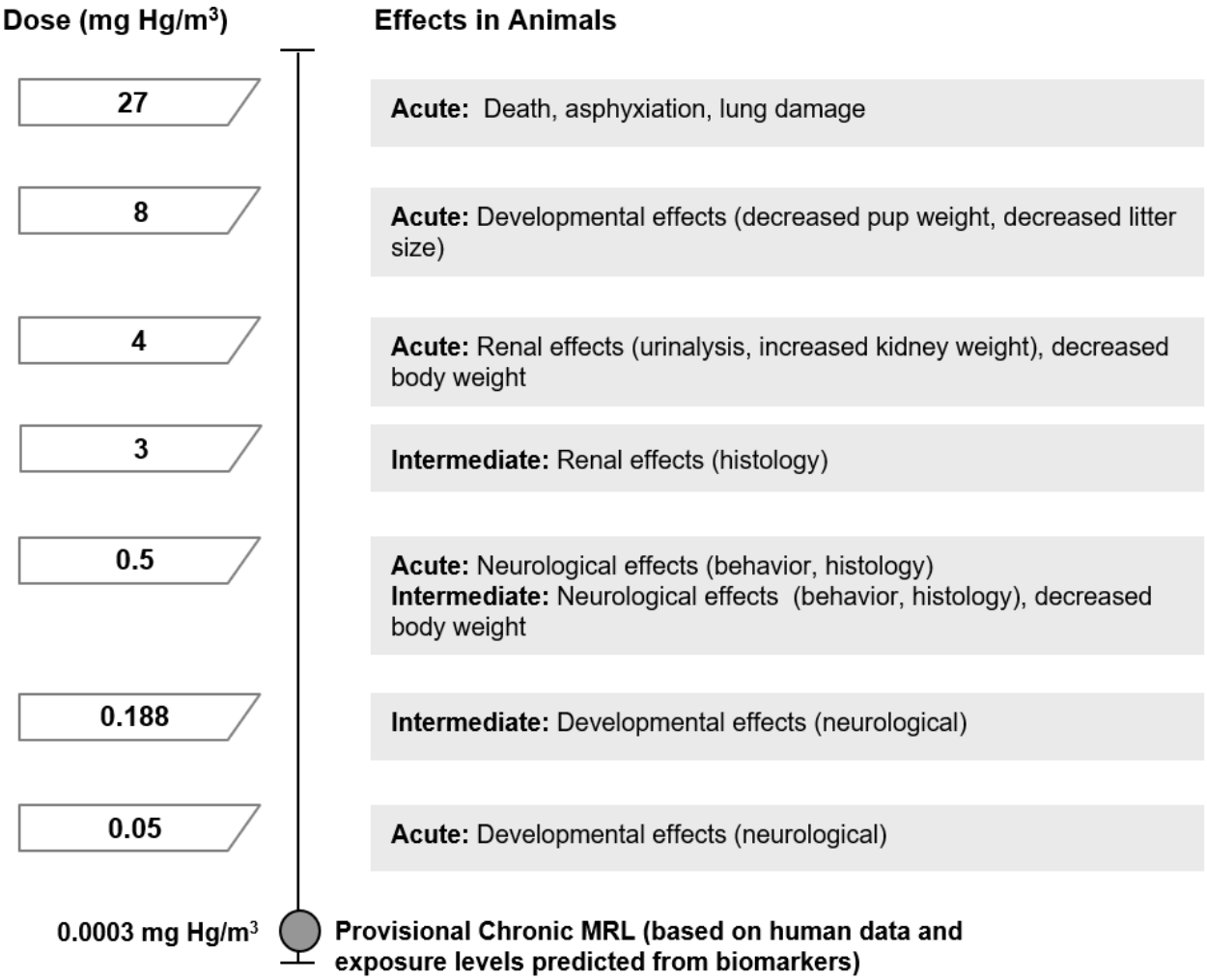
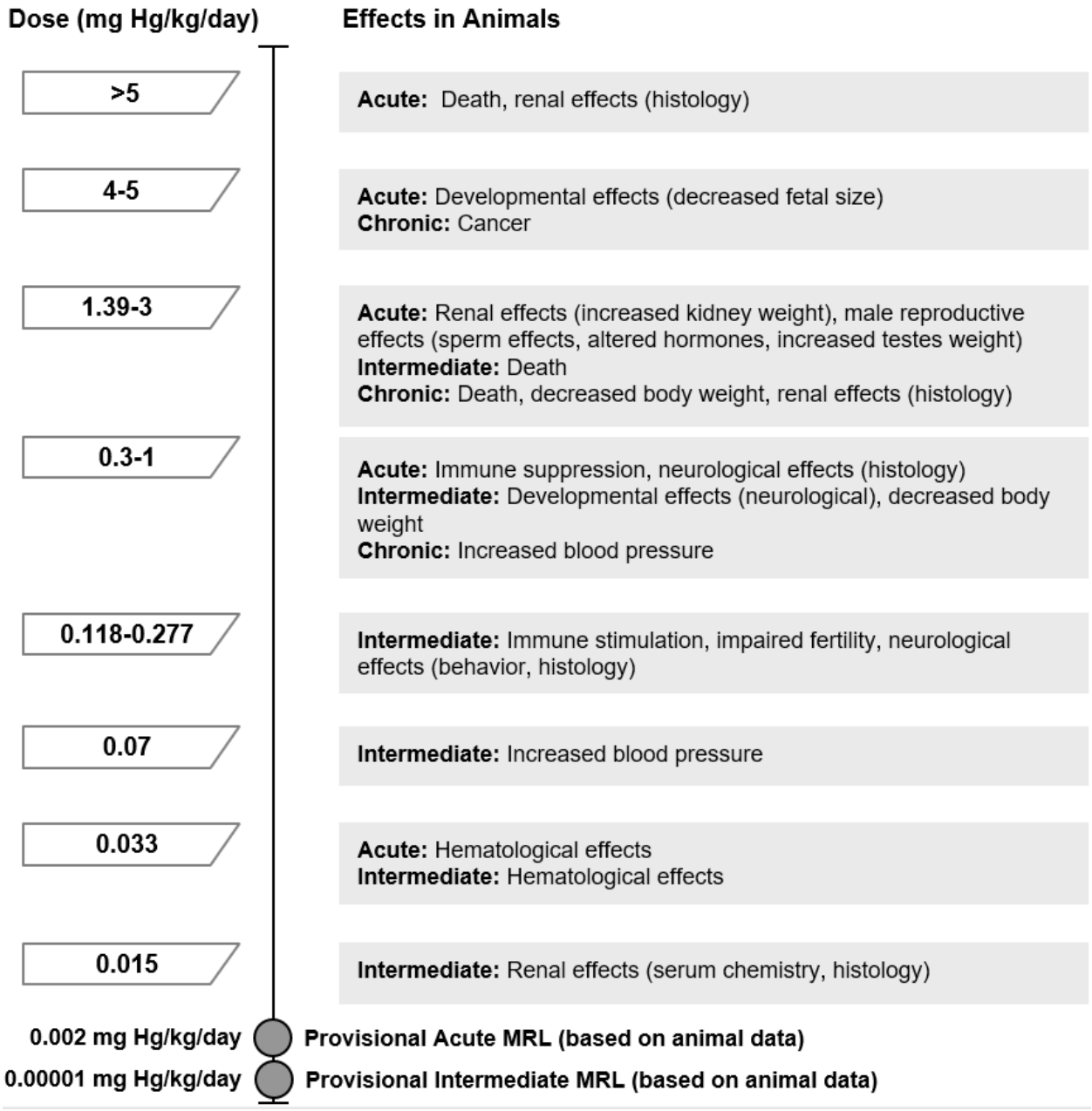
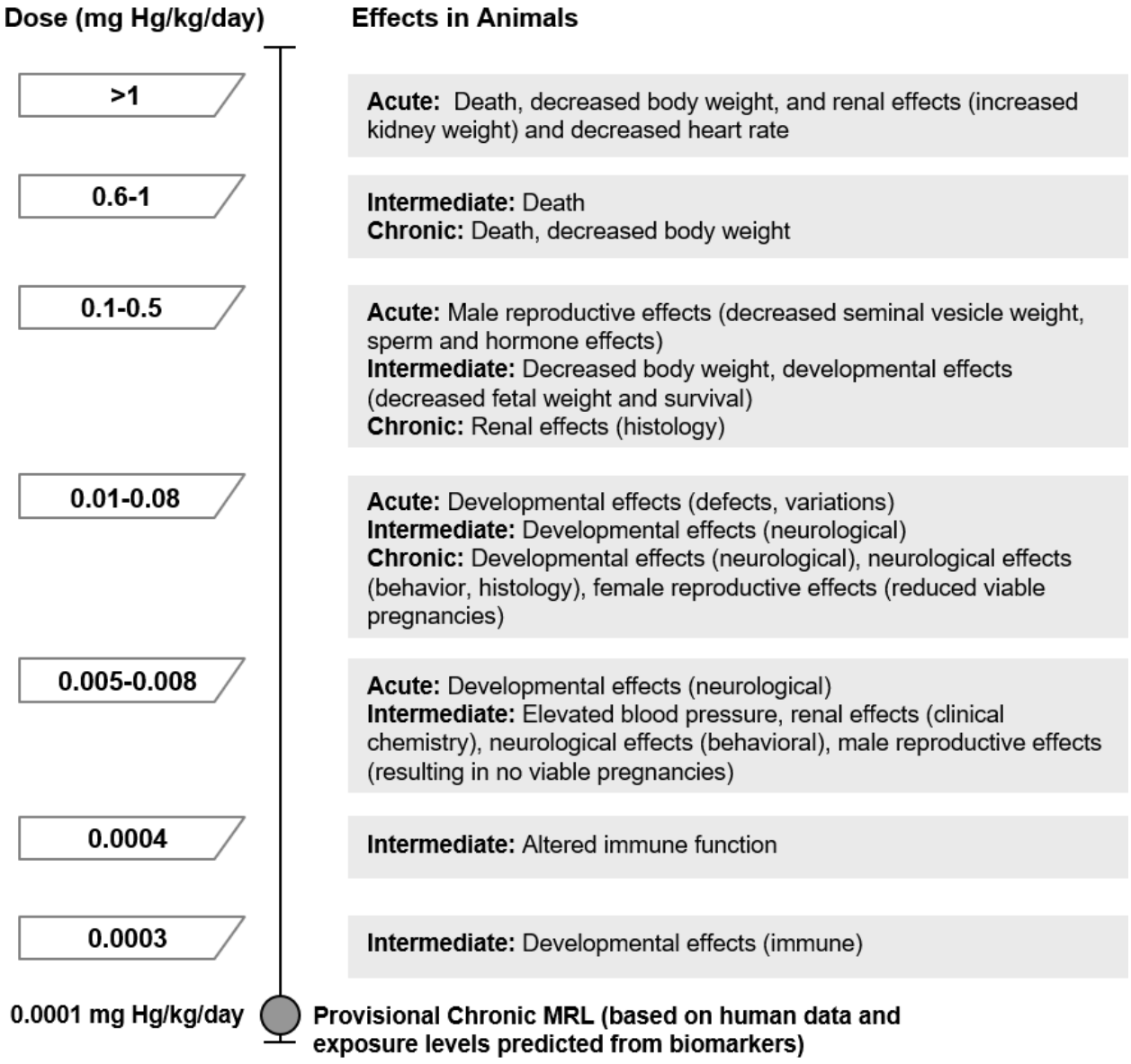


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Inorganic Mercuric Salts[a]



[a]Inorganic mercury studies primarily evaluated mercuric chloride, with a few acute-duration oral studies conducted on mercuric sulfide and mercuric acetate.

Figure 1-3. Health Effects Found in Animals Following Oral Exposure to Organic Mercury



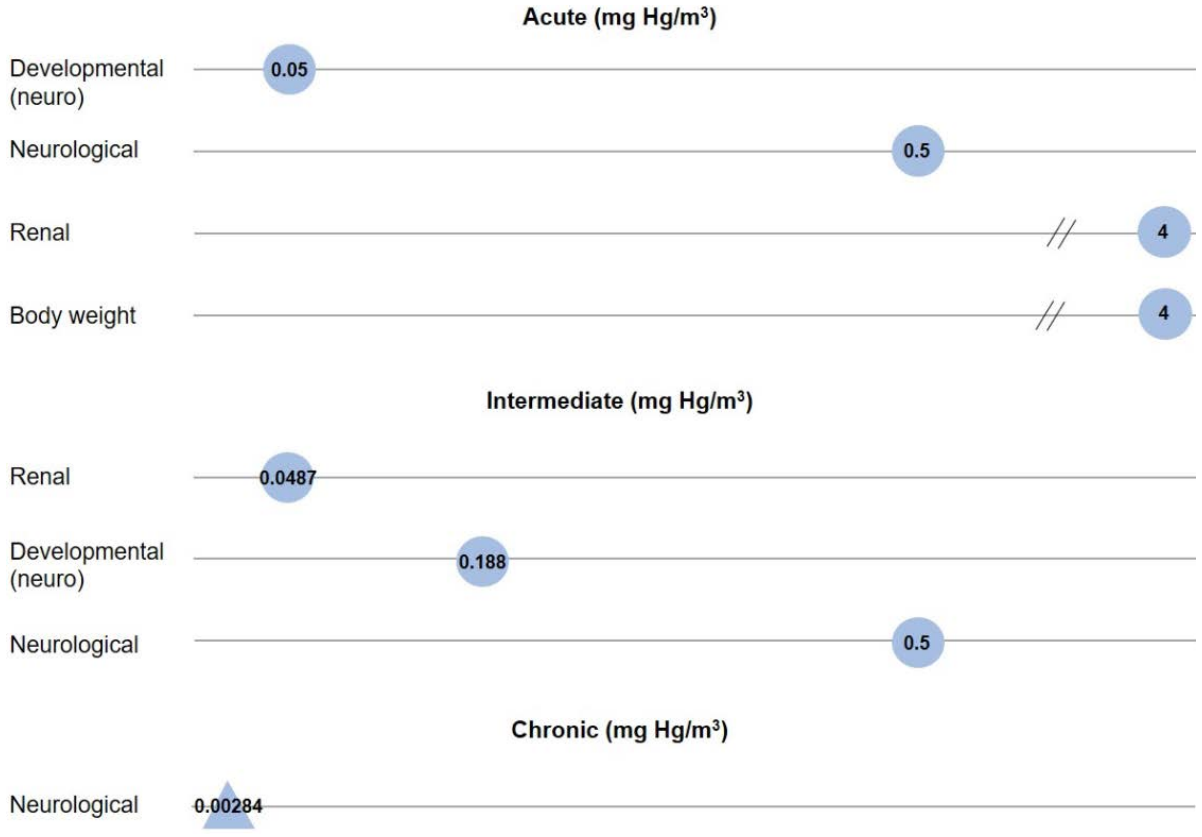
1.3 MINIMAL RISK LEVELS (MRLs)

MRLs have been developed for each class of mercury compounds. Figures 1-4, 1-5, and 1-6 show the most sensitive targets for inhaled elemental mercury, oral inorganic mercury salts in animals, and oral methylmercury, respectively. For elemental mercury, a chronic-duration inhalation MRL was derived based on neurological effects observed in epidemiological studies (Table 1-1). For inorganic mercury salts, acute- and intermediate-duration oral MRLs were developed from studies in animals showing renal toxicity (Table 1-2). For methylmercury, a chronic-duration oral MRL based on neurodevelopmental effects was derived using epidemiological data (Table 1-3). Details of MRL derivations are provided in Appendix A.

Figure 1-4. Summary of Sensitive Targets of Elemental Mercury – Inhalation

The developing nervous system and the adult neurological and renal systems are the most sensitive targets of elemental mercury inhalation exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals and the number in the triangle is the point-of-departure (POD) for the chronic-duration inhalation MRL based on human data[a].



[a]This value (0.00284 mg/m^3 or 2.84 µg/m^3) is the lower 95% confidence limit on the weighted mean for neurological effects (tremor) from seven occupational studies.

Figure 1-5. Summary of Sensitive Targets of Inorganic Mercuric Salts – Oral

The renal, cardiac, immune, and reproductive systems are the most sensitive targets of inorganic mercuric salts oral exposure.

Numbers in circles are the lowest reliable LOAELs for all health effects in animals.

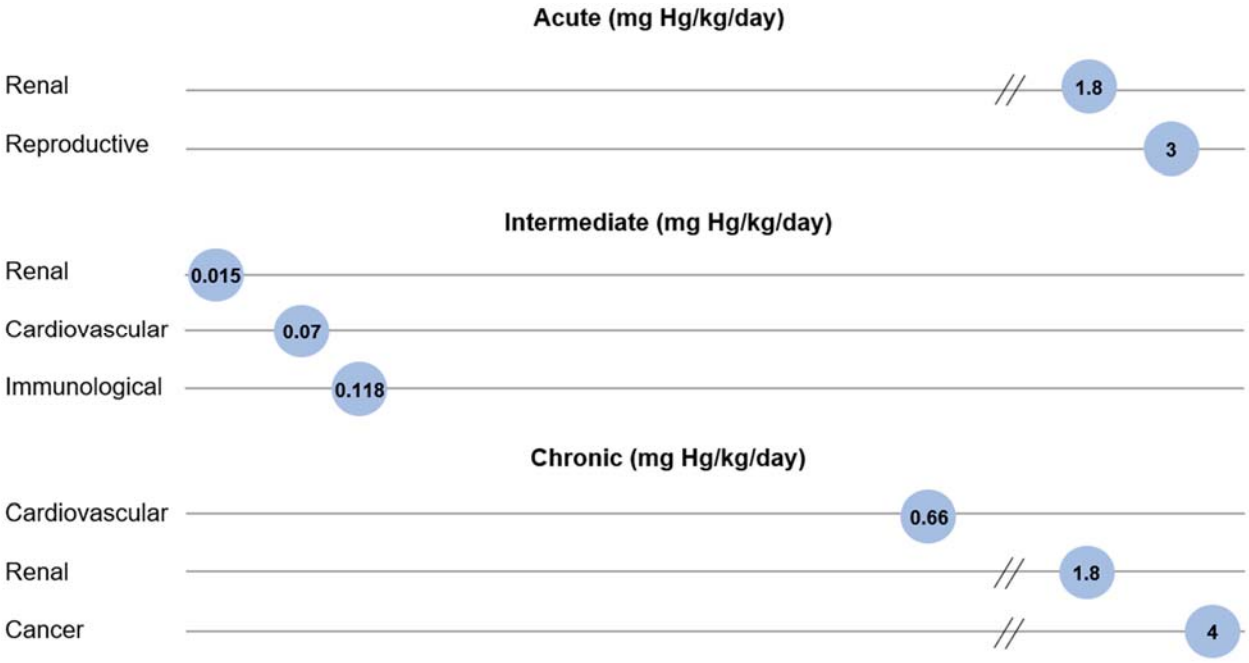
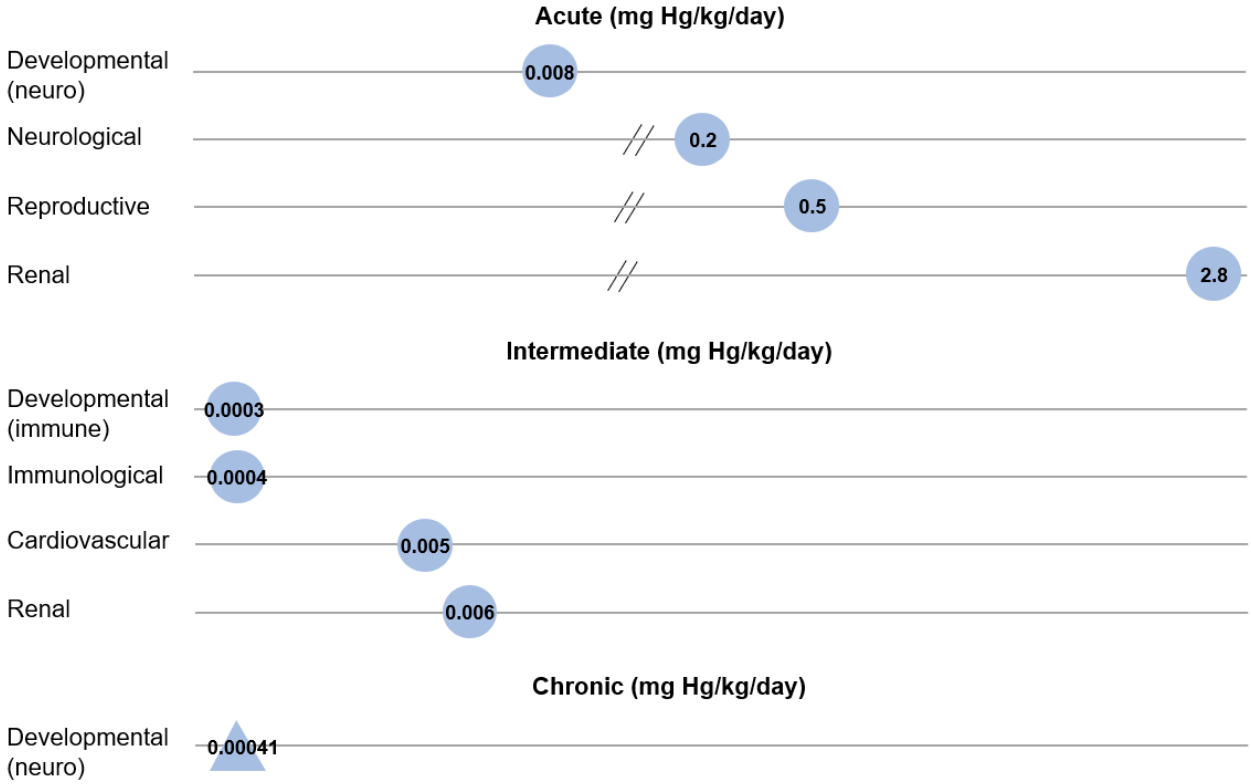


Figure 1-6. Summary of Sensitive Targets of Organic Mercury – Oral

The developing nervous and immune systems and the adult neurological, immune, male reproductive, renal, and cardiac systems are the most sensitive targets of organic mercury oral exposure in animals; the developing nervous system is the most sensitive target of methylmercury oral exposure in humans.

Numbers in circles are the lowest LOAELs for all health effects in animals and the number in the triangle is the point-of-departure (POD) for the chronic-duration oral MRL based on human data[a].



[a]This value (0.00041 mg Hg/kg/day or 0.41 µg Hg/kg/day) is the no-adverse-effect level for neurodevelopmental effects (decreased IQ) from a meta-analysis of three epidemiological studies (Axelrad et al. 2007a, 2007b).

Table 1-1. Minimal Risk Levels (MRLs) for Elemental Mercury[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty and modifying factor	Reference
Inhalation exposure (µg Hg/m^3)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic (provisional)	0.3	Tremor	Weighted median: 4.92 (95% lower confidence limit: 2.84)	UF: 10	Bast-Pettersen et al. 2005; Boogaard et al. 1996; Chapman et al. 1990; Ellingsen et al. 2001; Fawer et al. 1983; Langworth et al. 1992a; Wastensson et al. 2006, 2008
Oral exposure					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

UF = uncertainty factor

Table 1-2. Minimal Risk Levels (MRLs) for Inorganic Mercury Salts[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty and modifying factors	Reference
Inhalation exposure					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (µg Hg/kg/day)					
Acute (provisional)	2	Elevated relative kidney weight	$BMDL_{1SD}$: 290 ($BMDL_{ADJ}$: 210)	UF: 100	Dieter et al. 1992; NTP 1993
Intermediate (provisional)	0.01	Decreased renal function and histopathological changes	LOAEL: 15	UF: 1,000	Apaydin et al. 2016
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

ADJ = adjusted for continuous exposure; BMDL= 95% lower confidence limit on the benchmark dose (subscript denote benchmark response: exposure level associated with 1 SD change in endpoint); LOAEL = lowest-observed-adverse-effect level; SD = standard deviation; UF = uncertainty factor

Table 1-3. Minimal Risk Levels (MRLs) for Methylmercury[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty and modifying factors	Reference
Inhalation exposure					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (µg Hg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic (provisional)	0.1	Neurodevelopmental (decreased IQ)	NAEL: 0.41	UF: 3	Axelrad et al. 2007a, 2007b

[a]See Appendix A for additional information.

IQ = intelligence quotient; NAEL = no-adverse-effect level; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of mercury. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. The following figures provide overviews of the human and animal databases included in this chapter of the profile for elemental mercury (Figure 2-1), inorganic mercury (Figure 2-2), organic mercury (Figure 2-3), and for exposures where the predominant form mercury is unknown (general populations) (Figure 2-4). These studies evaluate the potential health effects associated with inhalation and oral exposure to mercury but are not inclusive of the entire body of literature.

Results of epidemiological studies are provided in each section of Chapter 2. Animal studies are presented as follows: inhaled elemental mercury, Table 2-1 and Figure 2-5; inhaled mercuric oxide, Table 2-2 and Figure 2-6; oral inorganic mercuric salts, Table 2-3 and Figure 2-7; and oral organic mercury, Table 2-4 and Figure 2-8. No quantitative dermal data were identified for mercury compounds.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant

dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of oral inorganic mercury are indicated in Table 2-3 and Figure 2-7; CELs for oral organic mercury are indicated in Table 2-4 and Figure 2-8.

A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

Mercury and mercury compounds have been used for industrial and medicinal purposes since ancient times and the toxicity of mercury compounds has long-been recognized (Clarkson 2006; Genchi et al. 2017). Environmental mercury exposures that could result in adverse health effects were only recognized in the early 1950s when residents of Minamata, Japan consumed methylmercury-contaminated fish and seafood (Ekino et al. 2007). Since the Minamata poisoning, an extensive database of epidemiological and animal studies has examined relationships between exposures to mercury and effects on health outcomes.

In this profile, mercury compounds are classified into three categories: (1) elemental mercury; (2) inorganic mercury compounds (primarily inorganic mercury salts); and (3) organic mercury compounds, with each mercury category exhibiting different properties. These properties play a significant role in defining the toxicokinetics and toxicity profiles for each mercury class. Mercury has no known physiological role in humans (Carocci et al. 2014). The focus of this profile is to summarize toxicological effects of the three mercury classes using epidemiological and animal studies that are relevant to the major sources of environmental exposure. Various consumer (e.g., skin lightening creams and soaps, herbal remedies, laxatives, tattooing dyes, fingerpaints, artists paints, and make-up paints) and medicinal products (e.g., thimerosal, an ethylmercury-containing compound that was used as a preservative in vaccines) that contain mercury or mercury compounds can contribute to exposure to

consumers (DeVito and Brooks 2013; McKelvey et al. 2011; Rastogi 1992; Wendroff 1990). Toxicity of consumer and medicinal products are not specifically considered or evaluated in this profile, as these exposures are not classified as environmental exposures. However, any mercury released into air, water, or soil via consumer use or disposal of mercury-containing products would contribute to exposures detected in environmental media and/or biomarkers of exposure in epidemiological studies. The toxicology of mercuric cyanide is not discussed in this profile because the exposure-response relationship for mercuric cyanide will reflect contributions of inorganic mercuric mercury and cyanide. The toxicology of inorganic mercuric mercury is described in this the profile. The toxicology of cyanide is described in the ATSDR Toxicological Profile for Cyanide.

Since the development of the previous Toxicological Profile on Mercury in 1999, the database for epidemiological studies has grown considerably, with more extensive investigations of populations with high dietary exposure to mercury-contaminated fish and of general populations with lower levels of mercury exposures. Studies have also expanded investigations to focus on effects and endpoints other than neurological. In addition, more epidemiological studies have included biomarkers of exposure (e.g., mercury in blood, hair, or urine). The literature database for studies in laboratory animals has expanded with evaluations of effects in other organ systems, and more recent studies have evaluated lower exposure levels than those used in earlier studies.

Literature Search Strategy and Inclusion Criteria. The literature database on health effects of mercury is enormous, with a large number of epidemiological studies, including studies in children, and studies in laboratory animals. Due to the extent of the literature database, it is not practical or realistic to cite all, or even most, of the studies on health effects of mercury. Thus, this profile does not attempt to provide a comprehensive review of all literature; instead, the profile summarizes the major lines of evidence regarding health effects. Due to the extensive number of available epidemiological studies, case reports are generally not included in the profile. However, exceptions include discussion of acute accidental or intentional exposure to near-fatal or fatal levels of mercury, and to describe portal-of-entry effects following acute exposures.

ATSDR's approach for assessing study quality and weight-of-evidence evaluation is described in ATSDR's Guidance for the Preparation of Toxicological Profiles document (https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf). For epidemiological studies, well-conducted and reported studies were considered for inclusion in the profile. Quality criteria were considered in selecting studies to include in the mercury profile and, in particular,

for consideration as support for MRLs. In general, epidemiological studies that attempted dose-response assessments (e.g., regression models) were included in the profile if the following criteria were met: (1) reported estimates of variance in the dose-response metrics (e.g., standard error [SE], confidence level [CL]); (2) included adjustments for confounding; and (3) reported biomarker data. For studies used to derive MRLs, reporting of quality assurance of analytical methods was also required. For most studies included in the profile, these inclusion criteria were followed, although there are a few exceptions. For example, biomarkers were not available for some mercury poisoning outbreaks from the 1950s–1970s because mercury exposure was not recognized as the cause of symptoms at the time of exposure (e.g., Minamata disease). However, these studies are included because they identified severe neurological and neurodevelopmental effects in populations exposed to environmental methylmercury, providing the rationale for subsequent environmental and biomarker-based epidemiological investigations of these endpoints.

For animal studies, all well-conducted and reported studies were considered for inclusion, with the focus on relevant routes of exposure. A large amount of parental (injection) studies in animals exist, with most focusing on induction of renal toxicity using high doses of inorganic mercury salts. These studies are not included for dose-response assessments because they do not provide information about effects at low doses of mercury, and parenteral administration is not a relevant route for human exposure.

Mechanism of Toxicity. There are many mechanisms involved in mercury toxicity. These include alteration or disruption of: regulation of intracellular calcium homeostasis, cytoskeleton, mitochondrial function, oxidative stress, neurotransmitter release, and DNA methylation. Mercury binding to thiolate anions may underlie many of these alterations or disruptions since: (1) thiolates are present in almost every biological system, and (2) Hg^{2+} and CH_3Hg^{2+} have high affinity for the thiolate anion and formation of Hg^{2+} and CH_3Hg^{2+} S-conjugates.

Mercury binds to and disrupts the activity of enzymes, transporters, and other proteins that depend on functional thiol groups. Mercury can also displace other physiological metals (e.g., iron, zinc) that regulate enzyme activity through interactions with protein thiols. While binding to thiol groups is reversible, the binding kinetics are sufficiently fast enough that Hg^{2+} and CH_3Hg^{2+} migrate from one accessible thiolate anion to another.

Low molecular weight thiols also serve as important ligands for mercury transport in and out of cells. Conjugates of Hg^{2+} and CH_3Hg^{2+} with extracellular thiols (e.g., cysteine, glycinyl-cysteine, glutathione)

are recognized by physiological transport systems for amino acids (e.g., molecular mimicry) and, once in cells, mercury can distribute to other critical intracellular thiol groups. Transport of mercury S-conjugates has been shown to be important in a variety of tissues, including brain, intestines, kidneys, liver, placenta, and RBCs. The high lipid solubility of elemental mercury (Hg^0) contributes to partitioning of inhaled mercury vapor into blood and delivery of Hg^0 to the brain where it can be oxidized to Hg^{2+} and form Hg^{2+}-thiol conjugates.

Toxicokinetics of Mercury Compounds. Humans are exposed to many forms of mercury, and these exhibit route-dependent and chemical-species-dependent toxicokinetics. The major categories discussed in this section are elemental mercury (Hg^0, e.g., mercury vapor) and inorganic mercuric (Hg^{2+}, e.g., mercuric chloride), inorganic mercurous (Hg^+, calomel), and organic mercuric (Hg^{2+}, e.g., methylmercury, dimethylmercury, phenylmercury) compounds.

Elemental mercury. Absorption of inhaled mercury vapor was estimated to range from 69 to 85% in human adults. Absorption of elemental mercury ingested as mercury amalgam was estimated to be 0.04% in human adults. Systemic absorption of mercury has been shown to occur in human adults following skin exposure to mercury vapor (approximately 2% of absorption from inhalation during a full-body immersion in mercury vapor) (Hursh et al. 1989).

Following inhalation exposure to mercury vapor, mercury distributes throughout the body, with the highest concentrations occurring in the kidneys. Vascular proximity of the heart and brain coupled with a limiting oxidation rate of Hg^0 in blood contributes to a first-pass effect on uptake of Hg^0 in these tissues following inhalation of mercury vapor. Inhaled mercury vapor can be transferred from the mother to the fetus and also from the mother to infants via maternal milk.

Absorbed Hg^0 is eliminated in exhaled air and by oxidation to mercuric mercury (Hg^{2+}). The major oxidative pathway for Hg^0 is catalyzed by the enzyme catalase. Following oxidation of Hg^0 in blood and tissues, Hg^{2+} is excreted in urine and feces.

Following inhalation of mercury vapor, mercury elimination kinetics exhibit multiple phases. The terminal half-time, thought to largely reflect urinary and fecal excretion of Hg^{2+}, has been estimated in humans to range from 30 to 90 days. Several pharmacokinetics models of inorganic mercury have been published. Of these, two models were developed to predict the absorption and distribution of inhaled mercury vapor (Jonsson et al. 1999; Leggett et al. 2001).

Inorganic mercuric mercury. Following accidental inhalation exposures to mercuric oxide (^{203}HgO), mercury was detected in various body regions, including head, kidneys, pelvis, and in the legs, indicating systemic absorption. Absorption of mercury following ingestion of inorganic mercury compounds was estimated to range from 1 to 16% in human adults. Studies conducted in rodents have found that gastrointestinal absorption is higher in younger rats. Inorganic mercuric mercury was shown to be absorbed across isolated human and pig skin. Following ingestion of mercuric chloride, mercury distributes throughout the body, with the highest concentrations occurring in the kidneys and liver.

Inorganic mercury is found in human cord blood, placenta, and breast milk, indicating transfer to the fetus and infant, respectively. Exhaled Hg^0 was observed in mice following parenteral doses of mercuric chloride, suggesting that Hg^{2+} had been reduced to Hg^0. Salivary and gastrointestinal bacteria have been shown to methylate Hg^{2+}; however, the quantitative significance of methylation in the disposition of absorbed Hg^{2+} remains uncertain. The major routes of excretion of absorbed mercuric mercury are feces and urine.

Kinetics of elimination of absorbed inorganic mercuric mercury exhibits multiple phases. The terminal half-time has been estimated in humans to range from 49 to 120 days (Farris et al. 2008). Several pharmacokinetics models of inorganic mercury have been published. These models are based on studies of pharmacokinetics of absorbed inorganic mercuric mercury.

Inorganic mercurous mercury. No studies were located that provide quantitative information on the absorption, distribution, metabolism, or excretion of mercury following exposure to inorganic mercurous compounds. Pharmacological and cosmetic uses of calomel (mercurous chloride) ointments (skin lightening creams, acne) have resulted in elevated urinary mercury levels and mercury poisoning, indicating that absorption of mercury can occur following oral and/or dermal exposure to inorganic mercurous compounds. Toxicity may have been from absorbed inorganic mercuric mercury, as the low pH and high chloride concentration of the gastric environment favor oxidation of ingested Hg^1 to Hg^{2+}.

Organic Mercuric Mercury. No studies were found that have estimated absorption of inhaled organic mercuric mercury. Studies conducted in humans, monkeys, and rodents have shown that gastrointestinal absorption of mercury is close to 100% following ingestion of methylmercury chloride or when incorporated into fish or other ingested protein. Dimethylmercury is rapidly absorbed through human skin.

Following ingestion of methylmercury, mercury distributes throughout the body, with the highest concentrations occurring in the liver, kidneys, and brain. Methylmercury is also found in human cord blood, placenta, and breast milk, indicating transfer to the fetus and infant, respectively. Studies conducted in humans and in a variety of other mammalian species have observed both methylmercury and inorganic mercury in tissues and excreta following exposure to methylmercury. Demethylation occurs in liver, phagocytes, brain, and other tissues. The major routes of excretion of absorbed methylmercury are feces, urine, and hair. Following exposure to phenylmercury, absorbed mercury is eliminated in bile, feces, urine, and hair.

Kinetics of elimination of absorbed methylmercury exhibits multiple phases. The terminal half-times have been estimated in humans to range from 50 to 130 days. Pharmacokinetics models of methylmercury have been developed for humans and a variety of other animal species.

Routes of Exposure and Mercury Sources. Relevant routes of exposure for humans vary based on the category of mercury compound.

- *Elemental mercury*. The most relevant route of exposure to elemental mercury is through inhalation of mercury vapor. Exposure of workers to elemental mercury vapor has occurred in several occupational settings, including chloralkali processing (i.e., production of chlorine and sodium hydroxide), fluorescent lamp production, gold mining and processing, lithium-6 purification (column exchange [COLEX] process), mercury amalgam dentistry, mercury battery production, natural gas production, recycling, and thermometer production. Humans can also be exposed to elemental mercury from inhalation and ingestion of mercury released from mercury amalgam dental restorations.
- *Inorganic mercury salts.* Oral exposure is the primary route of exposure to inorganic mercury salts. Exposure may occur through diet or contaminated environmental media (e.g., soil). Exposure to inorganic mercury salts is currently not a predominant exposure for the general U.S. population.
- *Organic mercury compounds*. Methylmercury is by far the predominant form for organic mercury exposure in populations. Exposure to methylmercury occurs worldwide through the diet, with fish as the main dietary source of methylmercury.

Epidemiological Studies. Numerous epidemiological studies have examined effects of environmental exposures to mercury compounds. The following provides a brief overview of the epidemiological database and important considerations for epidemiological studies.

Metrics of exposure (biomarkers). Humans are exposed to a mixture of methylmercury and inorganic mercury (primarily mercuric and elemental) in their local environments, with either being more or less pronounced under certain circumstances (e.g., occupational exposure to Hg^0 vapor, consumption of methylmercury in fish). Exposure to mercury that leads to absorption of mercury in any form can be detected from measurement of total mercury (inorganic plus organic) in blood or urine. A change in exposure will be reflected in a change in blood (BHg) or urine total mercury (UHg). Measurements of total mercury in blood and urine can be considered biomarkers of total mercury exposure. These measurements do not provide information to confidently estimate the magnitude of exposures specifically to methylmercury, inorganic mercury compounds, or elemental mercury.

Biomarkers that are more strongly correlated to methylmercury exposure are blood methylmercury concentration or total mercury concentrations in hair (HHg) or RBCs. Blood and hair are more significant depots for accumulation of methylmercury than inorganic mercury. Biomarkers that are more strongly correlated to exposure to inorganic forms of mercury (primarily mercuric and elemental) are inorganic mercury in blood (or plasma) and inorganic mercury or total mercury in urine. However, demethylation after absorption contributes inorganic mercury to blood and urine; this complicates distinguishing exposures to inorganic mercury from exposures to methylmercury based solely on measurements of total mercury in blood or urine.

In workers exposed to high levels of mercury vapor, elemental mercury is likely to be the dominant form, and total mercury in urine can serve as a reliable biomarker of exposure. Epidemiological studies of methylmercury have focused on populations that consume large amounts of fish or marine animals. In these populations, methylmercury is likely to be the dominant contributor to exposure, and total mercury in blood or hair can serve as a reliable exposure biomarker.

Duration of exposure. With few exceptions, the duration of exposure to mercury in epidemiological studies is considered to be chronic. Exceptions include intermediate-duration exposures in an occupational study in elemental mercury workers and studies on the Iraq methylmercury poisoning outbreak. No epidemiological studies examining populations exposed to mercury for acute durations were identified.

Study populations and sources of exposure. All populations are exposed to a combination of elemental, inorganic, and organic mercury compounds; thus, no population is exposed to only one mercury category. In this profile, epidemiological study populations are classified as follows: (1) predominant exposure to elemental mercury; (2) predominant exposure to methylmercury; and (3) general populations in which the predominant form of mercury is unknown and cannot be discerned from the reported biomarker measurements. Details of these population are described below. Information on exposure of humans to inorganic mercury compounds is limited to reports of acute accidental or intentional exposure to near-fatal or fatal levels. Clinical findings associated with these high-dose, acute exposures are reviewed in Section 2.2.

Elemental Mercury. Populations exposed predominantly to elemental mercury consist of occupational exposures and exposures to mercury amalgam in dental patients. Studies of exposures to mercury vapor have been conducted in workers of various industries including chloralkali, fluorescent lamp production, gold mining and processing, lithium-6 purification (COLEX process), dentistry applications of mercury amalgam, mercury battery production, natural gas production, recycling, and thermometer production. In some occupational studies, work area or breathing zone mercury levels in a subset of the study group were reported. The most common biomarker reported is mercury concentration in urine (UHg; expressed in terms of µg/L or µg/g creatinine). The timing of measurement varied across studies. In some cross-sectional studies, these were based on measurements made at a single time, typically at the time of outcome assessment. For some retrospective studies, urine mercury estimates were derived from historical industrial hygiene monitoring data. In some studies, the individual subject data were aggregated into metrics of cumulative exposure (e.g., sum of quarterly average values for all exposure years) or exposure intensity (sum/exposure years). Most occupational studies have assessed health outcomes by comparison of exposed and reference (unexposed) groups. Inhalation is the primary route of exposure. Exposures of workers may be relatively constant during the workday (e.g., chloralkali workers) or highly intermittent (e.g., dental workers). For exposure of populations with amalgam fillings, biomarker levels are typically lower than those observed in occupational populations.

Methylmercury. Studies of associations between health outcomes and exposure to methylmercury have focused on populations in which methylmercury was the dominant contributor to total mercury exposure. These studies fall into two general categories: studies of outbreaks of mercury poisoning related to exposure to methylmercury and studies of populations that consume large amounts of fish and/or marine mammals. Two major outbreaks of methylmercury poisoning have been extensively studied.

- *Minamata poisoning outbreak.* In the Minamata outbreak, discharges of wastewater from an acetaldehyde production facility into the Shiranui Sea located in the Kumamato Prefecture of Japan resulted in elevated levels of methylmercury in fish and shellfish (Harada 1995). Methylmercury entered the waste stream as a side product of the acetaldehyde production process, which used mercury sulfate as a reactant. In the mid-1950s, an outbreak of a neurological disorder (Minamata disease and congenital Minamata disease) occurred in the area. The timing of the outbreak appears to have been related to the expansion of acetaldehyde production at the facility (Harada 1995). Exposure to methylmercury resulted from ingestion of locally harvested fish and shellfish. Studies of health outcomes in this population focused on neurological and neurodevelopmental effects. Measurements of mercury in blood and hair were not made until several years following the period of most intense exposure and, therefore, do not provide reliable estimates of exposures that may have contributed to Minamata disease.
- *Iraq poisoning outbreak.* An outbreak of methylmercury poisoning occurred in Iraq in 1972–1973 as a result of widespread consumption of bread made from wheat that had been treated with a methylmercuric fungicide (Al-Mufti et al. 1976; Bakir et al. 1973; Clarkson et al. 1976). Studies of health outcomes in this population focused on neurological and neurodevelopmental effects. Based on measurements of methylmercury in flour used to bake contaminated bread and estimates of bread consumption, methylmercury intake was estimated to have ranged from 80 to 1,000 mg over a 3-month period (Al-Mufti et al. 1976). Blood mercury levels in poisoning cases measured approximately 65 days after exposure ranged from 10 to 3,000 µg/L (Clarkson et al. 1976). Prenatal exposures were reconstructed from segmental analysis of single maternal hair strands and used to derive prenatal dose-response relationships for neurodevelopmental outcomes (Cox et al. 1989; Crump et al. 1995; Marsh et al. 1987).
- *Studies of populations with high fish diets.* Biomagnification of mercury levels in aquatic systems contributes to relatively high levels of methylmercury in predatory fish and marine mammals. As a result, methylmercury can be the dominant form of mercury exposure in populations that consume large amounts of these organisms. In these populations, BHg or HHg levels are typical biomarkers of methylmercury exposure. Several populations of high fish consumers have been extensively studied for associations between exposure to methylmercury and health outcomes. Examples include studies conducted on populations in the Republic of Seychelles, Faroe Islands, North Island New Zealand, Nunavik region of arctic Canada, and Amazon River basin. In each of these populations, BHg or HHg levels positively correlated with consumption of fish.

Predominant Mercury Form Unknown (General Populations). Numerous epidemiological studies have examined association between mercury biomarkers and health effects in adults and children. Many of these studies do not identify the predominant form of mercury. In general populations that do not have mercury amalgam dental restorations, dietary exposure is assumed as the primary exposure. In people who have amalgams, mercury released from the amalgams will contribute to exposure. In people who have 7–13 amalgam restorations, amalgam mercury can contribute approximately half of the mercury absorbed from all sources (Mackert and Berglund 1997; Snapp et al. 1989). Biomarkers used to quantify exposures in studies of general populations vary and include BHg, HHg, and UHg. The study population sizes have varied greatly from <100 to almost 50,000 and included prospective studies and cross-sectional studies in large populations, such as participants in the U.S. National Health and Nutrition Examination Survey (NHANES) and the Korea National Health and Nutrition Examination Survey (KNHANES).

Potentials sources of bias. Bias can occur in epidemiological studies when the background risk of the outcome being measured is not the same in the exposed and reference groups. Confounders are factors that account for all or part of the difference in the measured outcome between groups and are not a direct effect of exposure. Not adjusting for confounders may attenuate or strengthen the apparent associations between mercury exposure and the outcome, depending on whether it is a negative or positive confounding variable. Confounders can be addressed in epidemiological studies using a variety of strategies including stratification and matching of subjects, or, in regression models, including these factors as co-variables in the models.

Because of the importance of dietary fish consumption as a source of exposure to methylmercury, fish consumption is a particularly important potential confounder between exposure to methylmercury and health outcomes. For example, fish contain nutrients that have been shown to be important modifiers of development (e.g., 3-omega long-chain polyunsaturated fatty acids, LCPUFA) (Cheatham 2008; Muldoon et al. 2014). In populations consuming marine mammals, dietary intake of polychlorinated biphenyls (PCBs) and selenium that accumulate in marine mammal tissue, can also be a source of confounding bias (Boersma and Lanting 2000; Park et al. 2010; Skroder et al. 2017).

The list of factors than can introduce bias into assessment outcome association with mercury exposure can be quite large. For example, assessing potential associations between mercury exposure and human developmental outcomes involves accounting for many confounders. These factors may include (but are not limited to) child sex, birth weight, birth order, gestational age, and breastfeeding; maternal age,

alcohol and tobacco use, and medical history; parental education, caregiver general intelligence, family income, family language; home learning, language, and social stimulation; exposure to other neurotoxins (e.g., lead, PCBs); nutritional factors (e.g., fish consumption); history of neurological disease or head injuries; and genetic factors that may influence mercury toxicity.

Effect modification. Effect modifiers occur when the relationship between an exposure and an outcome vary by a third variable (the effect measure modifier). For example, renal disease from any cause can affect blood pressure and could thereby interact with mercury to change blood pressure. A variable may act as both an effect modifier and a confounder, depending on a variety of factors. Effect modifiers may be investigated, often to identify susceptible populations or co-exposures that may interact with mercury and change the association of mercury exposure with a health outcome to produce a synergistic or antagonistic effect.

Studies in Laboratory Animals. Animal studies focus on the relevant exposure routes as discussed above for epidemiological studies. For elemental mercury vapor, the animal database consists of acute- and intermediate-duration inhalation studies. No adequate studies were identified for chronic-duration inhalation of elemental mercury vapor or for oral or dermal exposure to elemental mercury. The animal database for inorganic mercury salts includes acute-, intermediate-, and chronic-duration oral studies on mercuric chloride, with a few acute- and intermediate-duration oral studies conducted on mercuric sulfide and one acute-duration study conducted on mercuric acetate. In addition, two intermediate-duration inhalation studies were conducted on mercuric oxide. For organic mercury compounds, acute-, intermediate-, and chronic-duration oral studies were conducted in animals.

Most studies evaluated effects of methylmercury (chemical form not specified) or methylmercury chloride; other compounds tested include methylmercury hydroxide, methylmercuric sulfide, bis(methylmercury)sulfide, tris(methylmercury)sulphonium ion, and phenylmercuric acetate. For all animal studies, doses are expressed in terms of mercury, not the mercury compound that was administered. Additionally, exposure to methylmercury (chemical form not specified) or methylmercury chloride in oral animal studies is referred to as “methylmercury exposure” when discussing toxicity effects since methylmercury chloride rapidly dissociates upon ingestion. Specific mercury compounds tested in each study are included in the LSE tables.

Overview of Health Effects of Mercury Compounds. The health effects of mercury identified from studies in humans and animals are summarized below for the three chemical categories of mercury. For

all forms of mercury, neurological and renal effects have been consistently observed in epidemiological and/or animal studies.

Elemental mercury. Neurological and renal effects have been observed in humans and animals exposed to elemental mercury vapor. Case reports of exposure to elemental mercury at fatal or near-fatal levels have reported severe adverse respiratory effects, including lung inflammation, pneumonitis, and respiratory failure due to pulmonary edema. No evidence for other targets of elemental mercury were identified in epidemiological or animal studies.

- **Neurological Effects:**
    - **Epidemiological studies.** Epidemiological studies provide consistent evidence of neurological effects in adults, including tremor, vision, nerve conduction, motor speed and coordination, cognitive performance (memory, integrative function), and subjective physiological symptoms (mood swings, irritability, nervousness, timidity, loss of confidence).
    - **Animal studies.** Some evidence of neurodevelopmental effects (altered learning and behavior, altered motor activity, impaired habituation) and impaired motor function and damage to the central nervous system in adult animals.
- **Renal Effects:**
    - **Epidemiological studies.** Some evidence of decrements in glomerular function and tubular injury.
    - **Animal studies.** Evidence of dose- and duration-dependent increases in severity of nephrotoxicity (damage to proximal tubules, distal tubules, and glomerular membrane, loss of brush border membranes, necrosis).

Inorganic mercury salts. Neurological and renal toxicity have been consistently observed in animals orally exposed to inorganic mercury salts. Other findings in animal studies provide some evidence of cardiovascular, immunological, and reproductive effects. In addition, there is some evidence of carcinogenicity in male rats. No epidemiological studies specific for exposure to inorganic mercury salts were identified.

- **Neurological Effects:** Consistent evidence of neurodevelopmental effects, including hyperactivity, impaired motor coordination, impaired memory, and decreased sociability. In adult animals, neurobehavioral effects have included hyperactivity, impaired coordination, and

impaired learning and memory. Adult animals have also shown overt neurotoxic signs such as hindlimb crossing, ataxia, tremor, and partial paralysis as well as neuropathological changes to sensorimotor regions in the central nervous system (dorsal spinal route, cerebellum).

- **Renal Effects:** Consistent evidence of dose- and duration-dependent increases in severity of nephrotoxicity (damage to proximal tubules, distal tubules, and glomerular membrane, loss of brush border membranes, necrosis).
- **Cardiovascular Effects:** Evidence of increased blood pressure, altered cardiac function, positive inotropic effects, and altered baroreceptor reflex sensitivity.
- **Immunological Effects:** Evidence of immune stimulation and immune complex disease in genetically susceptible strains of mice.
- **Reproductive Effects:** Evidence of dose-dependent impairment of fertility and decreased sperm motility and number.
- **Cancer:** Some evidence of carcinogenicity in male rats (forestomach and thyroid tumors).

Organic mercury. There is no dispute that neurological and neurodevelopmental effects of organic mercury compounds are established as the most sensitive effect of exposure to organic mercury compounds.

- **Neurological Effects:**
    - **Epidemiological studies (children).** Evidence of cognitive, neuromotor and neurosensory effects associated with prenatal exposure to methylmercury.
    - **Epidemiological studies (adults).** Evidence of decreased performance on tests of fine motor coordination and speed, muscle strength, tactile sensation, color vision and visual contrast sensitivity, and memory and learning.
    - **Animals.** Consistent evidence of dose-dependent neurological effects (sensorimotor dysfunction, vision and hearing deficits, impaired learning and memory) and overt signs of neurotoxicity were observed (clumsiness, gross and fine motor incoordination, lethargy, hindlimb crossing, tremor, ataxia, partial paralysis). Developing animals are more sensitive to methylmercury-induced neurotoxic effects than adult animals.

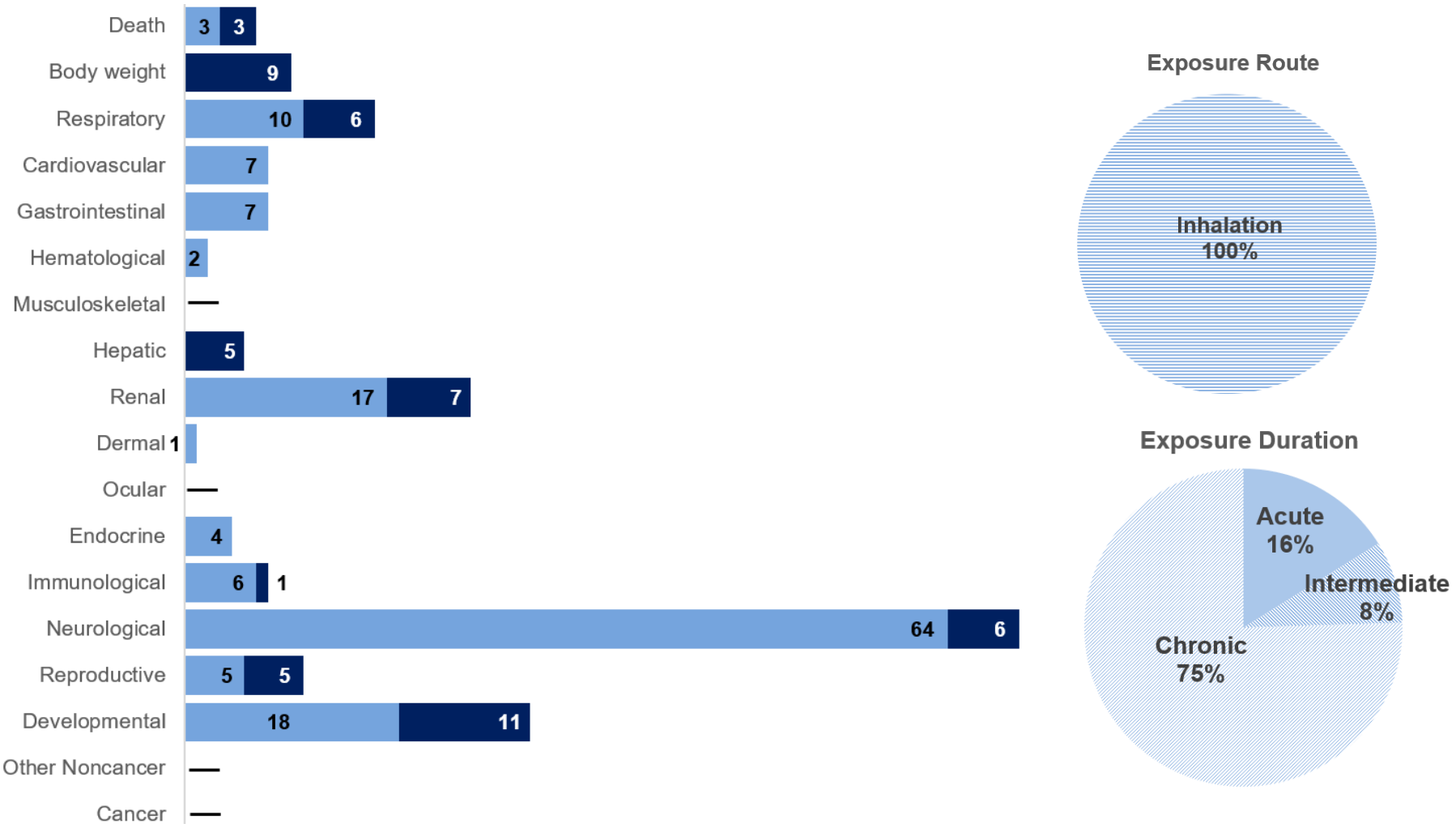
Other systems have not been as extensively studied, although there is some evidence of effects in humans and/or animals, including renal (animal), cardiovascular (humans and animals), immune (humans and animals), reproductive (animal), and developmental (other than neurodevelopmental; humans and animals) effects. However, it does not appear that these effects are sensitive targets for environmental

exposures to methylmercury. In general, these effects occur at much higher levels than those found in the environment.

- **Renal Effects:**
  - **Animal studies.** Consistent evidence of dose- and duration-dependent increases in severity of nephrotoxicity (damage to proximal tubules, distal tubules, and glomerular membrane, loss of brush border membranes, necrosis).
- **Cardiovascular Effects:**
  - **Epidemiological studies.** Inconsistent evidence of small increases in blood pressure, clinical hypertension, and altered cardiac function.
  - **Animal studies.** Evidence of increased blood pressure, positive inotropism, and decreased baroreflex sensitivity.
- **Immunological Effects:**
  - **Epidemiological studies.** Some evidence of alterations in some immune markers (serum cytokine levels, immunoglobulins, and immune cell counts), but unclear if immune system function is affected.
  - **Animal studies.** Evidence of immune stimulation and immune complex disease in genetically susceptible strains of mice and some evidence of immune suppression in non-susceptible animals.
- **Reproductive Effects:**
  - **Animal studies.** Consistent evidence of dose-related impairment in fertility.
- **Developmental Effects (other than Neurodevelopmental):**
  - **Epidemiological studies.** Evidence of congenital effects (polydactyly, syndactyly, craniofacial malformations, microcornea, undescended testicles, enlarged colon, and protrusion of the coccyx) in the Minamata poisoning outbreak.
  - **Animal studies.** Consistent evidence of dose- and duration-dependent decreases in offspring survival, increased fetal malformations and variations (cleft palate, skeletal malformations [ribs, sternebrae], and hydronephrosis), and decreased fetal weight.

Figure 2-1. Overview of the Number of Studies Examining Elemental Mercury Health Effects in Chapter 2*

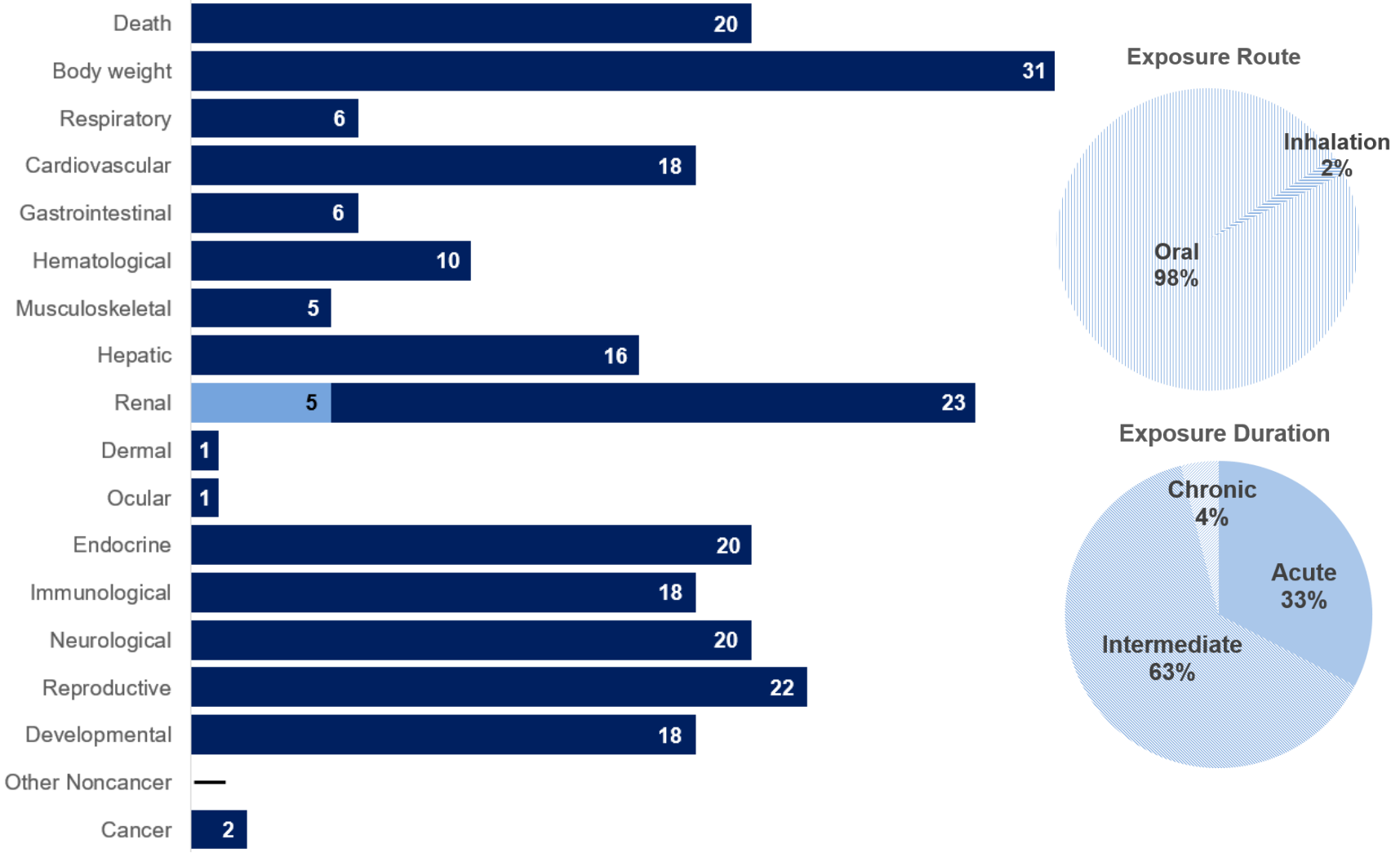
Most studies examined the potential neurological, developmental, and renal effects of elemental mercury
Fewer studies evaluated health effects in **animals** than **humans** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 155 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Figure 2-2. Overview of the Number of Studies Examining Inorganic Mercuric Salts Health Effects in Chapter 2*

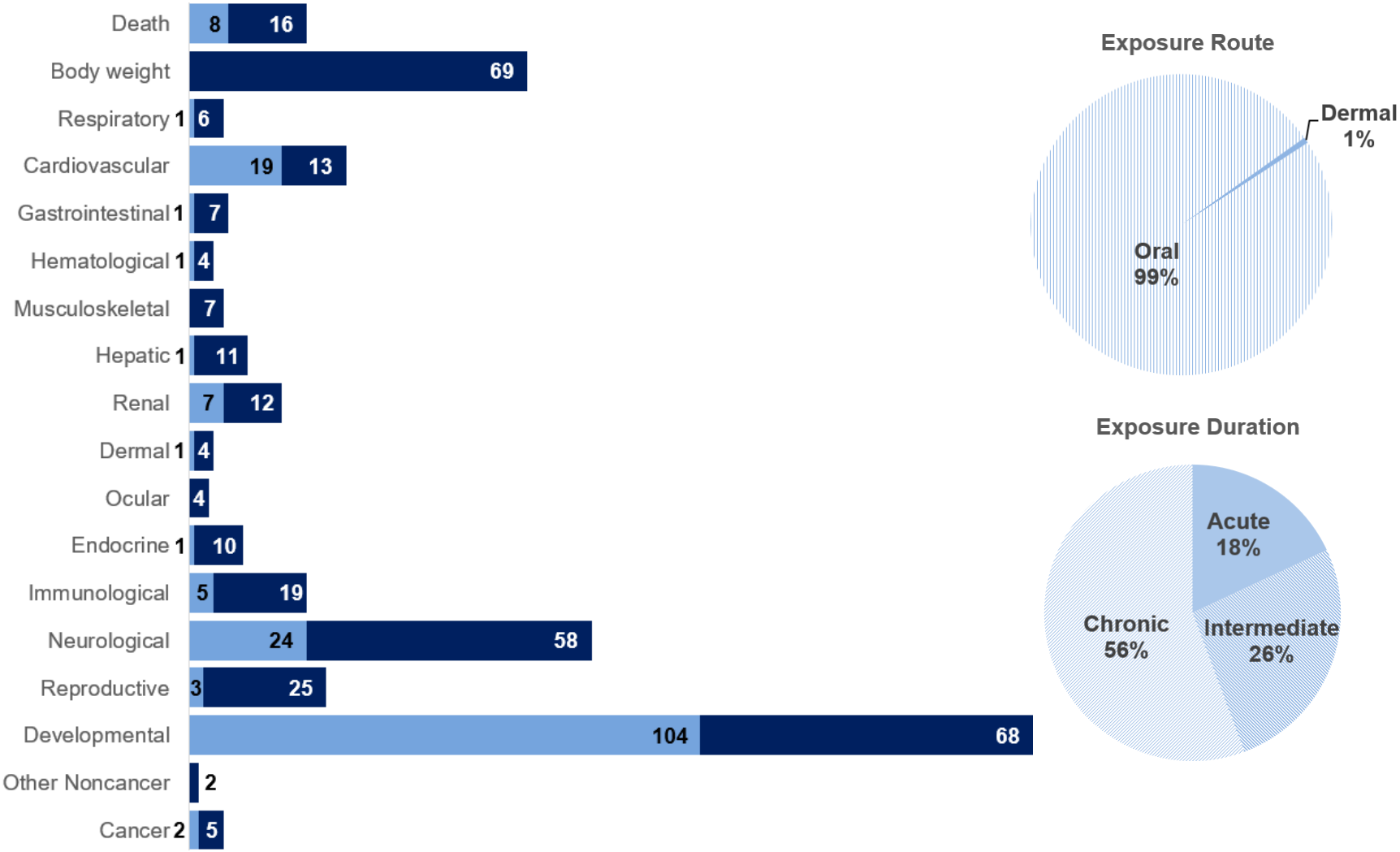
Most studies examined the potential body weight, renal, and reproductive effects of inorganic mercury
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 101 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Figure 2-3. Overview of the Number of Studies Examining Organic Mercury Health Effects in Chapter 2*

Most studies examined the potential developmental, neurological, and body weight effects of organic mercury
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)

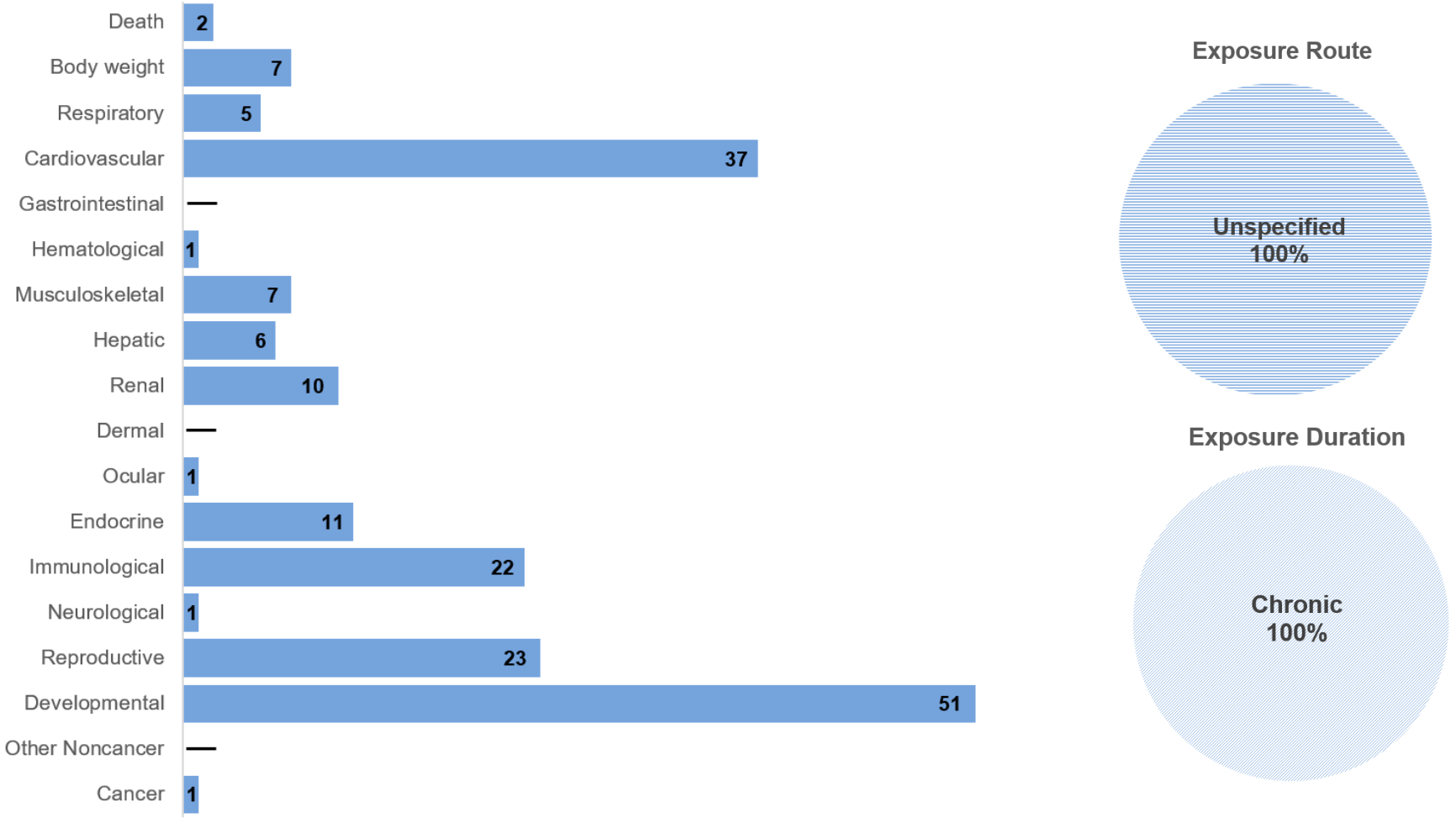


*Includes studies discussed in Chapter 2. A total of 312 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Figure 2-4. Overview of the Number of Studies Examining Mercury Health Effects—Unspecified General Population Exposure in Chapter 2*

Most studies examined the potential developmental, cardiovascular, and reproductive effects of mercury (unspecified mercury form and route of exposure)

General population studies in **humans** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 78 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Elemental Mercury – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Hg/m^3)	Parameters monitored	Endpoint	NOAEL (mg Hg/m^3)	Less serious LOAEL (mg Hg/m^3)	Serious LOAEL (mg Hg/m^3)	Effects
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 12 F	8 days GDs 11–14 and GDs 17–20 1 or 3 hours/day (WB)	0, 1.8	BW, CS, DX	Bd wt	1.8			
					Develop[b]		1.8		Decreased spontaneous locomotion, rearing, and total activity at 3 months; reduced novel environment habituation at 7 months
Danielsson et al. 1993 [Behavior assessed in adult offspring: activity (3, 14 months), habituation (7 months), and spatial learning (4, 7, 15 months).]									
2	Rat (Sprague-Dawley) 8–18 F	11 days 2 hours/day (N)	0, 1, 2, 4	BW, BC, OF, OW	Bd wt	2	4		17% decrease in final body weight
					Repro	1	2		Prolonged estrous cycle at ≥2 mg Hg/m^3; decreased serum estradiol and increased serum progesterone at 4 mg Hg/m^3
Davis et al. 2001									
3	Rat (Sprague-Dawley) 5–6 F	8 days (premating) 2 hours/day (N)	0, 2	BC, GN, OF	Repro	2			
Davis et al. 2001									
4	Rat (Sprague-Dawley) 6 F	8 days (postmating) 2 hours/day (N)	0, 1, 2	BC, GN, OF	Repro	2			
Davis et al. 2001									
5	Rat (Sprague-Dawley) 6 F	1–8 days 2 hours/day (N)	0, 2	BC, HP, OF, OW	Repro		2		Prolonged estrous cycle after 6–8 days of exposure; immature corpora lutea during estrus and metestrus phases
Davis et al. 2001									

Table 2-1. Levels of Significant Exposure to Elemental Mercury – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Hg/m^3)	Parameters monitored	Endpoint	NOAEL (mg Hg/m^3)	Less serious LOAEL (mg Hg/m^3)	Serious LOAEL (mg Hg/m^3)	Effects
6	Rat (Sprague-Dawley) 8–10 M	7 days PNDs 11–17 1 hour/day (WB)	0, 0.05	DX	Develop[b]		0.05		Increased spontaneous locomotion and decreased rearing at 4 months of age; impaired spatial learning at 6 months of age
Fredriksson et al. 1992 [Behavior assessed in adulthood: motor activity (2, 4 months) and spatial learning (5, 6 months).]									
7	Rat (Sprague-Dawley) 8–10 M	7 days PNDs 11–17 4 hours/day (WB)	0, 0.05	DX	Develop[b]		0.05		Increased spontaneous locomotion and decreased rearing at 2 months of age; decreased spontaneous locomotion and rearing at 4 months of age; and impaired spatial learning at 6 months of age
Fredriksson et al. 1992 [Behavior assessed in adulthood: motor activity (2, 4 months) and spatial learning (5, 6 months).]									
8	Rat (Sprague-Dawley) 12 F	6 days GDs 14–19 1.5 hours/day (WB)	0, 1.8	BW, CS, DX	Bd wt	1.8			
					Develop[b]		1.8		Increased spontaneous locomotion, rearing, and total activity at 4 months of age; impaired spatial learning at 4.5 months of age
Fredriksson et al. 1996 [Behavior assessed in adult male offspring at 4–5 months of age.]									
9	Rat (Long-Evans) 10–12 F	10 days GDs 6–15 2 hours/day (N)	0, 4	DX	Develop[b]	4			
Herr et al. 2004 [Sensory evoked potentials measured in adult offspring.]									
10	Rat (Wistar) 32 M	2 hours (WB)	0, 27.0	BW, CS, HP, LE	Death			27	20/32 died prior to scheduled sacrifice (none survived longer than 5 days post-exposure)
					Bd wt			27	15–25% body weight loss
					Resp			27	Dyspnea and asphyxiation; lung edema, necrosis of alveolar epithelium, hyaline membranes, occasional fibrosis
Livardjani et al. 1991 [Animals sacrificed 1, 2, 3, 4, 5, 6, 7, or 15 days post-exposure (4/group).]									

Table 2-1. Levels of Significant Exposure to Elemental Mercury – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Hg/m^3)	Parameters monitored	Endpoint	NOAEL (mg Hg/m^3)	Less serious LOAEL (mg Hg/m^3)	Serious LOAEL (mg Hg/m^3)	Effects
11	Rat (Wistar) 32 M	1 hour (WB)	0, 26.6	BW, CS, GN, LE	Bd wt	26.6			
					Resp	26.6			
Livardjani et al. 1991 [Animals sacrificed 1, 2, 3, 4, 5, 6, 7, or 15 days post-exposure (4/group)]									
12	Rat (Long-Evans) 5 F	2 hours GD 6 (N)	0, 1, 2, 4, 8	BW, CS, DX, HP, OW, UR	Bd wt	8			
					Resp	8			
					Hepatic	8			
					Renal	8			
					Develop	8			
Morgan et al. 2002									
13	Rat (Long-Evans) 5 F	5 days GDs 6–10 2 hours/day (N)	0, 1, 2, 4, 8	BW, CS, DX, HP, OW, UR	Bd wt	4	8		10% decrease in maternal body weight
					Resp	8			
					Hepatic	8			
					Renal	8			
					Develop	8			
Morgan et al. 2002									
14	Rat (Long-Evans) 10 F	10 days GDs 6–15 2 hours/day (N)	0, 1, 2, 4, 8	BW, CS, DX, HP, OW, UR	Bd wt	2	4	8	>10% decrease in maternal body weight at 4 mg Hg/m^3; 17% maternal body weight loss at 8 mg Hg/m^3
					Resp	8			
					Hepatic	8			
					Renal	2	4		Elevated maternal relative kidney weight (32% on GD 15); increased urinary protein and ALP
					Neuro	4	8		Mild tremor, lethargy, unsteady gait
					Develop	4	8		Increased resorptions, decreased litter size and pup weight
Morgan et al. 2002 [50% of dams sacrificed on GD 15 and 50% sacrificed on PND 1.]									

Table 2-1. Levels of Significant Exposure to Elemental Mercury – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Hg/m^3)	Parameters monitored	Endpoint	NOAEL (mg Hg/m^3)	Less serious LOAEL (mg Hg/m^3)	Serious LOAEL (mg Hg/m^3)	Effects
15	Mouse (129S/v) 6 F	4 hours (WB)	0, 0.5	NX, HP	Neuro		0.5		Reduced grip strength 4–7 months post-exposure, decreased motor axon diameter 7 months post-exposure
Stankovic 2006									
INTERMEDIATE EXPOSURE									
16	Monkey (squirrel) 5–6 F	15–17 weeks Last 2/3 gestation 5 days/week 4 or 7 hours/day (WB)	0, 0.5, 1.0	NX, CS, DX	Develop[b]		0.5		Impaired operant training in offspring
Newland et al. 1996 [Offspring behavioral testing at 0.8–4 years old.]									
17	Rat (Sprague-Dawley) 6 M	6 weeks 7 days/week 9 hours/day (WB)	0, 1	HP	Repro			1	Seminiferous tubule atrophy; damage to spermatogenic cells; decreased testicular and seminiferous tubule volume, decreased seminiferous tubule diameter; decreased Sertoli cells, spermatogonia, spermatocytes, and spermatids
Altunkaynak et al. 2015									
18	Rat (Wistar) 12–14 M	12–42 weeks 5 day/week 3 hours/day (WB)	0, 3	CS, NX, BW, HP, LE	Bd wt			3	Body weight loss (magnitude not reported)
					Resp	3			
					Hepatic	3			
					Renal		3		Dense black deposits in tubular cells, lysosomal inclusions, slight degeneration of tubular cells
					Neuro		3		Tremors; altered neurobehavior (decline in conditioned avoidance, increased escape response latency)
Kishi et al. 1978									

Table 2-1. Levels of Significant Exposure to Elemental Mercury – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Hg/m^3)	Parameters monitored	Endpoint	NOAEL (mg Hg/m^3)	Less serious LOAEL (mg Hg/m^3)	Serious LOAEL (mg Hg/m^3)	Effects
19	Rat (Wistar) 12 M	8 weeks 4–5 days/week 5 hours/day (WB)	0, 0.5	BW, CS, HP	Bd wt		0.5		17% decrease in body weight gain
					Neuro		0.5		Irritability, aggressiveness; loss of Purkinje and granular cells in cerebellum
Sørensen et al. 2000									
20	Rat (Wistar) 6 F	45 days 24 hours/day (WB)	0, 1	HP	Hepatic			1	Extensive hepatocyte degeneration; enlarged blood vessels, dilated sinusoids, increased perivascular connective tissue; increased liver volume; increased number and density of binucleated hepatocytes
Yahyazedeh et al. 2017									
21	Mouse (SJL/N) 10–14 F	10 weeks, 5 days/week, 0.5–9 hours/day (WB)	TWA: 0, 0.01, 0.03, 0.06, 0.08, 0.1, 0.4	BI, BC, IX	Immuno	0.01	0.03		Serum antinucleolar antibodies at ≥0.03 mg Hg/m^3; increased serum immunoglobins and renal immune complex deposits at ≥0.06 mg Hg/m^3
Warfvinge et al. 1995 [Autoimmune susceptible mouse strain. TWA doses were calculated due to varying daily exposure duration.]									
22	Mouse (C57BL/6) NS F	19 days GDs 0–18 6 hours/day (WB)	0, 0.03	DX	Develop[b]	0.03			
Yoshida et al. 2011 [Motor activity, learning and memory assessed at PND 56.]									
23	Mouse (C57BL/6J) 7–8 F	27 days PNDs 2–28 24 hours/day (WB)	0, 0.188	DX	Develop[b]		0.188		Decreased motor activity at PND 77
Yoshida et al. 2018 [Motor activity, learning and memory assessed at PNDs 77–84.]									
24	Mouse (C57BL/6) 6 F	20 days PNDs 1–20 24 hours/day (WB)	0, 0.057	DX	Develop[b]	0.057			
Yoshida et al. 2013 [Motor activity, learning and memory assessed at 3 and 15 months.]									

Table 2-1. Levels of Significant Exposure to Elemental Mercury – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Hg/m^3)	Parameters monitored	Endpoint	NOAEL (mg Hg/m^3)	Less serious LOAEL (mg Hg/m^3)	Serious LOAEL (mg Hg/m^3)	Effects
25	Rabbit (NS) 6 M	13 weeks 4 days/week 6 hours/day (WB)	4.0	NX	Neuro		4		Clonus and tremors after 11 weeks, exaggerated reflexes
Fukuda 1971									
CHRONIC EXPOSURE									
26	Human 18–85 per study	Occupational	0.00457–0.00874	NX	Neuro				Tremor; weighted median of 0.00492 mg Hg/m^3 (95% lower confidence limit of 0.00284 mg Hg/m^3)[c]
Bast-Pettersen et al. 2005; Boogaard et al. 1996; Chapman et al. 1990; Ellingsen et al. 2001; Fawer et al. 1983; Langworth et al. 1992a; Wastensson et al. 2006, 2008									

[a]The number corresponds to entries in Figure 2-5; differences in levels of health effects between male and females are not indicated in Figure 2-5. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]The neurodevelopmental effects are discussed in Section 2.16 (Neurological).
[c]Used to derive a provisional chronic-duration inhalation MRL of 0.0003 mg Hg/m^3 (0.3 µg Hg/m^3) for elemental mercury; based on a 95% lower confidence limit of the weighted median of 0.00284 mg Hg/m^3 from seven occupational exposure studies and divided by an uncertainty factor of 10 for human variability; see Appendix A for more detailed information regarding the provisional MRL.

Principal studies for the MRLs

ALP = alkaline phosphatase; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; CS = clinical signs; Develop = developmental; DX = developmental toxicity; F = female(s); GD = gestation day; GN = gross necropsy; HP = histopathology; Immuno = immunological; IX = immune function; LCL = lower confidence limit; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; N = nose-only; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; TWA = time-weighted average; UR = urinalysis; WB = whole body

Figure 2-5. Levels of Significant Exposure to Elemental Mercury – Inhalation
Acute (≤14 days)

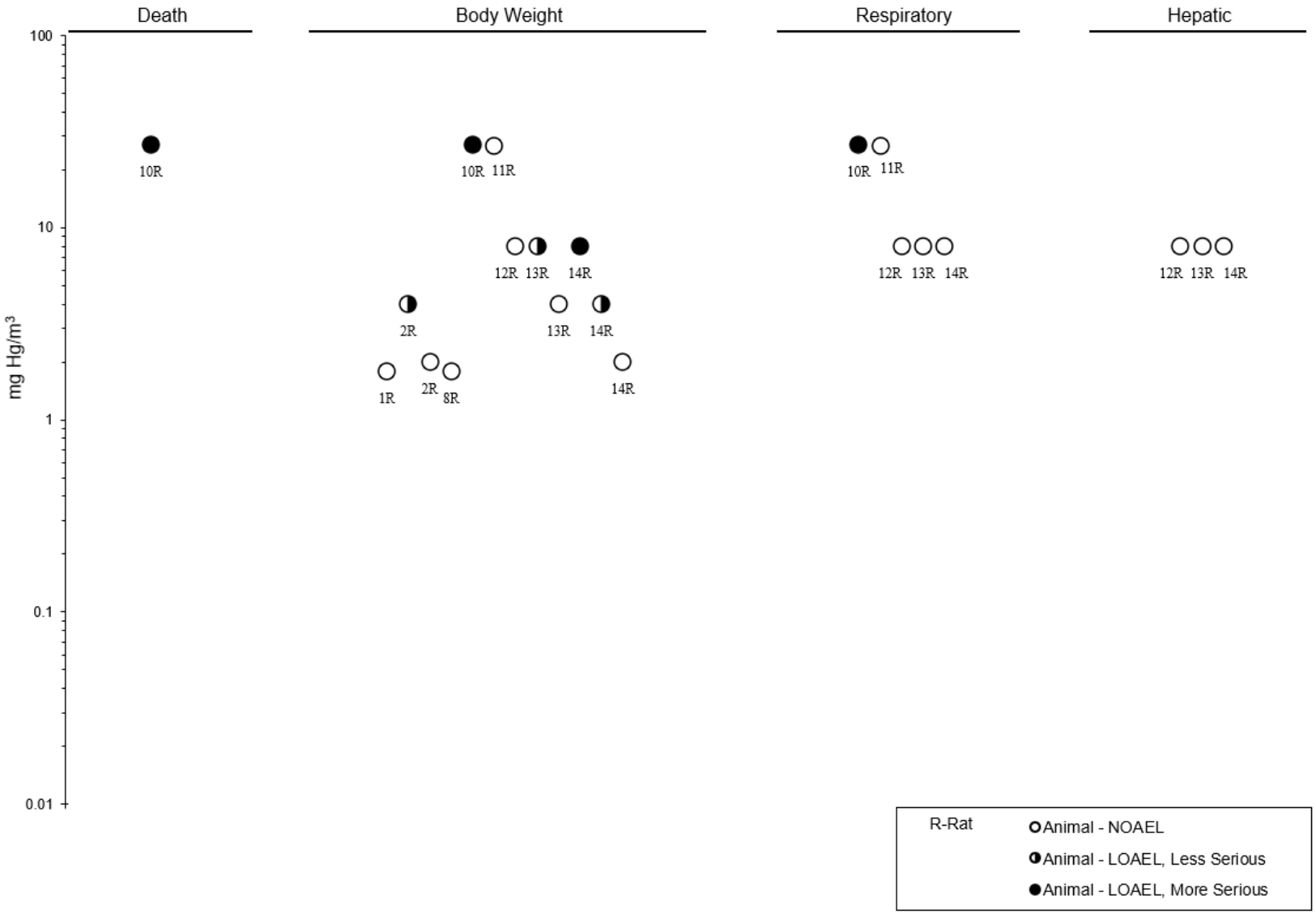


Figure 2-5. Levels of Significant Exposure to Elemental Mercury – Inhalation
Acute (≤14 days)

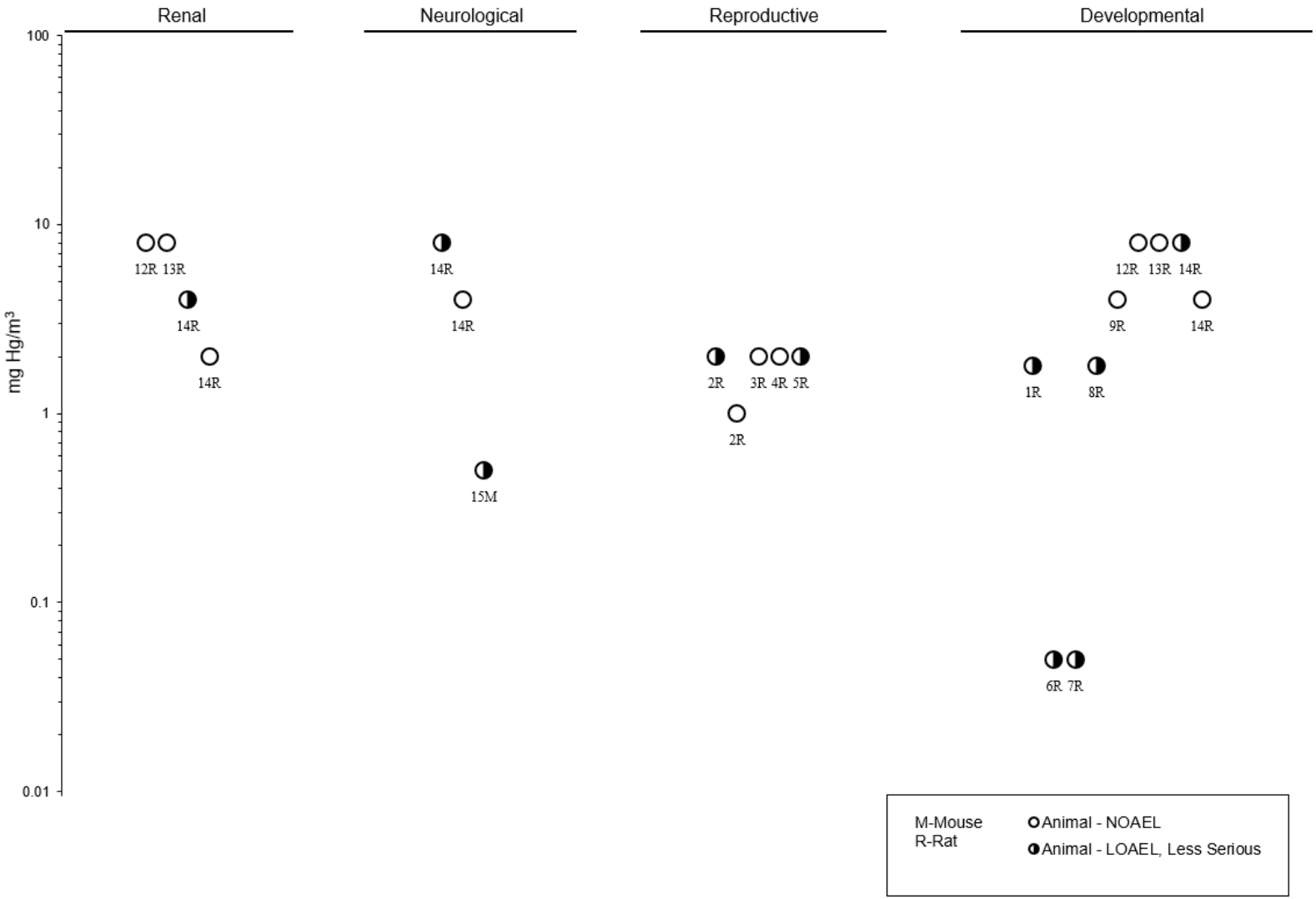


Figure 2-5. Levels of Significant Exposure to Elemental Mercury – Inhalation
Intermediate (15–364 days)

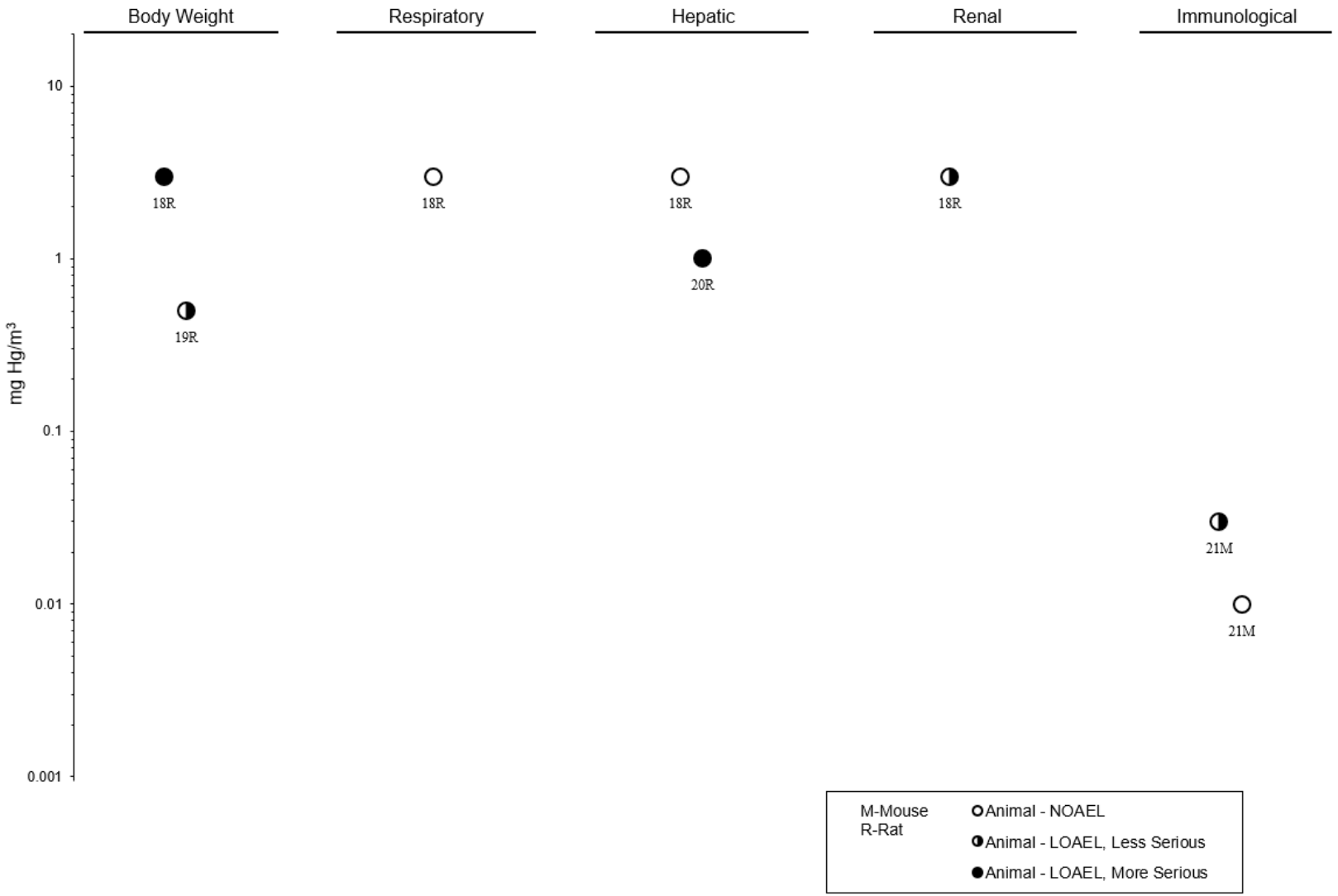


Figure 2-5. Levels of Significant Exposure to Elemental Mercury – Inhalation

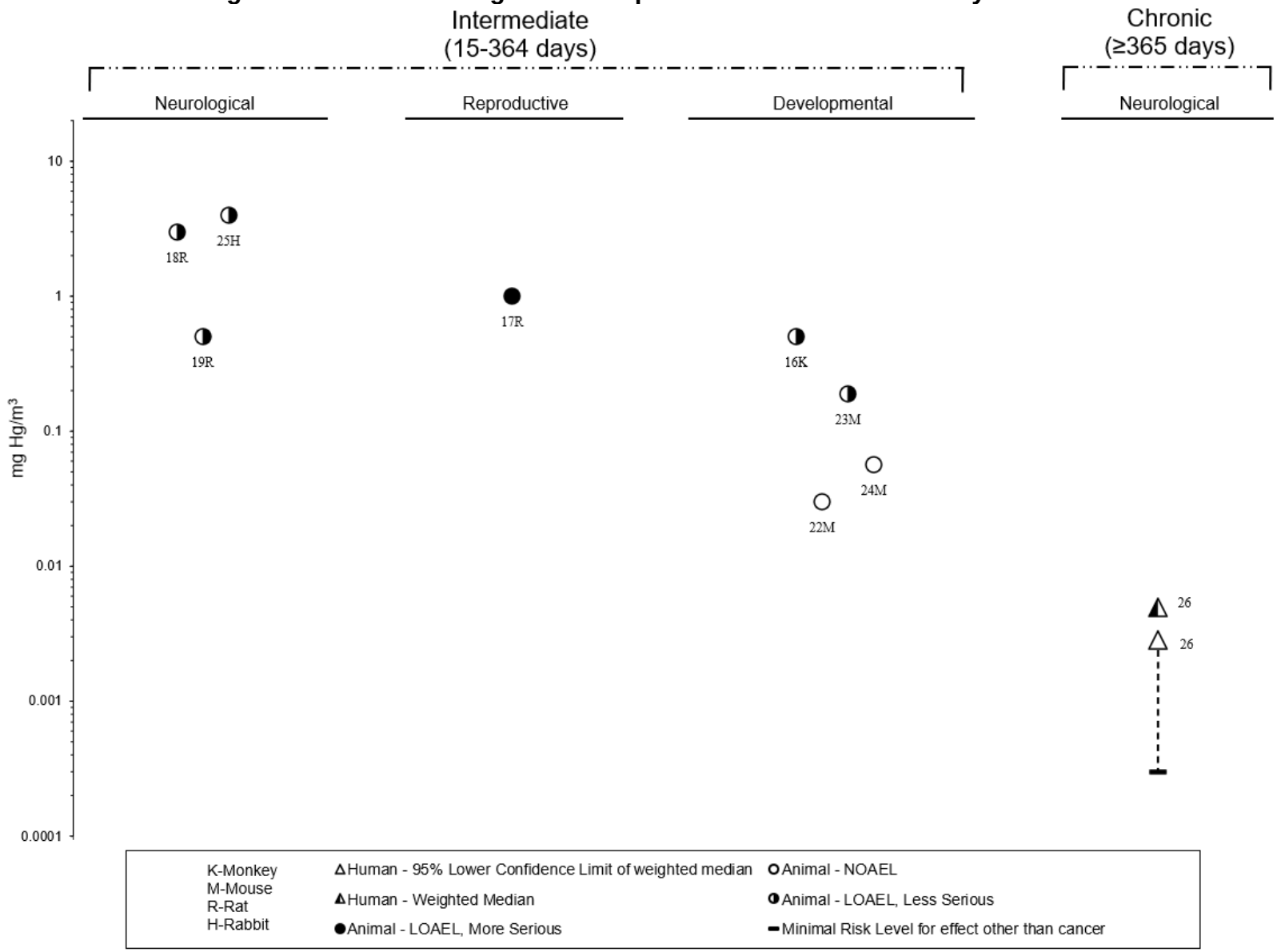


Table 2-2. Levels of Significant Exposure to Mercuric Oxide – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Hg/m^3)	Parameters monitored	Endpoint	NOAEL (mg Hg/m^3)	Less serious LOAEL (mg Hg/m^3)	Serious LOAEL (mg Hg/m^3)	Effects
INTERMEDIATE EXPOSURE									
1	Rat (Wistar) 6 F	45 days 9 hours/day (WB)	0, 1	HP	Neuro		1		Decreased cerebellar volume and cerebellar damage (gliosis, vacuolization, loss of Purkinje cells)
Mercuric oxide Altunkaynak et al. 2019									
2	Rat (Wistar) 6 F	45 days 24 hours/day (WB)	0, 0.9	HP	Repro		0.9		38% reduction in ovary volume, 33–50% decrease in ovarian follicles, histopathological changes in ovaries
Mercuric oxide Altunkaynak et al. 2016									

[a]The number corresponds to entries in Figure 2-6.

F = female(s); HP = histopathology; LOAEL = lowest-observed-adverse-effect level; Neuro = neurological; NOAEL = no-observed-adverse-effect level; Repro = reproductive; WB = whole body

Figure 2-6. Levels of Significant Exposure to Mercuric Oxide – Inhalation
Intermediate (15–364 days)

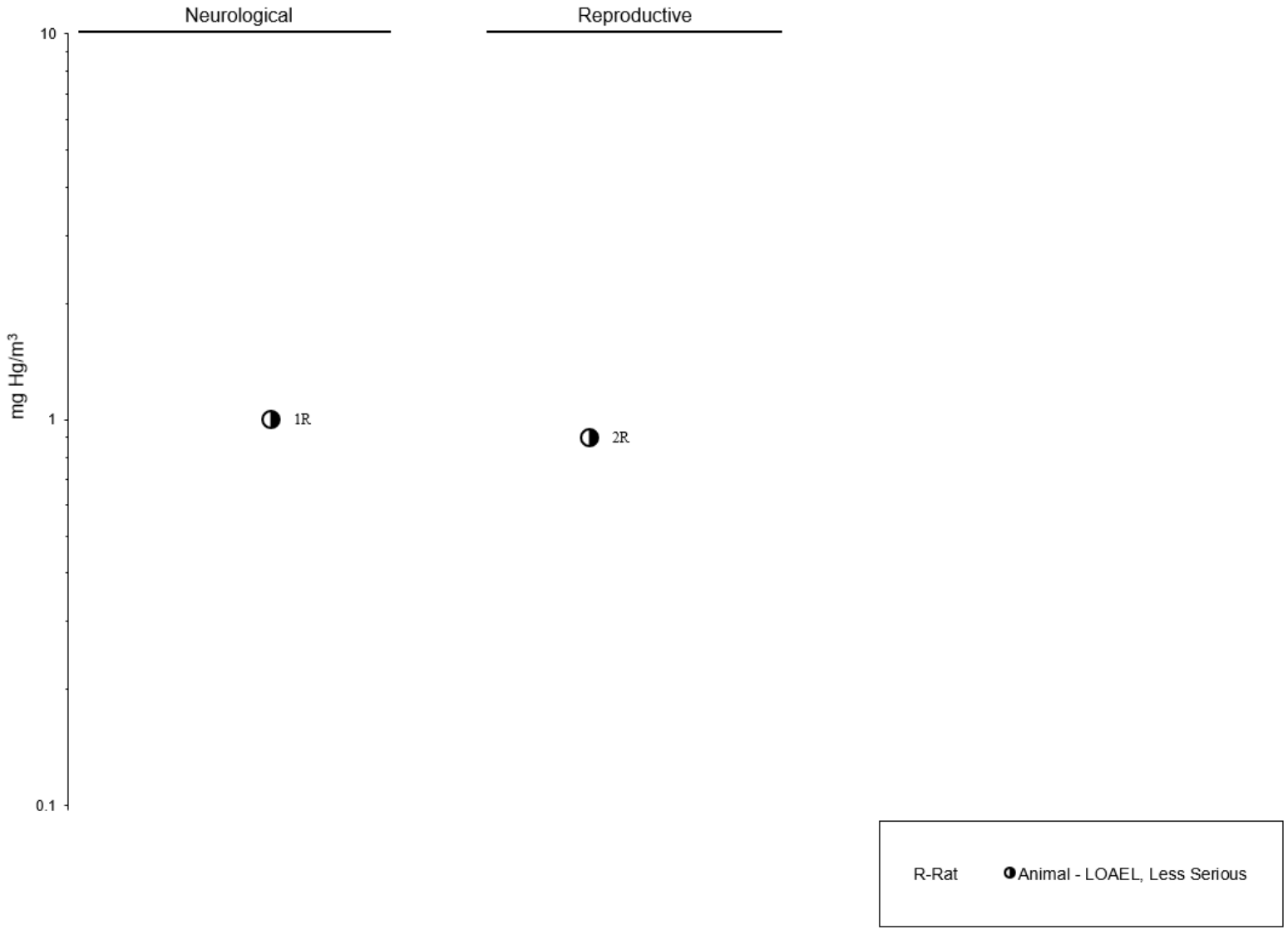


Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	Rat (Wistar) 6 M	3 or 7 days (W)	0, 3, 6	BW, FI, WI, BC, BI, OW, HP, RX	Repro		3		Decreased sperm number and motility; non-monotonic changes in serum testosterone
Mercuric chloride Boujbiha et al. 2009									
2	Rat (Holtzman) 4 M	1–2 weeks (G)	0, 0.7	CS, BW, HP	Bd wt	0.7			
					Neuro		0.7		Ultrastructural changes in dorsal root ganglia and cerebellum
Mercuric chloride Chang and Hartmann 1972a									
3	Rat (Sprague-Dawley) 6 M	5 days (GW)	0, 860	NX	Neuro		860		Impairment of compound muscle action potential recovery after tetany
Mercuric sulfide Chuu et al. 2007									
4	Rat (Sprague-Dawley) 6 M	14 days (GW)	0, 860	BW, NX	Bd wt	860			
					Neuro		860		Transient suppression of compound muscle action potentials followed by incomplete recovery after tetany
Mercuric sulfide Chuu et al. 2007									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
5	Rat (Fischer-344) 5 M, 5 F	16 days 5 days/week (GW)	0, 0.923, 1.8, 4, 7.4, 15	LE, BW, GN, OW, HP	Death			15 M	2/5 died after 4–5 days of exposure
					Bd wt	4	7.4	15	LOAEL: 17–18% decrease in body weight gain Serious LOAEL: 30–41% decrease in body weight gain in both sexes, 11% decrease in body weight in females
					Gastro	15			
					Renal	1.8 F 0.923[b] M	4 F 1.8 M	15 F 7.4 M	LOAEL: ≥17% increase in relative kidney weight Serious LOAEL: acute renal necrosis $BMDL_{1SD}$=0.29 mg Hg/kg/day
Mercuric chloride Dieter et al. 1992; NTP 1993									
6	Rat (Long-Evans) 8–12 F	6 days (GW)	0, 7.4	OF	Endocr		7.4		Increased thyroid function (accelerated release and turnover of radiolabeled iodine)
Mercuric chloride Goldman and Blackburn 1979									
7	Rat (albino) 6 B	Once (G)	6 unspecified dose levels	LE	Death			25.9	LD_{50} in 2-week-old rats
Mercuric chloride Kostial et al. 1978									
8	Rat (albino) 6 F	Once (G)	6 unspecified dose levels	LE	Death			77.7	LD_{50} in 3-week-old rats
Mercuric chloride Kostial et al. 1978									
9	Rat (albino) 6 F	Once (G)	6 unspecified dose levels	LE	Death			68.1	LD_{50} in 6-week-old rats
Mercuric chloride Kostial et al. 1978									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
10	Rat (albino) 6 F	Once (G)	6 unspecified dose levels	LE	Death			37	LD_{50} in 18-week-old rats
Mercuric chloride Kostial et al. 1978									
11	Rat (albino) 6 F	Once (G)	6 unspecified dose levels	LE	Death			37	LD_{50} in 54-week-old rats
Mercuric chloride Kostial et al. 1978									
12	Rat (Sprague-Dawley) 10 F	Once (GO)	0, 7.4, 9.24	LE, CS, BW, FI, BC, HE, OW, GN, HP	Bd wt	9.24			
					Resp	9.24			
					Cardio	9.24			
					Gastro	9.24			
					Hemato		7.4		9–10% decrease in erythrocyte count, hemoglobin, and hematocrit
					Musc/skel	9.24			
					Hepatic	9.24			
					Renal		7.4		Mild histopathological changes (protein casts, cellular casts, interstitial sclerosis)
					Dermal	9.24			
					Ocular	9.24			
					Endocr	9.24			
					Immuno	9.24			
					Neuro	9.24			
					Repro	9.24			
Mercuric chloride Lecavalier et al. 1994									
13	Rat (albino) 5–20 NS	Once (NS)	0, 0.684	HE	Hemato		0.684		Increased bleeding and clotting time; 10% increase in WBC count
Mercuric chloride Mahour and Saxena 2009									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
14	Rat (albino) 5–20 NS	7 or 14 days (NS)	0, 0.033	HE	Hemato		0.033		Increased bleeding and clotting time; 7–9% decrease in hemoglobin; 10–21% increase in erythrocyte sedimentation rate; 13% increase in WBC count (14 days only)
Mercuric chloride **Mahour and Saxena 2009**									
15	Rat (Wistar) 8 F	11 days GDs 5–15 (GW)	0, 0.4, 0.8, 1.6	DX	Develop[c]	1.6 M			
Mercuric chloride **Papp et al. 2005** [Neurophysiological recordings in male offspring at PND 84.]									
16	Mouse (ICR) 16 M	2 weeks (GW)	0, 3.7	BC, BI, HP	Endocr		3.7		~17% increase in baseline plasma insulin and ~60% decrease in fasting plasma insulin; ~15% decrease in blood glucose and impaired glucose tolerance; apoptosis in pancreatic islet cells
Mercuric chloride **Chen et al. 2012**									
17	Mouse (NS) 8–10 M	7 days (G)	0, 86, 860	NX	Neuro	86	860		Reversible hearing loss
Mercuric sulfide **Chuu et al. 2001a** [Vehicle was saline.]									
18	Mouse (SJL/N) 5 F	2 weeks (W)	0, 0.7	IX	Immuno		0.7		Increased lymphoproliferation in response to T- and B-cell mitogens
Mercuric chloride **Hultman and Johansson 1991** [Autoimmune susceptible mice]									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
19	Mouse (DBA/2) 5 F	2 weeks (W)	0, 0.7	IX	Immuno	0.7			
Mercuric chloride **Hultman and Johansson 1991** [Autoimmune resistant mice]									
20	Mouse (BALB/c) 4 M	14 days (W)	0, 0.06, 0.31, 1.39, 4.81	BC, FI, WI, HE, OW	Hemato		0.06		11–19% decrease in RBC count at 0.06 mg Hg/kg/day; 91% increase in WBC count at 4.81 mg Hg/kg/day
					Hepatic	4.81			
					Renal	0.31	1.39		11% increase in relative kidney weight
					Immuno	0.06	0.31		Decreased T-lymphocytes, T-helper, and T-suppressor in spleen; decreased T-suppressor cells in thymus at ≥1.39 mg Hg/kg/day
Mercuric chloride **Kim et al. 2003**									
21	Mouse (NMRI) 10–20 F	Once (GW)	0, 5, 10, 20, 40	BI, HP	Renal	5	10	20	Regeneration of proximal tubule at ≥10 mg Hg/kg/day; proximal tubule necrosis at ≥20 mg Hg/kg/day
Mercuric chloride **Nielsen et al. 1991**									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
22	Mouse (B6C3F1) 5 M, 5 F	16 days 5 days/week (GW)	0, 4, 7.4, 15, 30, 59	LE, HP	Death			59	5/5 males and 4/5 females died within 2–4 days
					Bd wt	30			
					Gastro	30	59		Inflammation of forestomach; necrosis of forestomach and glandular stomach
					Renal		4	30 M 59 F	LOAEL: ≥19% increase in relative kidney weight Serious LOAEL: acute renal necrosis
					Immuno	30			
Mercuric chloride NTP 1993									
23	Mouse (Swiss albino) 6 F	10 days (GW)	0, 6	BC	Endocr		6		59% decrease in serum T3
Mercuric sulfide Sin et al. 1990									
24	Mouse Swiss albino 6 F	10 days (GW)	0, 6	BC	Endocr		6		70% decrease in serum T3; 42% decrease in serum T4
Mercuric chloride Sin et al. 1990									
25	Guinea pig (Hartley) 14–90 F	7 days (G)	0, 8.6, 86, 860	HP, NX	Neuro	8.6	86		Abnormal vestibular ocular reflex, impaired equilibrium at ≥86 mg Hg/kg/day; Purkinje cell loss in cerebellum at 860 mg Hg/kg/day
Mercuric sulfide Chuu et al. 2001b [Vehicle was saline.]									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
26	Guinea pig (Hartley) 8–12 F	14 days (G)	0, 86	NX	Neuro		86		Abnormal vestibular ocular reflex
Mercuric sulfide **Chuu et al. 2001b** [Vehicle was saline.]									
27	Hamster Golden 3–10 F	Once GD 8 (GW)	0, 2.5, 5, 15.8, 22.1, 31.5, 47.3, 63	DX	Develop	2.5	5	15.8	Decreased crown-rump length at ≥5 mg Hg/kg/day; increased abnormal embryos and resorption at ≥15.8 mg Hg/kg/day
Mercuric acetate **Gale 1974**									
INTERMEDIATE EXPOSURE									
28	Rat (albino) 5 M	60 days (W)	0, 2.9, 5.8, 11.8	CS, BC, BI, OW	Endocr		2.9		31% increase in relative adrenal weight, 146% increase in adrenal corticosterone; nonmonotonic changes in plasma corticosterone
Mercuric chloride **Agrawal and Chansouria 1989**									
29	Rat (albino) 5 M	120 days (W)	0, 2.9, 5.8, 11.8	CS, BC, BI, OW	Endocr		2.9		19% increase in relative adrenal weight, 87% and 218% increase in plasma and adrenal corticosterone, respectively
Mercuric chloride **Agrawal and Chansouria 1989**									
30	Rat (albino) 5 M	180 days (W)	0, 2.9, 5.8, 11.8	CS, BC, BI, OW	Endocr		2.9		14% increase in relative adrenal gland weight
Mercuric chloride **Agrawal and Chansouria 1989**									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
31	Rat (Wistar) 5 M	6 months 7 days/week (NS)	0, 0.4	BW, BC, BI, HE	Bd wt	0.4			
					Hemato		0.4		140% increase in WBCs
					Hepatic		0.4		21–56% increase in AST, ALP, and LDH
Mercuric chloride Agrawal et al. 2014									
32	Rat (Wistar) 6 NS	28 days (GW)	0, 0.015	BC, BI, HP	Renal		0.015[d]		Altered serum chemistry (increased urea, uric acid, creatinine); tubular dilation and glomerular lobulation
Mercuric chloride Apaydin et al. 2016									
33	Rat (Sprague-Dawley) 15–25 M, 15–25 F	79–81 days/ generation; 2 generations (GW)	M: 0, 0.37, 0.74, 1.31 F: 0, 0.55, 1.11, 1.98	CS, BW, FI, CS, GN, OW, RX, DX	Death			1.98 F	50% mortality in F0 females
					Bd wt	0.55 F	0.37 M	1.11 F	Male: 16% decrease in adult F1 body weight at 0.37 mg Hg/kg/day; decreased F0 body weight at 1.31 mg Hg/kg/day Female: transient F0 body weight decreases up to ~21% during gestation at ≥1.11 mg Hg/kg/day
					Hepatic	1.31 M	0.55 F		>20% decrease in relative liver weight in F0 females
					Renal	0.55 F	0.37 M 1.11 F		>10% increase in relative kidney weights in F0 males and F1 females
					Endocr	1.31 M 1.98 F			

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Repro		0.37 M 0.55 F	0.74 M 1.11 F	LOAEL: decreased F0 fertility and implant efficiency, decreased F1 live birth index Serious LOAEL: ≥50% reduction in F0 fertility with reduced F1 implant efficiency, F2 live birth index, and F0 relative seminal vesicle weight
					Develop			0.55	~20% reduction in F1 pup body weight at 0.55 mg Hg/kg/day; reduced PND 4 survival for F1 and F2 pups at 1.98 and 1.11 mg Hg/kg/day, respectively
Mercuric chloride Atkinson et al. 2001									
34	Rat (Wistar) 8 M	350 days (W)	0, 6, 24	CS, HP, OF	Cardio		6		Increased aortic blood pressure; positive cardiac inotropism; decreased baroreceptor reflex sensitivity
					Renal		6		Tubular degeneration and membranous glomerulonephritis
Mercuric chloride Boscolo et al. 1989									
35	Rat (Sprague-Dawley) 8 M	350 days (W)	0, 6	CS, HP, OF	Cardio		6		Increased aortic blood pressure; positive cardiac inotropism; decreased baroreceptor reflex sensitivity
					Renal		6		Tubular degeneration and desquamation
Mercuric chloride Boscolo et al. 1989; Carmignani et al. 1989									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
36	Rat (Wistar) 6 M	15–90 days premating (W)	0, 3, 6	BW, FI, WI, BC, BI, OW, HP, RX	Repro		3	6	LOAEL: >10% increase in relative testes weight, sperm impairments, increased testicular testosterone, decreased serum and testicular estradiol, histopathological changes in testes, 36% decrease in viable embryos Serious LOAEL: 50% decrease in mating index and 76% decrease in viable embryos
Mercuric chloride **Boujbiha et al. 2009, 2011** [Males were mated to untreated females.]									
37	Rat (Wistar) 6 M	90 days (W)	0, 5.5, 11	HE	Hemato	5.5	11		10% decrease in RBC count and hemoglobin, 7% decrease in hematocrit
Mercuric chloride **Boujbiha et al. 2012**									
38	Rat (Sprague-Dawley) 10 M	320 days (W)	0, 6	OF	Cardio		6		Positive cardiac inotropism, reduced baroreflex sensitivity
Mercuric chloride **Carmignani and Boscolo 1984**									
39	Rat (Sprague-Dawley) 10 M	350 days (W)	0, 6	OF	Cardio		6		Increased systolic and diastolic blood pressure, positive cardiac inotropism, reduced baroreflex sensitivity
Mercuric chloride **Carmignani and Boscolo 1984**									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
40	Rat (Wistar) 8 M	180 days (W)	0, 24	CS, BW, HP, OF	Cardio		24		Increased systolic and diastolic blood pressure
					Renal		24		Mesangial proliferative glomerulonephritis
Mercuric chloride Carmignani et al. 1992									
41	Rat (Holtzman) 4 M	11 weeks (G)	0, 0.7	CS, BW, HP	Bd wt			0.7	Body weight loss
					Neuro			0.7	Hindlimb crossing, ataxia, tremor; cellular degeneration and ultrastructural changes in dorsal root ganglia and cerebellum
Mercuric chloride Chang and Hartmann 1972a									
42	Rat (Wistar) 10 F	21 days GDs 1–21 (W)	0, 6.1, 9.6	WI, RX, DX	Repro		6.1		Reduced maternal care
					Develop[c]		6.1	9.6	LOAEL: 14% decrease in body weight, impaired/delayed sensorimotor development, decreased anxiety at PND 63 Serious LOAEL: 16% pup mortality and >20% decrease in body weight
Mercuric chloride Chehimi et al. 2012									
43	Rat (Fischer-344) 10 M, 10 F	26 weeks 5 days/week (GW)	0, 0.230, 0.462, 0.923, 1.8, 4	BW, BC, BW, GN, OW, HP	Bd wt	1.8 M 0.462 F	4 M 0.923 F		≥10% decrease in body weight gain
					Resp	4			
					Cardio	4			
					Gastro	4			
					Musc/skel	4			
					Hepatic	4			

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal		0.23		8–10% increase in relative kidney weight at 0.23 mg Hg/kg/day; increased severity of nephropathy in males at ≥0.923 mg Hg/kg/day; minimal nephropathy in females at 4 mg Hg/kg/day
					Endocr	4			
					Immuno	4			
					Neuro	4			
					Repro	4			
Mercuric chloride Dieter et al. 1992; NTP 1993									
44	Rat (Long-Evans) 8–12 F	40 days (G)	0, 9.4	BW, OW, OF	Bd wt	9.4			
					Endocr		9.4		28% increase in absolute thyroid weight, increased thyroid activity (increased uptake of radiolabeled iodine), decreased thyroid T3 synthesis
Mercuric chloride Goldman and Blackburn 1979									
45	Rat (Sprague-Dawley) 8–12 F	3 months (F)	0, 2.2	CS, BW, OF	Bd wt			2.2	37% decrease in final body weight
					Resp		2.2		Labored breathing
					Endocr		2.2		Impaired thyroid function (decreased uptake, release, and turnover of radiolabeled iodine)
					Neuro			2.2	Inactivity; abnormal gait; hindlimb spread
Mercuric chloride Goldman and Blackburn 1979									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
46	Rat (Sprague-Dawley) 20 F	60 days Premating (G)	0, 0.7, 1.5	CS, BW, BC, GN, OW, RX	Bd wt	1.5			
					Repro	0.7	1.5		15% decrease in implantation, increased dead/resorbed fetuses, 18% decrease in serum progesterone, 19% increase in pituitary LH
Mercuric chloride **Heath et al. 2009** [Vehicle was 0.15% nitric acid.]									
47	Rat (Sprague-Dawley) 10–11 M	60 days Premating (G)	0, 0.7, 1.5	CS, BW, BC, RX	Bd wt	0.7	1.5		>10% decrease in body weight
					Repro		0.7		30% decrease in testicular testosterone at 0.7 mg Hg/kg/day; 10% decrease in epididymis sperm counts; increased latency to impregnation and decreased fertility index at 1.5 mg Hg/kg/day
Mercuric chloride **Heath et al. 2012** [Vehicle was 0.15% nitric acid.]									
48	Rat (Wistar) 10 B	1 month (W)	0, 0.12	OF	Cardio		0.12		Altered left ventricular function; impaired baroreflex
Mercuric chloride **Jindal et al. 2011**									
49	Rat (Wistar) 5–10 M, 5–10 F	4 weeks (F)	M: 0, 5.8, 11.4, 20.9 F: 0, 6.1, 11.9, 23.6	BW, FI, WI, BC, HE, UR, OW, HP	Bd wt	5.8 M 11.9 F		11.4 M 23.6 F	>20% decrease in final body weight
					Hepatic	11.4 M 6.1 F	20.9 M 11.9 F		Male: Increased serum ALT and AST at 20.9 mg Hg/kg/day Female: Increased serum ALP at ≥11.9 mg Hg/kg/day; increased AST at 23.6 mg Hg/kg/day

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal		5.8 M 6.1 F		Nephrosis and proteinaceous casts, 13–16% increase in relative kidney weight; ketones in urine in males only
					Endocr	20.9 M 23.6 F			
Mercuric chloride Jonker et al. 1993									
50	Rat (Wistar) 5–10 M, 5–10 F	4 weeks (F)	M: 0, 0.61, 5.1 F: 0, 0.76, 5.5	BW, FI, WI, BC, UR, HE, OW, HP	Bd wt	5.1 M 5.5 F			
					Hemato	5.1 M 5.5 F			
					Renal	0.61 M	5.1 M 0.76 F		13–17% increase in relative kidney weight; ketones in urine and basophilic tubules in outer cortex in males only
					Endocr	5.1 M 5.5 F			
Mercuric chloride Jonker et al. 1993									
51	Rat (albino) 5–20 NS	21 days (NS)	0, 0.033	HE	Hemato		0.033		13% decrease in RBC count, 5% decrease in hemoglobin, 17% increase in WBC count; 41% increase in erythrocyte sedimentation rate
Mercuric chloride Mahour and Saxena 2009									
52	Rat (Wistar) 3–7 F	21 days GDs 0–20 (W)	0, 0.0002, 0.0004, 0.0085, 0.0301	BW, BC, OW, DX	Renal	0.0301			
					Develop	0.0301			
Mercuric chloride Oliveira et al. 2012									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
53	Rat (Wistar) 7–8 F	42 days GD 1–PND 21 (W)	0, 0.75, 3.8	DX	Develop[c]	3.8			
Mercuric chloride									
Oliveira et al. 2016 [Motor coordination was assessed in male offspring at PNDs 17–20.]									
54	Rat (Wistar) 8 F	38 days GDs 5–15 and PNDs 2–28 (GW)	0, 0.4, 0.8, 1.6	DX	Develop[c]	1.6			
Mercuric chloride									
Papp et al. 2005 [Neurophysiological recordings in male offspring at PND 84.]									
55	Rat (Wistar) 8 M	94 days GDs 5–15 and PNDs 2–28 (via dam) PNDs 29–84 (direct; 5 days/ week) (GW)	0, 0.4, 0.8, 1.6	DX	Develop[c]		0.4		Decreased peripheral sensory nerve conduction velocity at PND 84 at ≥0.4 mg Hg/kg/day; decreased spontaneous sensory cortex potentials at ≥0.8 mg Hg/kg/day
Mercuric chloride									
Papp et al. 2005									
56	Rat (Long-Evans) 16 F	6 months (W)	0, 0.33, 0.66, 1.3, 3.3	OF	Cardio	3.3			
Mercuric chloride									
Perry and Erlanger 1974									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
57	Rat (Wistar) 15 M	30 days (GW)	0, 0.7, 1.5	BC	Repro		0.7		Decreased serum testosterone and LH at ≥0.7 mg Hg/kg/day; decreased FSH and prolactin at 1.5 mg Hg/kg/day
Mercuric chloride Ramalingam et al. 2003									
58	Rat (Wistar) 5 F	7–8 weeks premating–PND 21 (W)	0, 0.6	CS, BW, FI, WI, RX, DX	Bd wt	0.6			
					Repro	0.6			
					Develop[c]		0.6		Increased susceptibility to seizure activity at PND 90
Mercuric chloride Szász et al. 2002									
59	Rat (Wistar) 10 M	21 weeks (F)	0, 0.06, 0.17, 0.51, 1.7	BW, BC, UR, OW, OF	Bd wt	1.7			
					Cardio	0.51	1.7		23% increase in relative heart weight; elevated plasma angiotensin-II
					Hepatic	0.51	1.7		16% decrease in plasma HDL
					Renal		0.06		11% increase in relative kidney weight at 0.06 mg Hg/kg/day; elevated urinary protein at 1.7 mg Hg/kg/day
Mercuric chloride Takahashi et al. 2000a									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
60	Rat (SHR Wistar) 18 M	12 weeks (F)	0, 0.07, 0.21, 0.72, 2.2	BW, BC, UR, OW, OF	Bd wt	2.2			
					Cardio		0.07		Transient 6–9% increase in systolic blood pressure at 5 weeks
					Hepatic		0.07		18% decrease in plasma HDL; 45% decrease in plasma triglycerides
					Renal	0.72	2.2		Elevated relative kidney weight; elevated urinary amino acids and ALP
Mercuric chloride **Takahashi et al. 2000b** [Spontaneously hypertensive rat strain]									
61	Rat (Wistar) 10 M	45 days (GW)	0, 0.277	NX	Neuro		0.277		Reduced motor activity, impaired motor coordination
Mercuric chloride **Teixeira et al. 2014**									
62	Rat (Wistar) 20 M	45 days (GW)	0, 0.277	BW, BI, NX	Bd wt	0.277			
					Neuro		0.277		Impaired motor coordination and balance; apoptosis and loss of neurons and astrocytes in motor cortex
Mercuric chloride **Teixeira et al. 2018**									
63	Rat (Wistar) 10 M	45 days (GW)	0, 0.277	BW, BI, NX	Bd wt	0.277			
					Neuro		0.277		Decreased motor activity; impaired learning and memory
Mercuric chloride **Teixeira et al. 2019**									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
64	Rat (Wistar) 5–6 M	4 weeks (W)	0, 0.005, 0.010, 0.021, 0.037, 0.244, 1.18, 2.07, 5.91	LE, BW, OW, OF	Death			5.91	100% mortality
					Bd wt	2.07		5.91	Weight loss
					Cardio	5.91			
					Renal	0.037	0.244		15% increase in relative kidney weight
Mercuric chloride Wildemann et al. 2015a									
65	Rat (Wistar) 5–6 M	4 weeks (W)	0, 0.038, 0.244	BW, OW, OF	Bd wt	0.244			
					Cardio	0.244			
Mercuric chloride Wildemann et al. 2015b									
66	Rat (Wistar) 5–6 M	4 weeks (W)	0, 0.264, 2.955	BC, BI, UR, OF	Cardio	2.955			
					Renal	2.955			
Mercuric chloride Wildemann et al. 2016									
67	Mouse (ICR) 16 M	4 or 6 weeks (GW)	0, 3.7	BC	Endocr		3.7		~70–95% decrease in plasma insulin; ~35% increase in blood glucose
Mercuric chloride Chen et al. 2012									
68	Mouse (B6C3F1) 10 M	7 weeks (W)	0, 0.4, 2, 11	BW, BC, BI, HE, OW, HP, IX	Bd wt	2	11		14% decrease in body weight
					Hemato		0.4		Nonmonotonic alterations in WBCs and lymphocytes (35% increase at 0.4 mg Hg/kg/day, 36% decrease at 11 mg Hg/kg/day)
					Hepatic	0.4	2		14% decrease in absolute liver weight; >50% increase in serum cholinesterase

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal	0.4	2		19% increase in absolute kidney weight at 2 mg Hg/kg/day; minimal renal nephropathy at 11 mg Hg/kg/day
					Endocr	11			
					Immuno	0.4	2		≥25% decrease in lymphoproliferation in response to T-cell mitogens at ≥2 mg Hg/kg/day; >60% decrease in antibody response to T-dependent antigen at 11 mg Hg/kg/day
					Neuro	11			
Mercuric chloride Dieter et al. 1983									
69	Mouse (ICR) 12–15 M	7 weeks PNDs 21–70 (GW)	0, 0.4	DX	Develop[c]		0.4		Hyperactivity, impaired motor coordination, and hearing impairment at PND 70
Mercuric chloride Huang et al. 2011									
70	Mouse (ICR) 12–15 F	10–17 weeks Premating through PND 21 (via dam) Select pups: PNDs 21–70 (direct) (GW)	0, 0.4	RX, DX	Repro		0.4		14% decrease in litter size
					Develop[c]		0.4 M		Effects at PND 70: 12–15% decrease in pup weight, increased motor activity and impaired hearing (both groups), impaired motor coordination (direct group only)
Mercuric chloride Huang et al. 2011									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
71	Mouse (SJL/N) 7 F	10 weeks (W)	0, 0.07, 0.14, 0.28, 0.56	HP, IX	Immuno	0.07	0.14		Positive ANoA; evidence of immune-complex disease
Mercuric chloride **Hultman and Enestrom 1992** [Autoimmune susceptible mice]									
72	Mouse (A.SW) 8 M, 8 F	10 weeks (W)	M: 0, 0.121, 0.241, 0.464, 0.942 F: 0, 0.049, 0.105, 0.199, 0.401	BW, BC, BI, IX	Immuno	0.121 M 0.105 F	0.241 M 0.199 F		Positive ANoA at ≥0.241 mg Hg/kg/day in males and ≥0.199 mg Hg/kg/day in females; positive for ANA, splenic vessel immune deposits, polyclonal B-cell activation, and elevated IgE at ≥0.401 mg Hg/kg/day
Mercuric chloride **Hultman and Nielsen 2001; Nielsen and Hultman 2002** [Autoimmune susceptible mice]									
73	Mouse (B10.S) 8 M, 8 F	10 weeks (W)	M: 0, 0.134, 0.232, 0.479, 0.962, 1.872 F: 0, 0.118, 0.218, 0.444, 0.954, 1.774	BW, BC, BI, IX	Immuno		0.118		Polyclonal B-cell activation at ≥0.118 mg Hg/kg/day; positive ANoA and ANA, splenic and renal immune deposits, and elevated IgE at ≥0.444 mg Hg/kg/day
Mercuric chloride **Hultman and Nielsen 2001; Nielsen and Hultman 2002** [Autoimmune susceptible mice]									
74	Mouse (C57BL/6) 25 M, 25 F	61–79 days (premating through lactation) (GW)	0, 0.18, 0.37, 0.74	CS, BW, FI, BC, HE, GN, OW, HP, RX	Bd wt	0.74			
					Hepatic	0.74			
					Renal	0.18 F	0.18 M 0.37 F		Increased relative kidney weight
					Endocr	0.74			
					Neuro	0.74			
					Repro			0.18	28% decrease in fertility index at 0.18 mg Hg/kg/day; 81% decrease in viability index at 0.74 mg Hg/kg/day
Mercuric chloride **Khan et al. 2004**									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
75	Mouse (Swiss albino) 10 M	16–17 weeks GD 0–PND 21 (via dam) PND 21 through PNDs 63–70 (direct) (W)	0, 3.3	WI, DX	Develop[c]		3.3		Increased anxiety and impaired memory and sociability at PNDs 63–70
Mercuric chloride Malqui et al. 2018									
76	Mouse (B6C3F1) 10 M, 10 F	6 months 5 days/week (GW)	0, 0.923, 1.8, 4, 7.4, 15	LE, BW, BC, GN, OW, HP	Bd wt	7.4 M 15 F	15 M		12% decrease in body weight
					Resp	15			
					Cardio	15			
					Gastro	15			
					Musc/skel	15			
					Hepatic	15			
					Renal	1.8 M 15 F	4 M		Cytoplasmic vacuolation of tubule epithelium, ≥19% increase in kidney weight
					Endocr	15			
					Immuno	15			
					Neuro	15			
					Repro	15			
Mercuric chloride NTP 1993									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
77	Mouse (BALB/c) 6–7 F	3 weeks GDs 0–21 (W)	0, 1.5	DX	Develop[e]		1.5		Alteration in immune endpoints in offspring at PND 70 (increased splenocyte proliferation and IFNγ and IL-4 production in mitogen assay)
Mercuric chloride **Pilones et al. 2009** [DBF1 offspring; progeny of DBA/1 males × BALB/c females]									
78	Mouse (Swiss albino) 20 F	4 weeks (GW)	0, 6	BW, BC	Bd wt	6			
					Endocr		6		28–41% decreased plasma T4
Mercuric sulfide **Sin and Teh 1992**									
79	Mouse (ICR) 5 M	4 weeks (GW)	0, 17, 170, 1,700	BW, FI, WI, BC, OW, HP	Bd wt	1,700			
					Hepatic	1,700			
					Immuno		17		Altered T-cell populations in spleen at ≥17 mg Hg/kg/day; hyperplasia and/or increased lymphoid density in spleen and thymus at 1,700 mg Hg/kg/day
Mercuric sulfide **Son et al. 2010**									
80	Mouse (A.SW) 3–5 F	5 weeks GD 8 to PND 21 (W)	0, 2.7	DX, IX	Immuno		2.7		Induction of serum IgG antibodies to brain antigens
					Develop[c,e]		2.7		Altered immune endpoints in offspring at PNDs 21 and 70 (induction of serum IgG antibodies to brain antigens; IgG deposits in brain, brain inflammation); hyperactivity in female offspring
Mercuric chloride **Zhang et al. 2011** [Autoimmune susceptible mouse strain]									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
81	Mouse (A/WySnJ) 3–5 F	5 weeks GD 8 to PND 21 (W)	0, 2.7	DX, IX	Immuno	2.7			
					Develop[c,e]	2.7			
Mercuric chloride **Zhang et al. 2011** [Offspring immune and behavioral endpoints were evaluated at PNDs 21 and 70.]									
82	Mouse (SJL/J) 7 F	5 weeks GD 8 to PND 21 (W)	0, 2.7	DX, IX	Immuno		2.7		Elevated serum IgG
					Develop[c,e]		2.7		Altered immune endpoints in offspring at PNDs 21 and 70 (elevated serum IgG, IgG deposits in brain, brain inflammation); decreased sociability
Mercuric chloride **Zhang et al. 2013** [Offspring were SFvF1; autoimmune susceptible SJL/J females × wild-type FVB males.]									
83	Mouse (FVB) 6–7 F	5 weeks GD 8 to PND 21 (W)	0, 2.7	DX, IX	Immuno		2.7		Induction of serum IgG antibodies to brain antigens
					Develop[c,e]		2.7		Altered immune endpoints in offspring at PNDs 21 and 70 (elevated serum IgG, induction of serum IgG antibodies to brain antigens, IgG deposits in brain); decreased social interaction
Mercuric chloride **Zhang et al. 2013** [Offspring were FvSF1; autoimmune susceptible SJL/J males × wild-type FVB females.]									
84	Guinea pig (Hartley) 8–12 F	21 days (G)	0, 86	NX	Neuro		86		Abnormal vestibular ocular reflex
Mercuric sulfide **Chuu et al. 2001b** [Vehicle was saline.]									

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
CHRONIC EXPOSURE									
85	Rat (Fischer-344) 60 M, 60 F	2 years 5 days/week (GW)	0, 1.8, 4	LE, BW, BC, UR, GN, OW, HP	Death			1.8 M	Decreased survival (21%) compared to control (52%)
					Bd wt	1.8 F	1.8 M 4 F	4 M	16% decrease in body weight at 1.8 mg Hg/kg/day in males; 22 and 16% decrease in body weight at 4 mg Hg/kg/day in males and females, respectively
					Resp	1.8	4		Nasal mucosa inflammatory lesions
					Cardio	4 F	1.8 M		Heart mineralization (secondary to marked renal impairment)
					Gastro	1.8 F	1.8 M 4 F		Epithelial hyperplasia in males and females at ≥1.8 and 4 mg Hg/kg/day respectively; forestomach acanthosis in both sexes at 4 Hg mg/kg/day
					Musc/skel	4 F	1.8 M		Fibrous osteodystrophy (secondary to marked renal impairment)
					Hepatic	4			
					Renal	4 F		1.8 M	Marked thickening of glomerular and tubular basement membranes; degeneration and atrophy of tubule epithelium
					Endocr	4 F	1.8 M		Parathyroid hyperplasia (secondary to marked renal impairment)
					Immuno	4			
					Neuro	4			
					Repro	4			

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Cancer			4 M	CEL: Forestomach squamous cell papillomas and thyroid follicular cell carcinomas in males; no exposure-related neoplastic lesions in females
Mercuric chloride Dieter et al. 1992; NTP 1993									
86	Rat (Long-Evans) 16 F	1 year (W)	0, 0.33, 0.66, 1.3, 3.3	CS, BW, OF	Bd wt	1.3	3.3		13% decrease in final body weight
					Cardio	0.33	0.66		Increased systolic blood pressure
Mercuric chloride Perry and Erlanger 1974									
87	Mouse (B6C3F1) 60 M, 60 F	2 years 5 days/week (GW)	0, 4, 7.4	LE, BW, BC, UR, GN, OW, HP	Bd wt	7.4			
					Resp	4 M	7.4 M 4 F		Increased metaplasia in the olfactory epithelium in females at ≥4 mg Hg/kg/day and males at 7.4 mg Hg/kg/day; increased inflammatory lesions in both sexes at 7.4 mg Hg/kg/day
					Cardio	7.4			
					Gastro	7.4			
					Musc/skel	7.4			
					Hepatic	7.4			
					Renal		4		Increased incidence (females only) and/or severity of renal nephropathy; ≥20% increase in kidney weight
					Endocr	7.4			
					Immuno	7.4			
					Neuro	7.4			

Table 2-3. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Repro	7.4			
Mercuric chloride NTP 1993									

[a]The number corresponds to entries in Figure 2-7; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-7. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive a provisional acute-duration oral minimal risk level (MRL). Using BMD modeling, BMD_{1SD} and $BMDL_{1SD}$ values of 0.64 and 0.29 mg Hg/kg/day, respectively, were calculated for elevated relative kidney weight in male rats. The $BMDL_{1SD}$ was adjusted for continuous exposure (5 days/7 days) to a $BMDL_{ADJ}$ of 0.21 mg Hg/kg/day and divided by an uncertainty factor of 100 (10 for animal to human, and 10 for human variability), resulting in a provisional MRL of 0.002 mg Hg/kg/day.
[c]The neurodevelopmental effects are discussed in Section 2.16 (Neurological).
[d]Used to derive a provisional intermediate-duration oral MRL. The LOAEL of 0.015 mg Hg/kg/day was divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for animal to human, and 10 for human variability), resulting in a provisional MRL of 0.00001 mg Hg/kg/day ($1x10^{-5}$ mg Hg/kg/day; 0.01 µg Hg/kg/day).
[e]Immunodevelopmental effects are discussed with adult immune system effects in Section 2.15 (Immunological).

Principal studies for the MRLs

ADJ = adjusted; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANA = antinuclear antibodies; ANoA = antinucleolar antibodies; AST = aspartate aminotransferase; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; BMD = benchmark dose; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 SD change from the control); Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; DX = developmental toxicity; Endocr = endocrine; (F) = feed (dietary); F = female(s); FI = food intake; FSH = follicle stimulating hormone; (G) = gavage; (GO) = gavage in oil; (GW) = gavage in water; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HDL = high-density lipoprotein; HE = hematology; Hemato = hematological; HP = histopathology; IFNγ = interferon gamma; IgE = immunoglobulin E; IgG = immunoglobulin G; IL-4 = interleukin 4; Immuno = immunological; IX = immune function; LD_{50} = lethal dose, 50% kill; LDH = lactate dehydrogenase; LE = lethality; LH = luteinizing hormone; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; PND = postnatal day; RBC = red blood cell; Repro = reproductive; Resp = respiratory; RX = reproductive function; SD = standard deviation; T3 = triiodothyronine; T4 = thyroxine; UR = urinalysis; (W) = drinking water; WBC = white blood cell; WI = water intake

Figure 2-7. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral
Acute (≤14 days)

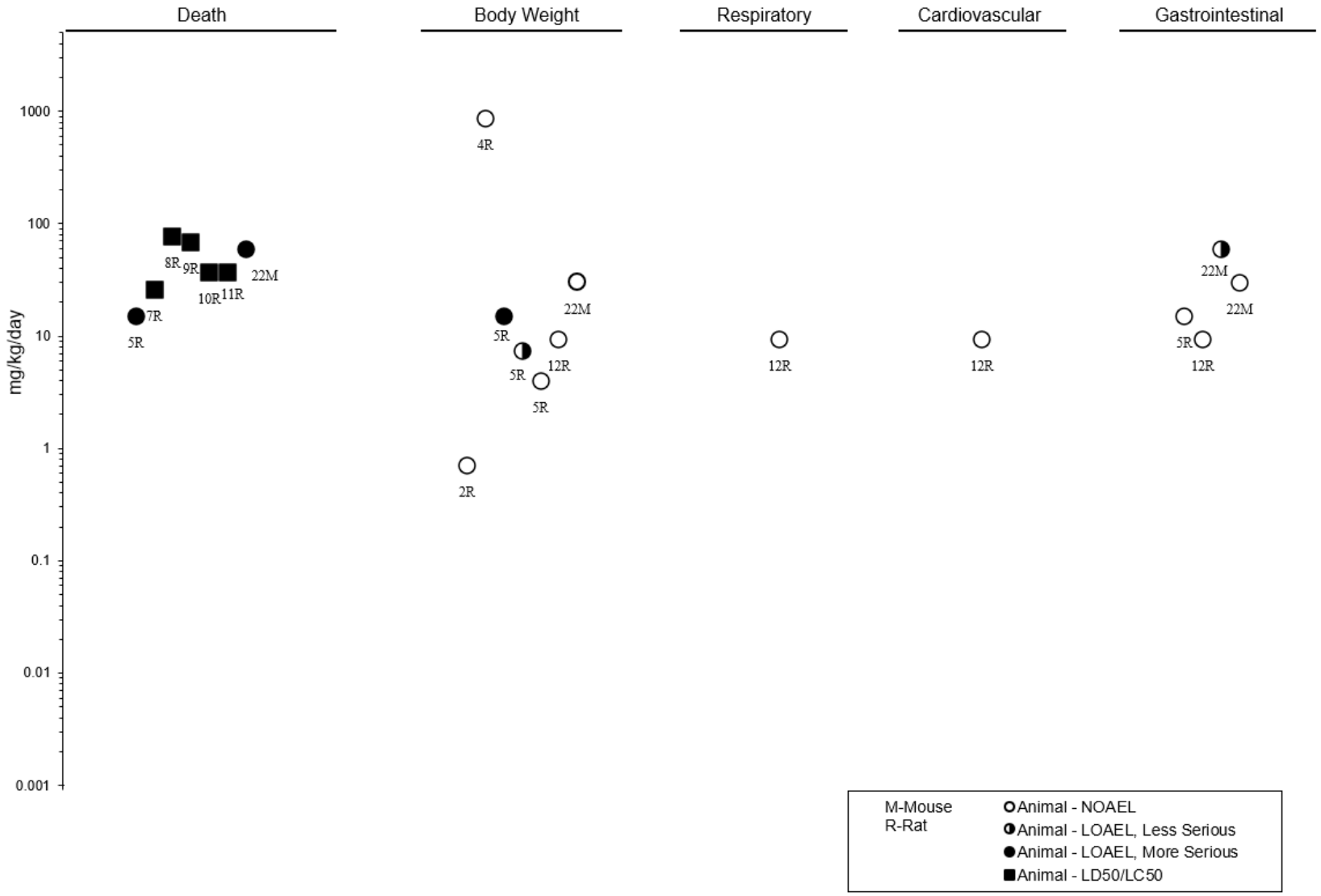


Figure 2-7. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral
Acute (≤14 days)

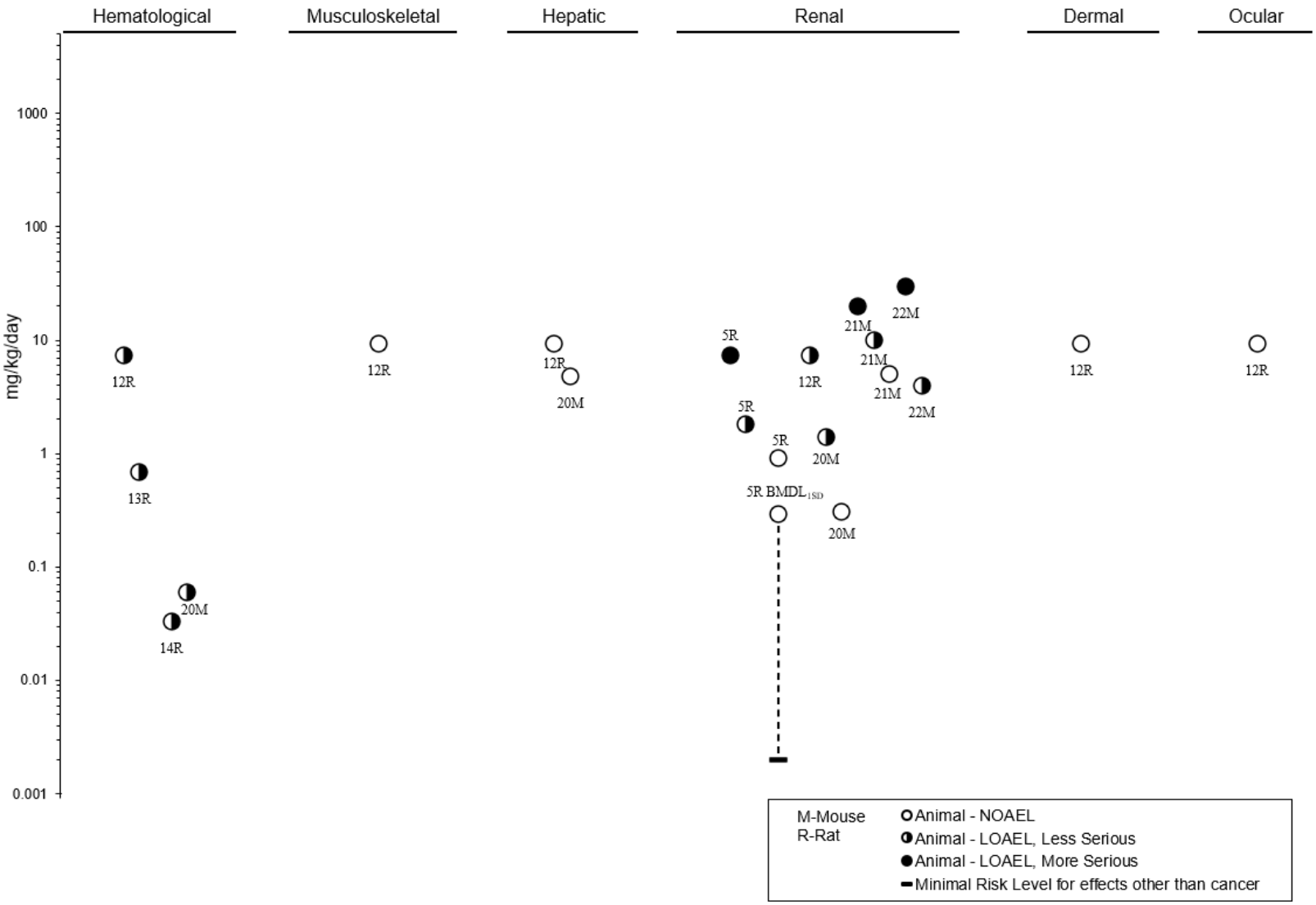


Figure 2-7. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral
Acute (≤14 days)

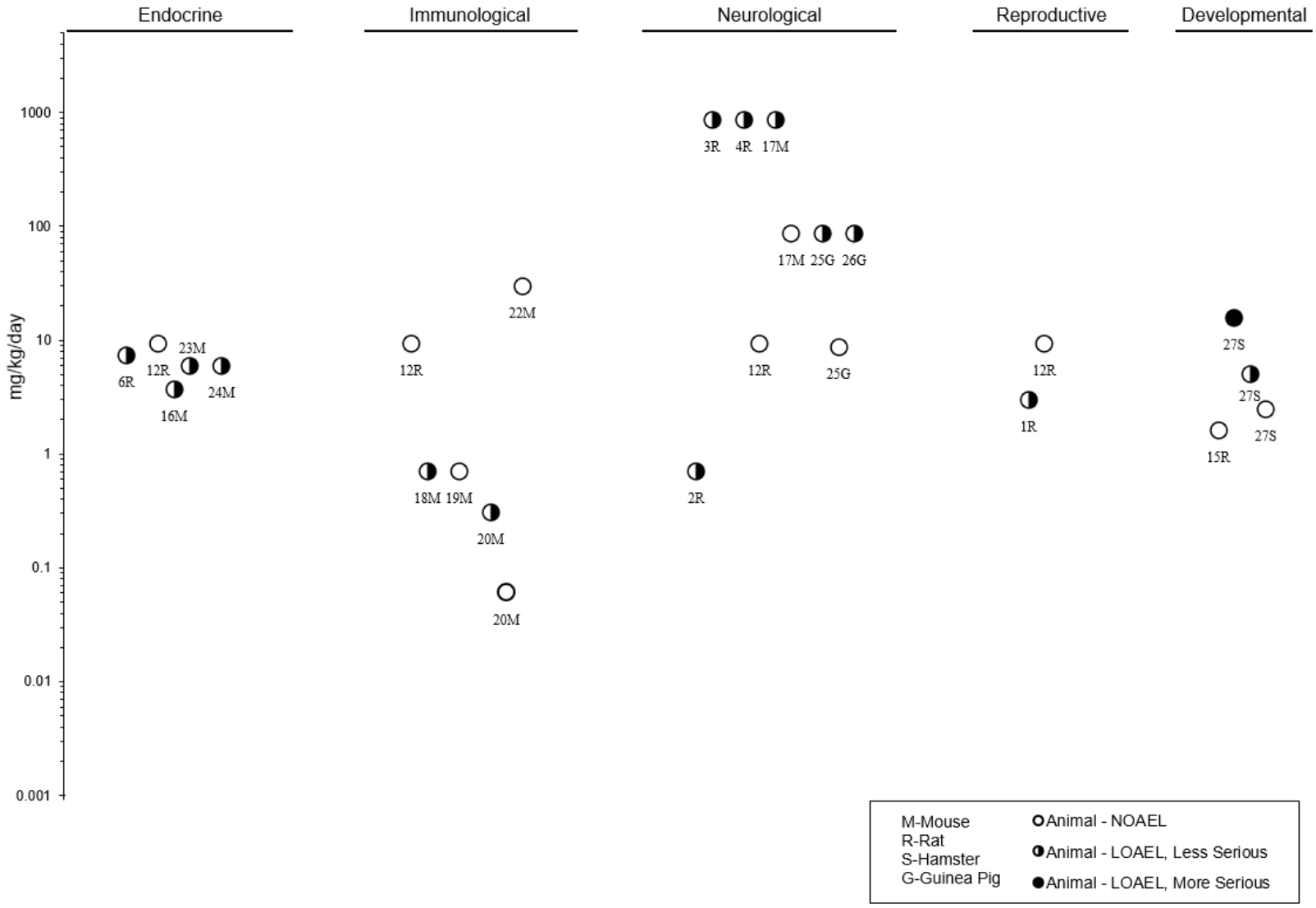


Figure 2-7. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral
Intermediate (15–364 days)

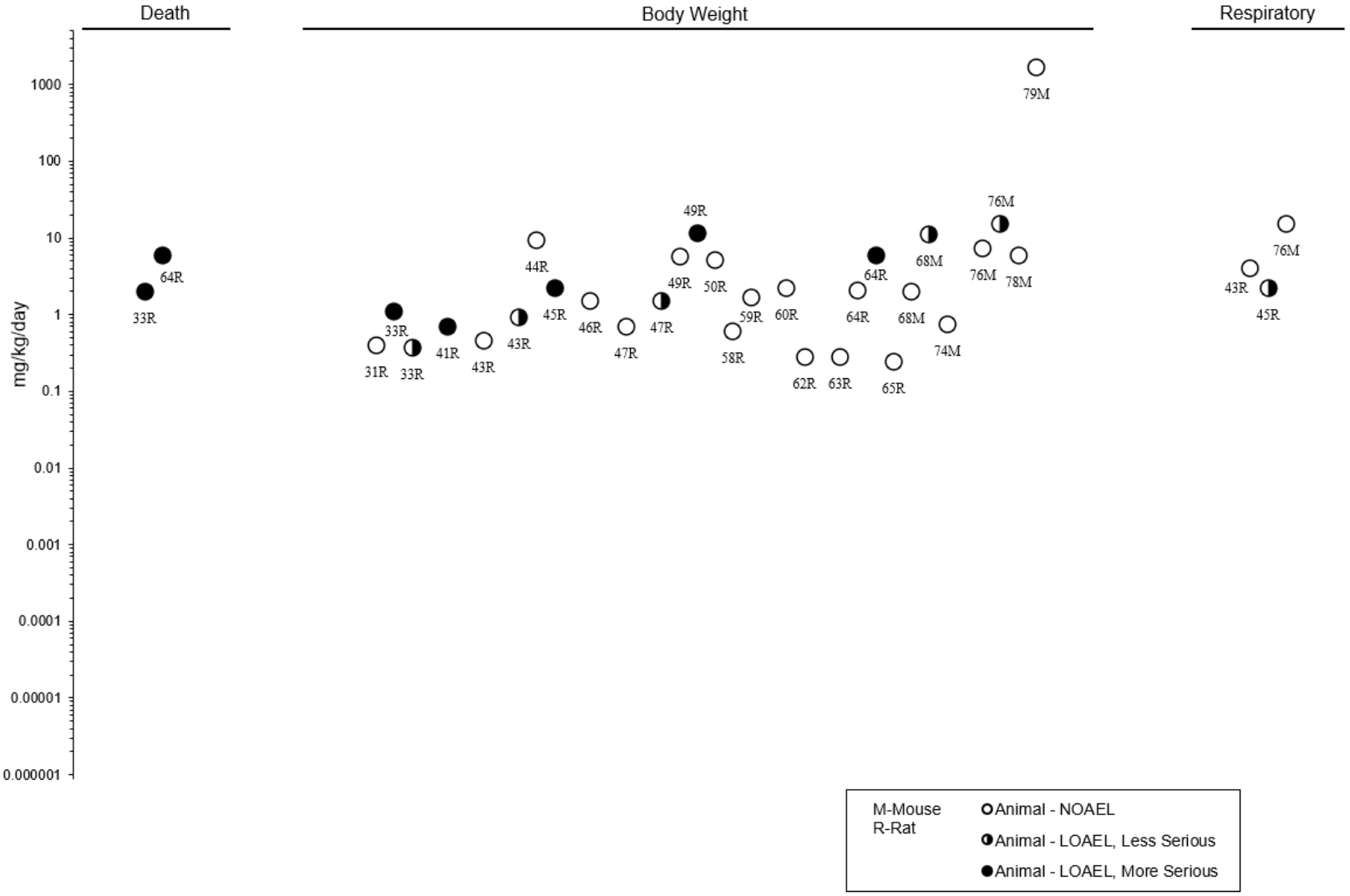


Figure 2-7. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral
Intermediate (15–364 days)

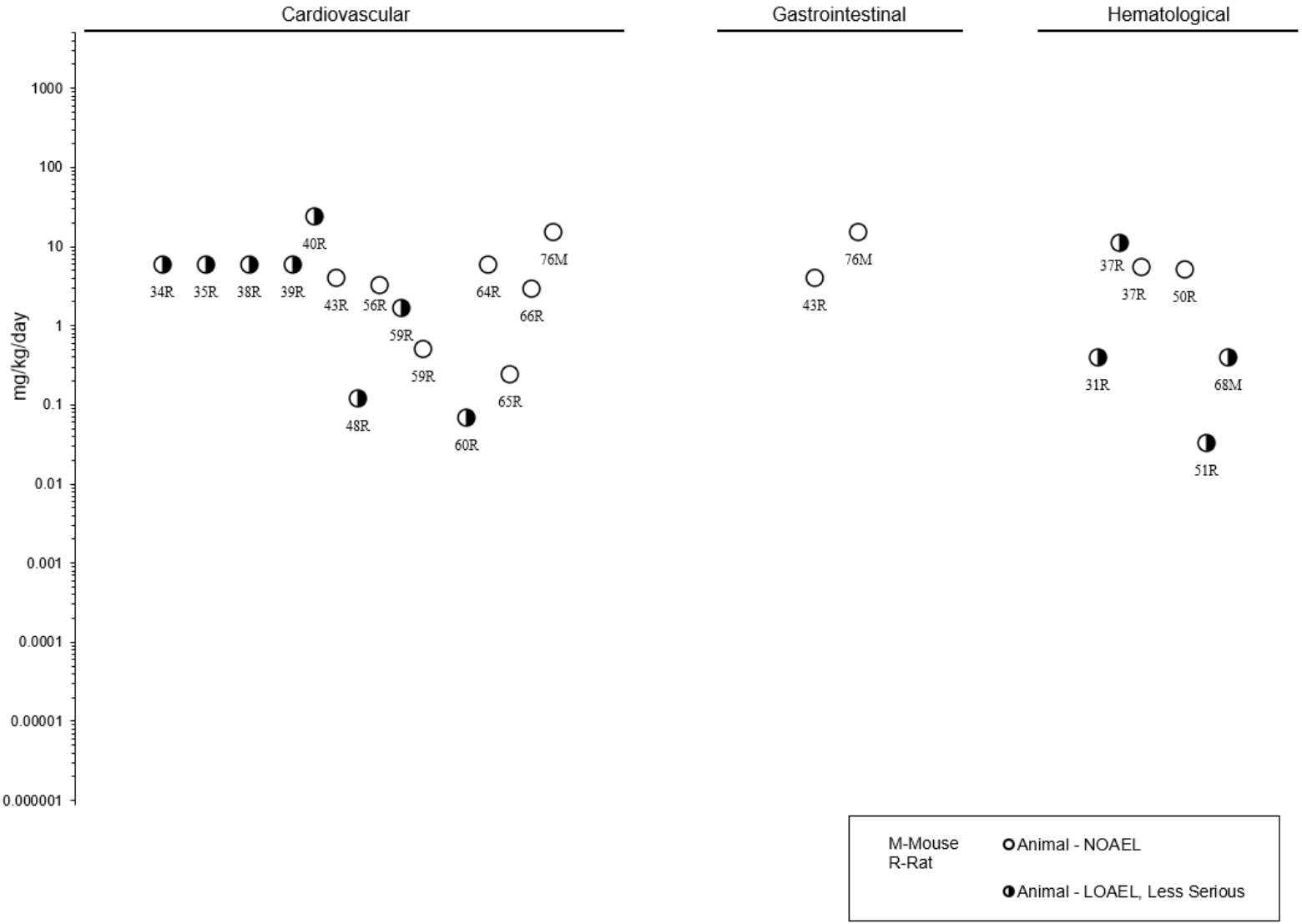


Figure 2-7. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral
Intermediate (15–364 days)

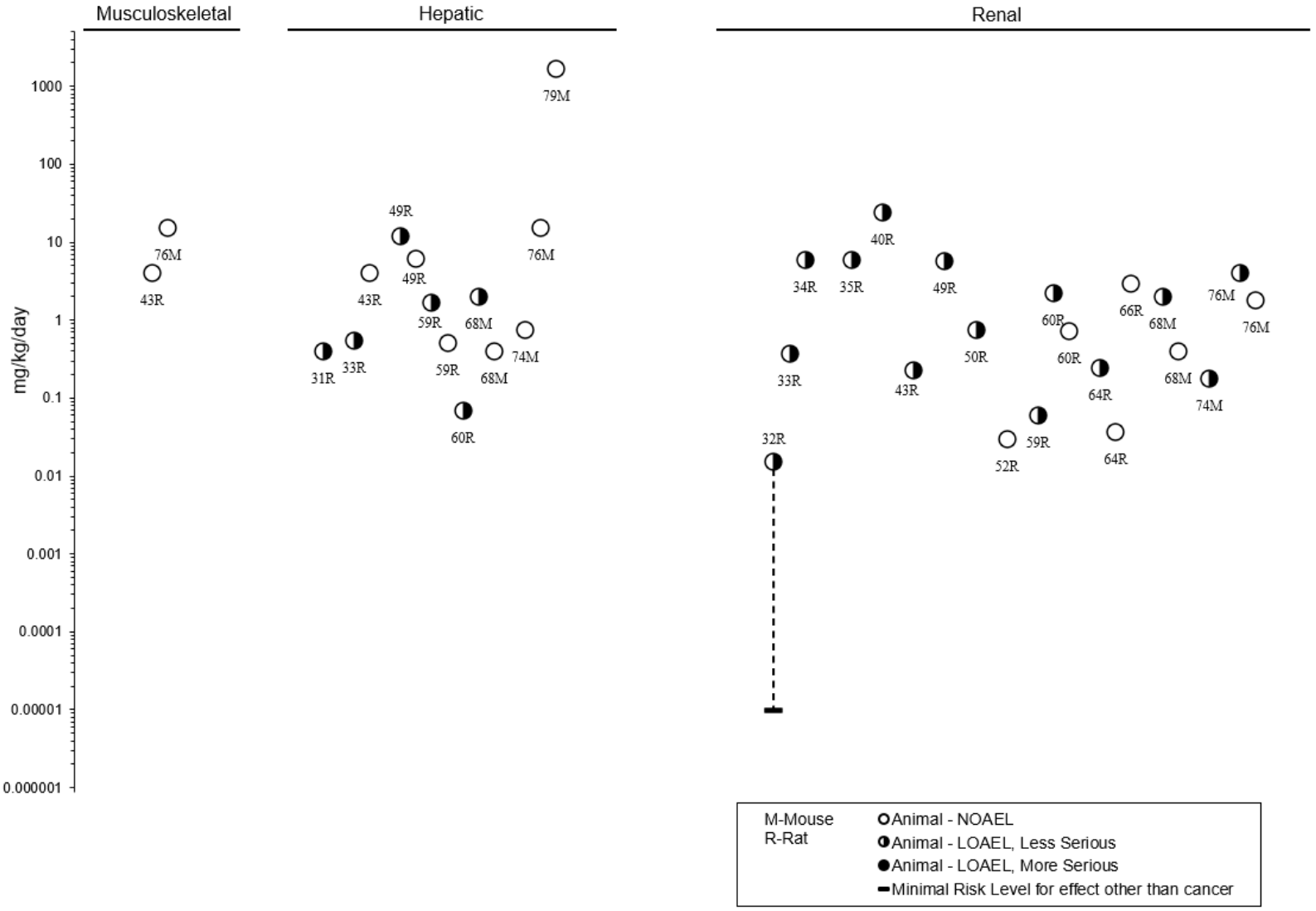


Figure 2-7. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral
Intermediate (15–364 days)

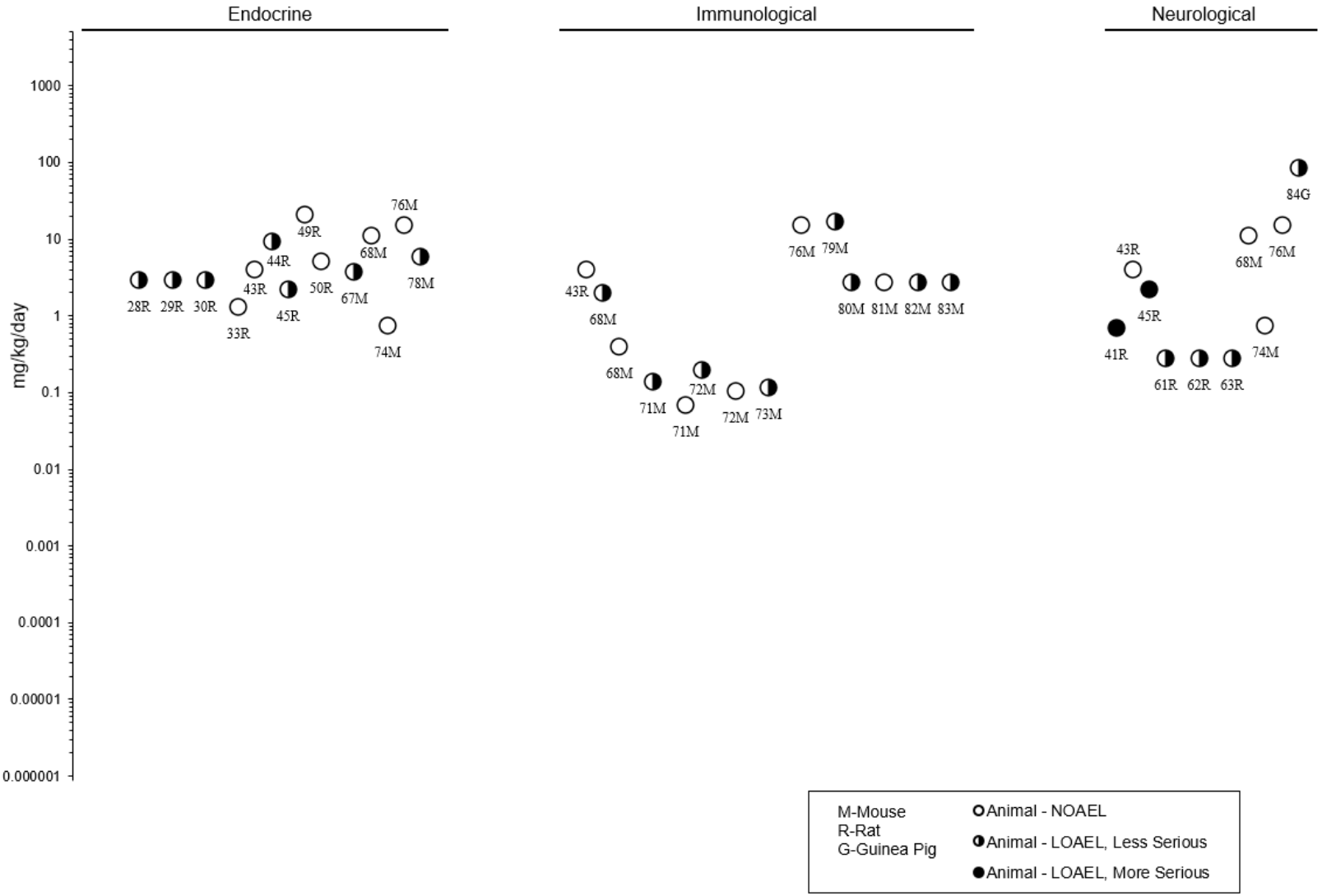


Figure 2-7. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral
Intermediate (15–364 days)

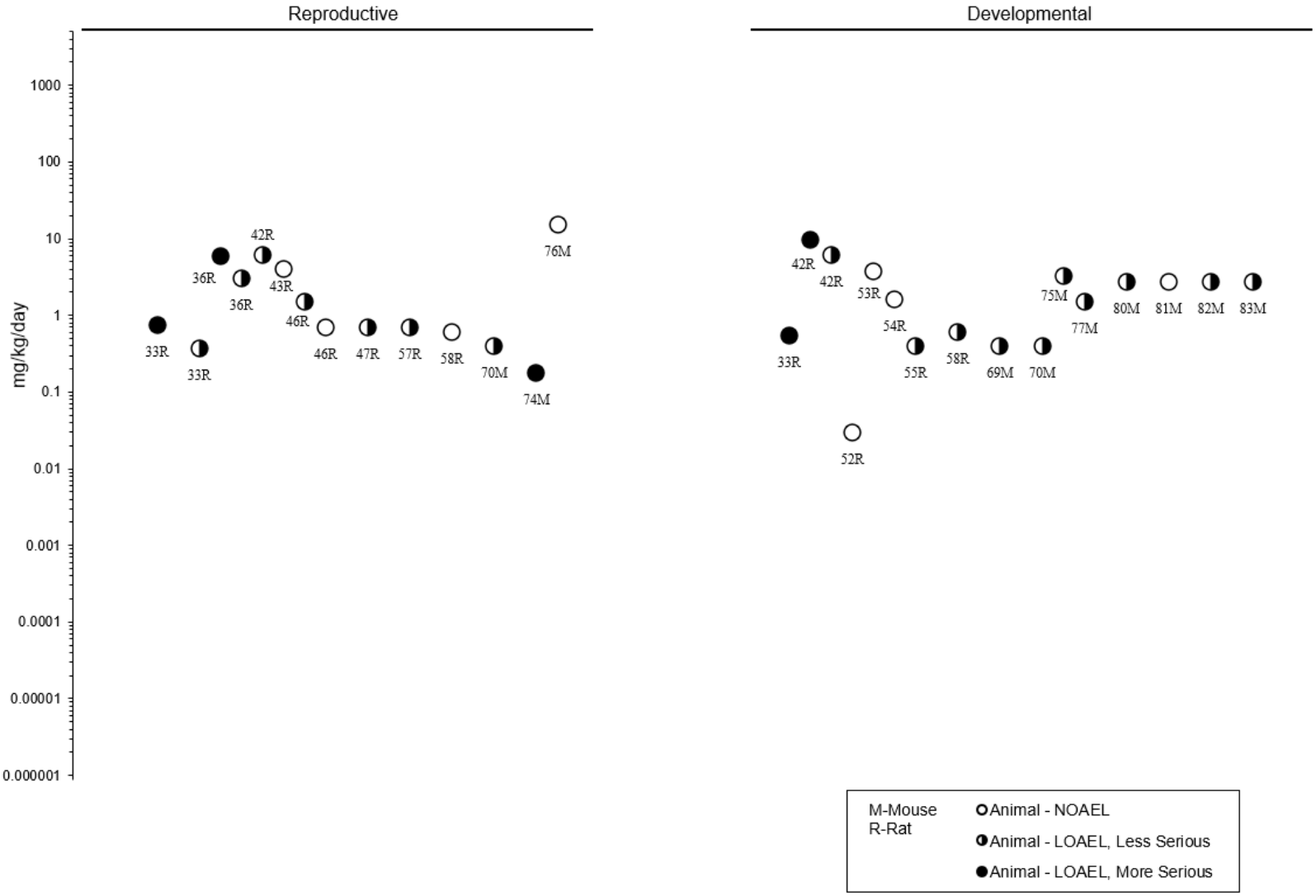


Figure 2-7. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral
Chronic (≥365 days)

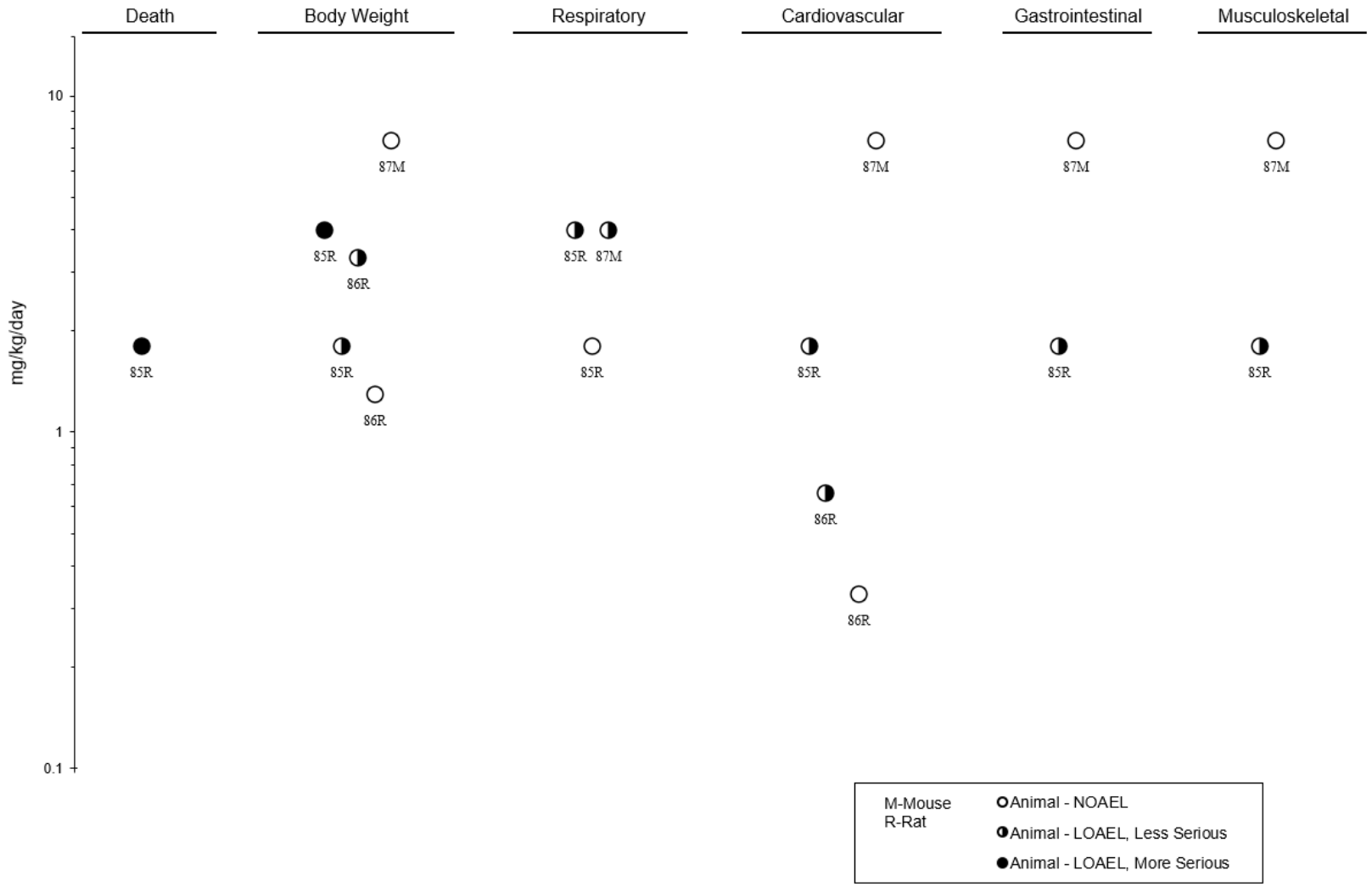


Figure 2-7. Levels of Significant Exposure to Inorganic Mercuric Salts – Oral
Chronic (≥365 days)

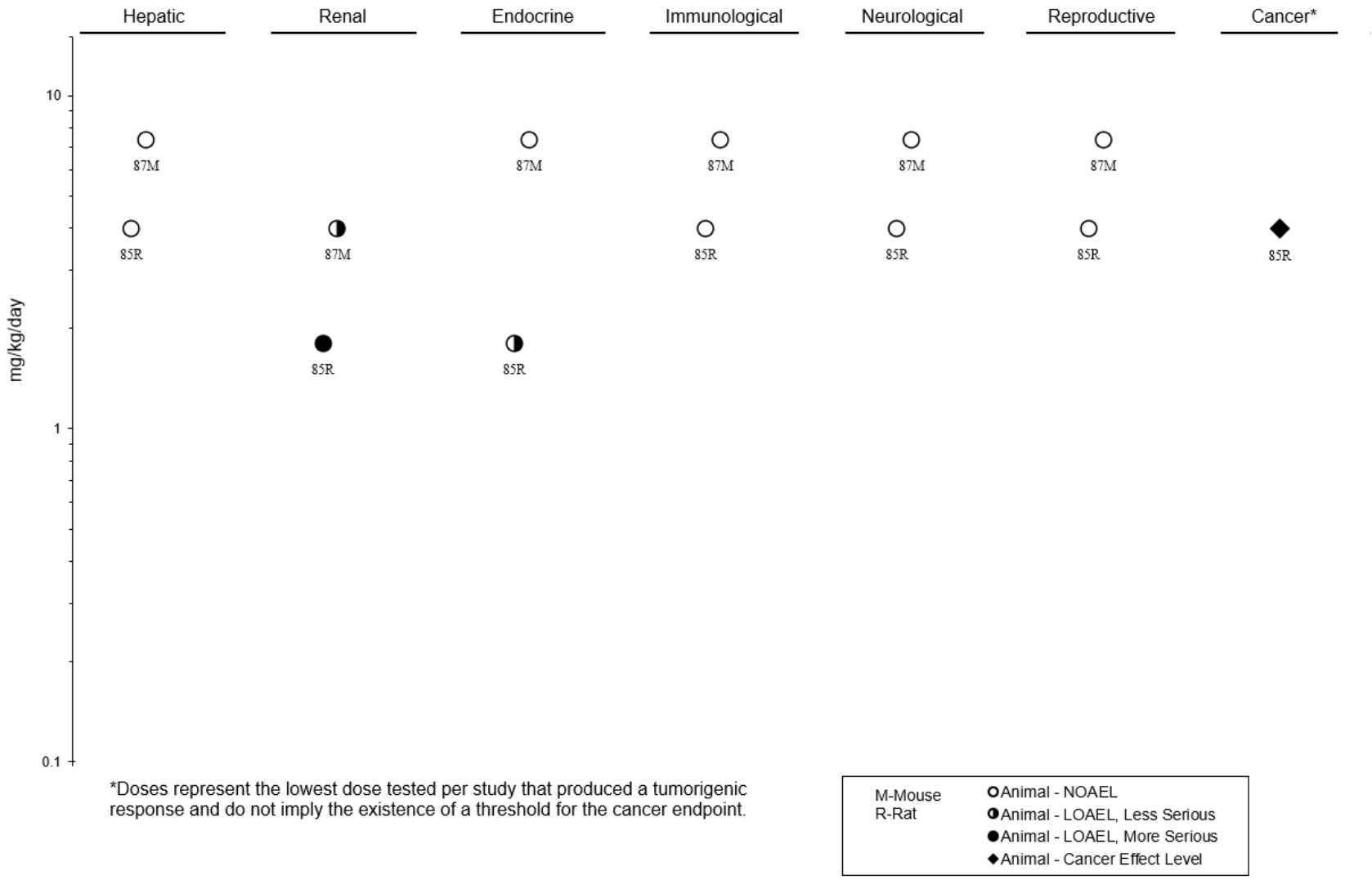


Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 4–16 M	2 days (GW)	0, 1.32, 4, 12	BI, NX	Neuro	1.32	4		Decreased paradoxical sleep and increased slow-wave sleep
Methylmercuric chloride Arito and Takahashi 1991									
2	Rat (Sprague-Dawley) 6 M	2 days (GW)	12	CS	Cardio		12		10–18% decrease in heart rate for up to 16 days post-exposure (compared to pre-exposure values)
					Other non-cancer		12		Hypothermia for >1 month post-exposure
Methylmercuric chloride Arito and Takahashi 1991									
3	Rat (Wistar) 10 M, 10 F	4 days GDs 6–9 (GW)	0, 0.004, 0.008, 0.035	DX	Develop[b]	0.004	0.008		Impaired operant conditioning at 4 months
Methylmercuric chloride Bornhausen et al. 1980									
4	Rat (Sprague-Dawley) NS F	Once GD 15 (G)	0, 6.4	DX	Develop[b]		6.4		Decreased avoidance latency in offspring on PND 60
Methylmercuric chloride Cagiano et al. 1990									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
5	Rat (Sprague-Dawley) 9–10 F	Once GD 8 or 15 (G)	0, 7	BW, DX	Bd wt	7			
					Develop[b]			7	Effects in male offspring: Decreased postnatal survival; 18% decrease in pup weight at PND 21 (GD 8 exposure only); decreased exploratory behavior and impaired habituation at PND 40
Methylmercury Carratu et al. 2006									
6	Rat (Sprague-Dawley) 10 F	Once GD 15 (G)	0, 7	DX	Develop[b]		7		Impaired associative learning and elevated corticosterone levels in male offspring at PND 90
Methylmercury Carratu et al. 2008									
7	Rat (Holtzman) 4 M	1–2 weeks (G)	0, 0.8	CS, BW, HP	Bd wt	0.8			
					Neuro		0.8		Ultrastructural changes in dorsal root ganglia and cerebellum
Methylmercuric chloride Chang and Hartmann 1972a									
8	Rat (Sprague-Dawley) 6 M	5 days (G)	0, 9	BI, HP, RX	Repro		9		Decreased sperm count and motility; disruption of germinal epithelium in seminiferous tubules with reduced spermatozoa; increased germ cell apoptosis
Methylmercuric chloride Chen et al. 2019 [Vehicle was sodium carbonate.]									
9	Rat (Sprague-Dawley) 6 M	5 days (GW)	0, 1.9	NX	Neuro		1.9		Impaired balance, suppression of compound muscle action potentials followed by incomplete recovery after tetany
Methylmercury Chuu et al. 2007									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
10	Rat (Sprague-Dawley) 6 M	14 days (GW)	0, 1.9	BW, NX	Bd wt		1.9		~10% decrease in body weight
					Neuro		1.9		Impaired balance, suppression of compound muscle action potentials followed by incomplete recovery after tetany; transient decrease in motor nerve conduction velocity and nociception
Methylmercury Chuu et al. 2007									
11	Rat (Sprague-Dawley) 8 M	10 days PNDs 14–23 (IN)	0, 0.6	DX	Develop[b]		0.6 M		Impaired associative learning (PND 90) and decreased rearing in open field (PNDs 31–45)
Methylmercuric chloride Coluccia et al. 2007 [Administered via micropipette as 1:1 ratio of methylmercury:L-cysteine in 10% condensed milk.]									
12	Rat (Wistar) 10 M	2 days (G)	0, 10, 20	HP, NX	Neuro		10	20	Impaired balance and coordination at ≥10 mg Hg/kg/day; decreased nerve conduction velocity and degeneration of peripheral nerves and dorsal nerve roots and ganglia at 20 mg Hg/kg/day
Methylmercuric chloride Fehling et al. 1975									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
13	Rat (Wistar) 15 M	14 days (GW)	0, 0.5, 0.93, 2.8	BW, BC, OW, HP	Bd wt	2.8			
					Renal	0.93	2.8		18% increase in relative kidney weight
					Repro		0.5		Nonmonotonic sperm effects (decreased count and motility, increased abnormal) at ≥0.5 mg Hg/kg/day; 65% decrease in serum testosterone and 28% decrease in relative seminal vesicle weight at 2.8 mg Hg/kg/day
Methylmercury **Fossato da Silva et al. 2011**									
14	Rat (Wistar) 10 M	14 days (GW)	0, 0.5, 0.93, 2.8	BW, OW, HP	Bd wt	2.8			
					Repro		0.5		Inflammatory foci and thickening of epithelium in prostate at ≥0.5 mg Hg/kg/day; progressing to epithelial atrophy and dilation of glandular acini at 2.8 mg Hg/kg/day
Methylmercury **Fossato da Silva et al. 2012**									
15	Rat (Sprague-Dawley) 12 F	4 days GDs 6–9 (G)	0, 1.86	CS, BW, DX	Bd wt	1.9			
					Develop[b]	1.9			
Methylmercury **Fredriksson et al. 1996** [Behavior was assessed in adult male offspring at 4–5 months of age.]									
16	Rat (Wistar) 20 F	8 days GDs 7–14 (GW)	0, 2, 4, 6	CS, BW, FI, WI, DX	Neuro	4		6	Spasms, gait disturbance, and hindlimb crossing in dams
					Develop	2		4	Decreased fetal weight; increased incidence of fetal malformations
Methylmercuric chloride **Fuyuta et al. 1978**									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
17	Rat (Wistar) 15–20 M	7 days (G)	0, 1, 2.5, 5	CS, BW, RX	Bd wt	5			
					Repro	2.5		5	Decreased fertility and decreased viable fetuses
Methylmercuric chloride **Khera 1973** [Males were mated to untreated females after exposure.]									
18	Rat (Fischer-344) 30 F	Once GD 7 (G)	0, 8, 16, 24	LE, BW, DX	Death			16	17% maternal death
					Bd wt		8	16	14% decrease in maternal body weight at 8 mg Hg/kg/day; >20% decrease in maternal body weight at >16 mg Hg/kg/day
					Develop			8	Decreased fetal survival; decrease in fetal weight and length, delayed ossification, spinal curvature
Methylmercuric chloride **Lee and Han 1995**									
19	Rat (Wistar) 5 M	10 days (IN)	0, 7.24	CS, BW, HP	Bd wt	7			
					Neuro			7	Ataxia and instability post-exposure; peripheral nerve degeneration
Methylmercuric sulfide **Miyakawa et al. 1974** [Rats were sacrificed 600 days post-exposure.]									
20	Rat (NS) 20 F	9 days GDs 6–14 (W)	0, 0.024, 0.23, 4.6	BW	Bd wt	0.23		4.6	55% depressed maternal weight gain
					Develop		0.024		Increased incidence of fetal urinary bladder defects and missing 5th sternebra
Methylmercuric chloride **Nolen et al. 1972**									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
21	Rat (Sprague-Dawley) 15 M	Once PND 15 or 21 (G)	0, 16	DX	Develop[b]		16		Transient lethargy and ataxia
Methylmercuric chloride **Post et al. 1973** [Behavioral tests were administered over a 60-day period post-weaning.]									
22	Rat (Sprague-Dawley) 15 M	Once (G)	0, 20	CS, HP, NX	Neuro		20		Transient lethargy and ataxia; impaired spatial learning; decreased motor activity
Methylmercuric chloride **Post et al. 1973** [Behavioral tests were administered over a 60-day period post-exposure.]									
23	Rat (Wistar) NS F	4 days GDs 6–9 (G)	0, 0.02, 0.04, 0.4, 4	CS, HP	Develop[b]	0.04	0.4	4	Increased startle response in adult offspring at ≥0.4 mg Hg/kg/day; altered behavior and dendritic spine abnormalities at 4 mg Hg/kg/day
Methylmercuric chloride **Stoltenburg-Didinger and Markwort 1990**									
24	Rat (Wistar) 4 NS	10 days (G)	0, 8	LE, CS, BW, HP	Death			8	14/34 rats died prior to scheduled sacrifice
					Bd wt			8	Body weight loss
					Musc/skel			8	Neurogenic atrophy of gluteal muscle
					Neuro			8	Ataxia, hindlimb crossing, weakness, degeneration of cortical and cerebellar neurons, large motor neurons in spinal cord, and myelinated fibers of spinal anterior roots
Methylmercuric chloride **Su et al. 1998** [Vehicle was L-cysteine; rats were sacrificed at intervals 1–8 days post-exposure.]									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
25	Rat (Wistar) NS M	12 days (GW)	0, 4	CS, BW, HP	Death			4	50% death by 3 weeks post-exposure
					Bd wt			4	37% decrease in body weight
					Musc/skel			4	Muscle weakness and wasting
					Neuro		4		Weakness, hindlimb crossing
Methylmercuric chloride Usuki et al. 1998									
26	Rat (Sprague-Dawley) NS F	Once GD 15 (G)	0, 6.4	DX	Develop[b]		6.4		Decreased passive avoidance latency in PND 42 offspring
Methylmercuric chloride Zanoli et al. 1994									
27	Mouse (CD-1) 10–12 F	Once GD 10 (GW)	0, 9.99	BW, OW, DX	Bd wt	9.99			
					Develop		9.99		17% decrease in fetal weight; increased incidence of cleft palate; delayed ossification
Methylmercuric chloride Belles et al. 2002									
28	Mouse (C57BL/6J) 22–29 B	5 days PNDs 29–33 (F)	0, 0.2, 0.8	DX	Develop[b]		0.2		Impaired balance and motor coordination on PND 38
Methylmercuric chloride Bellum et al. 2007									
29	Mouse (C57BL/6) 20–25 B	5 days (F)	0, 0.9	BI, NX	Neuro		0.9		Hypoactivity, motor incoordination
Methylmercuric chloride Bellum et al. 2013 [aged mice]									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
30	Mouse (ICR) 16 M	2 weeks (GW)	0, 1.6	BC, BI, HP	Endocr		1.6		~60–70% decrease in baseline and fasting plasma insulin; impaired glucose tolerance; apoptosis in pancreatic islet cells
Methylmercuric chloride Chen et al. 2012									
31	Mouse (NS) 8–10 M	7 days (G)	0, 0.2, 1.9, 9.3	LE, NX	Death			9.3	100% mortality
					Neuro		0.2	1.9	Reversible hearing loss at 0.2 mg Hg/kg/day; persistent hearing loss at 1.9 mg Hg/kg/day
Methylmercury Chuu et al. 2001a									
32	Mouse (Swiss-Webster) NS M	4 days (G)	0, 12	BW, BI, OW, HP	Bd wt			12	10% body weight loss
					Resp	12			22–23% increase in absolute and relative lung weight; reduced alveolar diameter and increased alveolar wall thickness; increased minimal surface tension
Methylmercuric chloride Das et al. 1997									
33	Mouse (Swiss) 13–14 M	7–14 days (W)	0, 4.7, 8.7	CS, WI, NX	Neuro		4.7		Impaired motor coordination, hypoactivity
Methylmercuric chloride Dietrich et al. 2005									
34	Mouse (C57BL/6) 10–21 F	3 days GDs 7–9 (G)	0, 3, 5	DX	Develop[b]		3	5	Impaired spatial memory at PND 49 at ≥3 mg Hg/kg/day; 28% decrease in postnatal survival at 5 mg Hg/kg/day
Methylmercuric chloride Dore et al. 2001 [Vehicle was phosphate-buffered saline.]									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
35	Mouse (C57BL/6) 10–21 F	3 days GDs 12–14 (G)	0, 3, 5	DX	Develop[b]		3	5	Hypoactivity at PND 42 at ≥3 mg Hg/kg/day; 26% decrease in postnatal survival and impaired spatial learning at PNDs 49–98 at 5 mg Hg/kg/day
Methylmercuric chloride **Dore et al. 2001** [Vehicle was phosphate-buffered saline/]									
36	Mouse (NMRI) NS M	Once PND 10 (GW)	0, 0.37, 3.7	DX	Develop[b]		0.37		Decreased motor activity and impaired learning and memory at 2–6 months of age at ≥0.37 mg Hg/kg/day; impaired exploratory habituation at 3.7 mg Hg/kg/day
Methylmercuric chloride **Fischer et al. 2008**									
37	Mouse (C57BL/6N) 9–10 F	8 days GDs 6–13 (GW)	0, 2, 4, 4.8, 6	CS, BW, FI, WI, DX	Develop			2	Increased incidence of fetal malformations
Methylmercuric chloride **Fuyuta et al. 1978**									
38	Mouse (ICR) 20 F	Once GD 10 (GW)	0, 8, 12, 16, 20	DX	Develop		8	12	Incomplete fusion of sternebrae at ≥8 mg Hg/kg/day; cleft palate and decreased fetal weight at ≥12 mg Hg/kg/day
Methylmercuric chloride **Fuyuta et al. 1979**									
39	Mouse (CFW) NS F	Once GD 8 (G)	0, 1, 2, 3, 5, 10	DX	Develop[b]	2	3	10	LOAEL: 35% decrease in litter size, 13% decrease in pup weight on PND 21, decreased conditioned avoidance Serious LOAEL: 73% decrease in litter size
Methylmercury hydroxide **Hughes and Annau 1976**									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
40	Mouse (C3H/HeN) 10 F	Once on GD 13, 14, 15, 16, or 17 (GW)	0, 16	DX	Develop[b]			16	Decreased survival of offspring; neurological effects in offspring (impaired righting response, altered gait, hindlimb crossing, decreased brain weight, dilated lateral ventricles, smaller caudate putamen)
Methylmercuric chloride Inouye et al. 1985									
41	Mouse (Swiss-Webster) 10–12 M	7 days (G)	0, 1, 2.5, 5	CS, BW, RX	Bd wt Repro	5 5			
Methylmercuric chloride Khera 1973 [Males were mated to untreated females after exposure.]									
42	Mouse (Swiss-Webster) 6–17 F	12 days GDs 6–17 (GO)	0, 0.001, 0.01, 0.1, 1, 10	LE, CS, BW, DX	Death Develop	 1		10	100% maternal mortality
Methylmercuric chloride Khera and Tabacova 1973									
43	Mouse (Swiss-Webster) 5–14 F	12 days GDs 6–17 (GO)	0, 0.001, 0.01, 1, 5	CS, BW, BI, DX	Develop[b]	0.01	1	5	LOAEL: delayed cerebellar development Serious LOAEL: 100% stillbirth
Methylmercuric chloride Khera and Tabacova 1973									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
44	Mouse (BALB/c) 6 F	3 days GDs 12–14 (G)	0, 3	CS, DX	Develop[b]		3 M		Effects in male offspring: 15% reduction in body weight; decreased motor activity and decreased anxiety-like behaviors at PND 42; altered nocturnal rhythm at PNDs 84–98
Methylmercury Kim et al. 2000									
45	Mouse (C57BL/ 6Cr) 5–6 F	3 days GDs 12–14 (G)	0, 3	CS, DX	Develop[b]		3 M		Effects in male offspring: decreased motor activity and rearing at PND 42; impaired spatial learning and memory at PND 56
Methylmercury Kim et al. 2000									
46	Mouse (C57BL/6J) 4 F	3 days GDs 12–14 (G)	0, 3	CS, DX	Develop[b]		3 M		Effects in male offspring: Impaired spatial learning on PND 56; increased grooming/preening behaviors on PND 42
Methylmercury Kim et al. 2000									
47	Mouse (C57BL/6N) NS M	7–14 days (IN)	0, 4.6	BW, NX	Bd wt Neuro	4.6 4.6			
Methylmercury Kirkpatrick et al. 2015 [Mice were given methylmercury-dosed cookies.]									
48	Mouse (C57BL/6) 6 F	11 days GDs 8–18 (F)	0, 0.009	DX	Develop[b]		0.009		Impaired learning and memory and decreased motor activity and coordination in adult offspring
Methylmercuric chloride Montgomery et al. 2008									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
49	Mouse (C57BL/6) 8 M	7 days (W)	0, 5.6	BC, BI, NX	Hepatic	5.6			
					Neuro	5.6			
Methylmercury Moreira et al. 2012									
50	Mouse (C57BL/6) 8 M	14 days (W)	0, 5.6	BC, BI, NX	Hepatic		5.6		Elevated plasma total cholesterol
					Neuro	5.6			
Methylmercury Moreira et al. 2012									
51	Mouse (JCL:ICR) 10 F	Once GD 10 or 12 (GW)	0, 10, 12, 16, 20	DX	Develop	12		16	Cleft palate; dilatation of renal pelvis; decreased fetal weight
Methylmercuric chloride Yasuda et al. 1985									
52	Mouse (C57BL/6N) 4–6 M, 4–6 F	Once (G)	0, 4, 8, 16, 24, 32, 40	LE, BC, HP, OF	Death			16 M 40 F	4/6 died
					Renal	8 M 24 F		16 M 32 F	Impaired renal function in males at ≥16 mg Hg/kg/day and females at ≥32 mg Hg/kg/day; increased serum creatinine in males at ≥32 mg Hg/kg
Methylmercuric chloride Yasutake et al. 1991									
53	Guinea pig (Hartley) 5–9 F	Once GD 21, 28, 35, 42, or 49 (GW)	0, 11.5	CS, FI, DX	Develop[b]			11.5	>30% total litter loss, 12–30% decrease in fetal body weight, abnormal fetal brain development
Methylmercuric chloride Inouye and Kajiwara 1988									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
54	Hamster (Golden Syrian) 10 F	Once (GD 10); or 6 days (GDs 10–15) (GW)	0, 1.6	DX	Develop[b]			1.6	Degeneration of cerebellar neurons in neonates
Methylmercuric chloride Reuhl et al. 1981a									
55	Hamster (Golden Syrian) 10 F	Once (GD 10); or 6 days (GDs 10–15) (GW)	0, 1.6	DX	Develop[b]			1.6	Degeneration of cerebellar neurons in adult offspring
Methylmercuric chloride Reuhl et al. 1981b									
INTERMEDIATE EXPOSURE									
56	Monkey (*Macaca fascicularis*) 4–5 F	6 months (IN)	0, 0.05	CS, OW, HP	Neuro		0.05		72% increase in reactive glia in the brain
Methylmercury hydroxide Charleston et al. 1994									
57	Monkey (*M. fascicularis*) NS F	6 months (IN)	0, 0.05	HP	Neuro		0.05		72% increased number of reactive glia
Methylmercury Charleston et al. 1995									
58	Monkey (*M. fascicularis*) 4 F	6 months (IN)	0, 0.05	BC, BW, CS, GN, HE, HP	Bd wt Hemato Neuro	0.05 0.05	 0.05		 Decreased astrocytes in thalamus
Methylmercury hydroxide Charleston et al. 1996; Vahter et al. 1994									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
59	Monkey (Marmoset) 4 M	up to 242 days (W)	0, 0.5	CS, BW, HP	Bd wt			0.5	Body weight loss
					Neuro		0.5		Mild ataxia; cerebral edema and gliosis, microcystic change in occipital white matter
Methylmercury Eto et al. 2001									
60	Monkey (*M. fascicularis*) 3 M	20 weeks (IN)	0, 0.046, 0.065	CS, BW, BC, HP, RX	Bd wt	0.065			
					Repro		0.046		Increased sperm tail-defects; decreased spermatozoa motility; decreased sperm speed and forward progression
Methylmercury Mohamed et al. 1987									
61	Monkey (*M. fascicularis*) 4–6 F	150 days (IN)	0, 0.0003, 0.0032, 0.04	CS, BW, CS	Bd wt	0.04			
					Neuro	0.04			
Methylmercuric chloride Petruccioli and Turillazzi 1991									
62	Monkey (*M. fascicularis*) 2 M, 2 F	28–29 days PNDs 0–28 or 29 (IN)	0, 0.5	DX	Develop[b]			0.5	Severe signs of neurotoxicity (loss of dexterity, decreased locomotor activity, ataxia, blindness, comatose); neuronal degeneration; body weight loss
Methylmercuric chloride Willes et al. 1978									
63	Rat (Sprague-Dawley) 8 F	3 weeks GDs 0–20 (GW)	0, 0.9, 1.8	DX	Develop		0.9		Incomplete skeletal ossification at ≥0.9 mg Hg/kg/day; 13–14% decrease in fetal weight, length, and head size and decrease in long bone width/length at 1.8 mg Hg/kg/day
Methylmercuric chloride Abd El-Aziz et al. 2012									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
64	Rat (Sprague-Dawley) 15 F	38 days GD 5–PND 21 (GW)	0, 0.2, 0.4	CS, DX	Develop[b]		0.2		Effects in male offspring at PND 40: impaired learning and memory at ≥0.2 mg Hg/kg/day; altered open field activity (decreased rearing) at 0.4 mg Hg/kg/day; no effects on PND 90
Methylmercuric chloride Albores-Garcia et al. 2016									
65	Rat (Sprague-Dawley) 8 F	7–8 weeks (4 weeks premating–GD 20) (GW)	0, 0.5, 0.9	CS, BW, FI, DX	Bd wt	0.9			
					Develop	0.5	0.9		6–9% decrease in pup body weight gain on PNDs 4– 41
Methylmercuric chloride Beyrouty et al. 2006 [Offspring neurobehavior was assessed on PNDs 17–38.]									
66	Rat (Wistar) 30 M	60 days (GO)	0, 0.04	BI, NX	Neuro		0.04		Impaired social and spatial memory; decreased number of mature neurons and astrocytes in hippocampus
Methylmercuric chloride Bittencourt et al. 2019									
67	Rat (Holtzman) 4 M	6 weeks (G)	0, 0.8	CS, BW, HP	Bd wt		0.8		Body weight loss
					Neuro			0.8	Hindlimb crossing, severe ataxia, tremor, partial paralysis; cellular degeneration and ultrastructural changes in dorsal root ganglia and cerebellum
Methylmercuric chloride Chang and Hartmann 1972a									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
68	Rat (Wistar) 3 F	6 weeks GD 1–PND 21 (W)	0, 0.05, 0.23	RX, DX	Repro	0.23			
					Develop[b]	0.05	0.23		Delayed acquisition of neurodevelopmental reflexes; impaired motor coordination PNDs 34–35; increased motor activity in females on PND 36
Methylmercury Cheng et al. 2015									
69	Rat (Wistar) 16 F	~60 days premating through lactation (W)	0, 0.19, 0.74	BW, RX, DX	Bd wt	0.74			
					Repro	0.74			
					Develop[b]		0.19		Impaired operant training and decreased ultrasonic vocalization in offspring
Methylmercuric chloride Elsner 1991									
70	Rat (Brown Norway) 5–14 M	19 weeks 2 days/week (G)	0, 0.0008, 0.008, 0.08	CS, BW, BC, OW, RX	Bd wt	0.08			
					Repro	0.0008		0.008	No viable litters produced at 0.008 mg Hg/kg/day; 100% infertility, 8% decrease in absolute testes weight, 17% reduction in caudal sperm count, and 44% reduction in testicular testosterone at 0.08 mg Hg/kg/day
Methylmercuric chloride Friedmann et al. 1998 [Males were mated to untreated females during Week 11.]									
71	Rat (Wistar) 3 F	6 weeks GD 1–PND 21 (W)	0, 0.05, 0.23, 0.5	RX, DX	Repro	0.23		0.5	No viable litters
					Develop[b]	0.05	0.23		Impaired motor coordination in PND 34–35 offspring
Methylmercury Fujimura et al. 2012									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
72	Rat (Wistar) 7–8 F	~17 days GD 5 until parturition (~GD 21) (G)	0, 0.5, 0.9, 1.9	CS, BW, DX	Bd wt	0.9		1.9	>50% decrease in maternal body weight gain
					Neuro	0.9		1.9	Incoordination, altered gait, hindlimb ataxia
					Develop		0.5	1.9	LOAEL: 12% decrease in mean litter weight on PND 1 Serious LOAEL: 100% full-litter resorption
Methylmercury Gandhi et al. 2013									
73	Rat (Sprague-Dawley) 7 F	22 days GD 7–PND 7 (W)	0, 0.5	BW, FI, WI, DX	Bd wt	0.5			
					Develop[b]		0.5		Increased motor activity at PND 14
Methylmercury hydroxide Giménez-Llort et al. 2001									
74	Rat (Wistar) 7 M	100 days (G)	0, 0.08	BW, BC, OF	Bd wt	0.08			
					Cardio		0.08		Increased systolic blood pressure
Methylmercuric chloride Grotto et al. 2009a									
75	Rat (Sprague-Dawley) 8 F	15 days PNDs 1–15 (via dam) (F)	0, 0.37	BW, DX	Bd wt	0.37			
					Develop[c]		0.37		7% decrease in pup weight; 13% decrease in relative spleen weight; altered immune function in offspring (decreased splenic lymphoproliferative response to mitogen)
Methylmercury Ilback et al. 1991									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
76	Rat (Sprague-Dawley) 8 F	~15 weeks 11 weeks premating through GD 21 (F)	0, 0.37	BW, DX	Bd wt Develop[c]	0.37 F	0.37		45% increase in WBCs in offspring on PND 15
Methylmercury Ilback et al. 1991									
77	Rat (Sprague-Dawley) 8 F	~17 weeks 11 weeks premating through PND 15 (F)	0, 0.37	BW, DX	Bd wt Develop[c]	0.37	0.37		9% decrease in pup weight; altered immune function in offspring (increased thymic lymphoproliferative response to mitogen, decreased cell-mediated cytotoxicity)
Methylmercury Ilback et al. 1991									
78	Rat (Wistar) 10 B	1 month (G)	0, 0.5	OF	Cardio		0.5		Altered left ventricular function; impaired baroreflex
Methylmercuric chloride Jindal et al. 2011									
79	Rat (Wistar) 6 F	25 days premating–GD 19 (GW)	0, 0.8	DX	Develop[b]			0.8	Evidence of neuronal damage on PNDs 1 and 3 (not PNDs 7–180); decreased cell numbers in amygdala and hippocampus on PND 70; impaired associative learning at PND 180
Methylmercuric chloride Kakita et al. 2000									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
80	Rat (Wistar) 14–19 M	95–125 days (G)	0, 0.1, 0.5, 1	CS, BW, RX	Bd wt	0.5		1	Body weight loss
					Repro	0.1		0.5	Decreased viable fetuses at ≥0.5 mg Hg/kg/day; decreased fertility at 1 mg Hg/kg/day
Methylmercuric chloride **Khera 1973** [Males were mated to untreated females concurrent with exposure.]									
81	Rat (Wistar) 35 F	up to 122 days 2 generations (F)	0, 0.002, 0.01, 0.05, 0.25	CS, BW, HP, DX	Bd wt	0.25			
					Renal	0.25			
					Repro	0.25			
					Develop	0.05	0.25		Increased incidence of ocular lesions (delayed eyelid separation, suborbital edema, corneal opacity)
Methylmercuric chloride **Khera and Tabacova 1973**									
82	Rat (Wistar) 10–18 M	19 days (GW)	0, 1.6	CS, BW, OW, HP	Bd wt			1.6	Body weight loss
					Neuro			1.6	Axonal destruction in dorsal root of spinal cord, loss of large motor neurons in dorsal root ganglia; clinical signs of neurotoxicity (apathy, hindlimb crossing, clumsiness, ataxia)
Methylmercuric chloride **Larsen and Brændgaard 1995; Schiønning et al. 1998a**									
83	Rat (Wistar) 10 M	8 weeks (W)	0, 3.2	BW, BC, OW, HP	Bd wt			3.2	29% decrease in final body weight
					Repro		3.2		98% decrease in serum testosterone; 54–73% decrease in testicular testosterone
Methylmercury **Moussa et al. 2010**									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
84	Rat (Long-Evans) 10 F	~10–13 weeks 4–7 weeks premating through PND 16 (W)	0, 0.045, 0.6	RX, DX	Repro	0.6			
					Develop[b]		0.045		Acceleration of age-related cognitive decline in operant training in offspring from 6 months to 2.5 years
Methylmercuric chloride Newland and Reile 1999; Newland and Rasmussen 2000; Newland et al. 2004									
85	Rat (Sprague-Dawley) 6 M	8 weeks (W)	0, 0.0004, 0.04	BC, BW, IX	Bd wt	0.04			
					Immuno		0.0004		Biphasic lymphocyte response to mitogen PHA (544% increase at 0.0004 mg Hg/kg/day; 56% decrease at 0.04 mg Hg/kg/day)
Methylmercuric chloride Ortega et al. 1997a									
86	Rat (Sprague-Dawley) 6 M	8 weeks (W)	0, 0.0004, 0.04	BC, BW, IX	Bd wt	0.04			
					Immuno		0.0004		278% increase in lymphocyte response to mitogen PHA at 0.0004 mg Hg/kg/day; no change at 0.04 mg Hg/kg/day
Methylmercuric sulfide Ortega et al. 1997a									
87	Rat (Sprague-Dawley) 6 M	8 weeks (W)	0, 0.0004, 0.04	BC, BW, IX	Bd wt	0.04			
					Immuno		0.0004		300% increase in lymphocyte response to mitogen PHA at 0.0004 mg Hg/kg/day; no change at 0.04 mg Hg/kg/day
Bis(methylmercury)sulfide Ortega et al. 1997a									

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
88	Rat (Sprague-Dawley) 6 M	8 weeks (W)	0, 0.0004, 0.04	BC, BW, IX	Bd wt	0.04			
					Immuno		0.0004		56% decrease in lymphocyte response to mitogen PHA
Tris(methylmercuric)sulphonium ion Ortega et al. 1997a									
89	Rat (Sprague-Dawley) 6 M	8 weeks (W)	0, 0.0004, 0.04	BC, IX	Endocr		0.0004		>100% increase in ACTH
					Immuno		0.0004		Biphasic lymphocyte response to mitogen Con-A (356% increase at 0.0004 mg Hg/kg/day; 54% decrease at 0.04 mg Hg/kg/day); >300% increase in IL-6 at both doses
Methylmercuric chloride Ortega et al. 1997b									
90	Rat (Sprague-Dawley) 6 M	8 weeks (W)	0, 0.0004, 0.04	BC, IX	Endocr		0.0004		>100% increase in ACTH
					Immuno		0.0004		>150% increase in lymphocyte response to Con-A at ≥0.0004 mg Hg/kg/day; 300% increase in IL-6 at 0.04 mg Hg/kg/day
Bis(methylmercury)sulfide Ortega et al. 1997b									
91	Rat (Sprague-Dawley) 6 M	16 weeks (W)	0, 0.0004, 0.04	BC, IX	Endocr		0.0004		>100% increase in ACTH
					Immuno		0.0004		>75% decrease in lymphocyte response to mitogen Con-A at ≥0.0004 mg Hg/kg/day; 1,275% increase in IL-6 at 0.04 mg Hg/kg/day
Methylmercuric chloride Ortega et al. 1997b									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
92	Rat (Sprague-Dawley) 6 M	16 weeks (W)	0, 0.0004, 0.04	BC, IX	Endocr	0.04			
					Immuno		0.0004		Biphasic lymphocyte response to mitogen Con-A (69% decrease at 0.0004 mg Hg/kg/day; 200% increase at 0.04 mg Hg/kg/day); >140% increase in IL-6 at both dose levels
Bis(methylmercury)sulfide Ortega et al. 1997b									
93	Rat (Sprague-Dawley) 8 F	22 days GD 7–PND 7 (W)	0, 0.474	BW, FI, WI, DX	Bd wt	0.474			
					Develop[b]	0.474 F	0.474 M		Decreased motor activity in male offspring at 6 months
Methylmercury hydroxide Rossi et al. 1997									
94	Rat (Wistar) 4–10 F	One generation 8 weeks premating through PND 30 (via dam) PNDs 31–55 (direct) (F)	0, 0.5	DX	Develop[b]		0.5		Impaired motor coordination and memory at PNDs 35–42; focal dysplastic lesions in cerebellum
Methylmercury Sakamoto et al. 2002									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
95	Rat (Wistar) 12 M	30 days PNDs 1–30 (IN)	0, 0.8, 2, 4	DX	Develop[b]		0.8	4	Impaired associative learning at 6 weeks of age at ≥0.8 mg Hg/kg/day; body weight loss, impaired motor coordination and hindlimb crossing/paralysis, widespread CNS degeneration and neuronal loss at 4 mg Hg/kg/day
Methylmercuric chloride **Sakamoto et al. 2004** [via micropipette in water and condensed milk]									
96	Rat (Wistar) 5 M	5 weeks (W)	0, 0.3, 1.4	BW, HP	Bd wt	0.3		1.4	Body weight loss
					Neuro			1.4	Severe damage and degeneration of sensory regions of the spinal cord (dorsal root ganglia, posterior roots, posterior column)
Methylmercuric chloride **Sakamoto et al. 2017**									
97	Rat (Wistar) 10 M	5 weeks (W)	0, 1.9, 9.72	BW, HP	Bd wt	1.9 M		9.72	Body weight loss
					Neuro			9.72	Severe damage and degeneration of sensory regions of the spinal cord (dorsal root ganglia, posterior roots, posterior column)
Methylmercuric chloride **Sakamoto et al. 2017**									
98	Rat (Wistar) 20 M	60 days (GO)	0, 0.037	BW, HP, NX	Bd wt	0.037			
					Neuro		0.037		Reduced motor activity and impaired motor coordination; decreased neuronal and astrocyte density in motor cortex
Methylmercury **Santana et al. 2019**									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
99	Rat (Wistar) 11–12 F	5 weeks GD 7–PND 21 (W)	0, 0.5, 1.9	CS, BW, FI, WI, DX	Bd wt	0.5		1.9	~30–40% decrease in maternal body weight with 10–20% decrease in food consumption
					Neuro	0.5		1.9	Ataxia
					Develop	0.5	1.9		~8–10% decrease in PND 21 pup weight; delayed development of righting reflex
Methylmercuric chloride Sitarek and Gralewicz 2009									
100	Rat (Wistar) 5 F	7–8 weeks premating–PND 21 (W)	0, 0.3	CS, BW, FI, WI, RX, DX	Bd wt	0.3			
					Repro	0.3			
					Develop[b]		0.3		11% decrease in birth weight; increased susceptibility to seizure activity at PNDs 28 and 90
Methylmercuric chloride Szász et al. 2002									
101	Rat (SHR/NCrj) 10 M, 10 F	26 days (NS)	0, 1.6	LE, CS, BW, NX, OF	Death			1.6 M	100% mortality
					Bd wt			1.6	Body weight loss; severe in males
					Cardio		1.6 F		Increased systolic blood pressure
					Neuro		1.6		Hindlimb crossing, disturbed righting reflex, abnormal gait
Methylmercuric chloride Tamashiro et al. 1986 [spontaneous hypertensive rat strain]									
102	Rat (Wistar) 11–14 F	26 days GD 6–PND 10 (GO)	0, 0.08, 0.3, 0.6, 0.8, 1.2, 1.6	LE, CS, BW, DX	Death			1.6	5/11 dams sacrificed moribund
					Bd wt	0.8	1.2	1.6	Decreased maternal weight at 1.2 mg Hg/kg/day; weight loss at 1.6 mg Hg/kg/day
					Neuro	1.2		1.6	Unsteady gait, partial hindlimb paralysis

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Develop[c]		0.08	0.8	Altered functional immune endpoints in PND 21–70 offspring at ≥0.08 mg Hg/kg/day; decreased body weight and prenatal/neonatal death at ≥0.8 mg Hg/kg/day
Methylmercuric chloride Tonk et al. 2010									
103	Rat (Wistar) 24 M	5 weeks 5 days/week (GW)	0, 0.5, 2.0	NX	Neuro		0.5		Decreased motor activity; altered acoustic startle response; altered electrophysiological responses in sensory cortices and hippocampus
Methylmercuric chloride Vezér et al. 2005									
104	Rat (Wistar) 8 F	6 weeks GD 0–PND 21 (W)	0, 0.347	DX	Develop[b]			0.347	>20% decrease in F1 body weight at PND 28; decreased spontaneous and evoked cortical potentials in F1 pups at PND 28
Methylmercuric chloride Vilagi et al. 2000									
105	Rat (Wistar) 9 M	23–28 days (G)	0, 0.4	CS, BW, OF	Bd wt	0.4			
					Cardio		0.4		Persistent increases in systolic blood pressure post-exposure
Methylmercuric chloride Wakita 1987									
106	Rat (Sprague-Dawley) NS M, F	14–16 weeks premating through PND 21 (W)	0, 0.0006, 0.06	BW, DX	Bd wt	0.06			
					Develop[c]		0.0006		Altered functional immune endpoints in PND 42 and 84 offspring (enhanced lympho-proliferation in response to mitogens; decreased natural killer cell activity)
Methylmercuric chloride Wild et al. 1997									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
107	Rat (Sprague-Dawley) NS M, F	14–16 weeks premating through PND 21 (W)	0, 0.0003	BW, DX	Bd wt	0.0003			
					Develop[c]		0.0003		Altered functional immune endpoints in PND 84 offspring (enhanced lymphoproliferation in response to mitogens)
Bis(methylmercury)sulfide Wild et al. 1997									
108	Rat (Wistar) 5–9 M	4 weeks (W)	0, 0.002, 0.005, 0.009, 0.018, 0.036, 0.216, 0.879	BW, OW, OF	Bd wt	0.216		0.879	66% decrease in body weight gain
					Cardio	0.002	0.005		Elevated systolic blood pressure and pulse pressure at ≥0.005 mg Hg/kg/day; elevated diastolic blood pressure at ≥0.009 mg/kg/day
Methylmercuric chloride Wildemann et al. 2015a									
109	Rat (Wistar) 5–6 M	4 weeks (W)	0, 0.018, 0.216	BW, OW, OF	Bd wt	0.216			
					Cardio	0.018	0.216		Elevated systolic blood pressure and pulse pressure
Methylmercuric chloride Wildemann et al. 2015b									
110	Rat (Wistar) 5–6 M	4 weeks (W)	0, 0.006, 0.285	BC, BI, UR, OF	Cardio		0.006		Elevated systolic blood pressure at ≥0.006 mg Hg/kg/day; elevated diastolic at 0.285 mg/kg/day
					Renal		0.006		Elevated urinary creatinine
Methylmercuric chloride Wildemann et al. 2016									
111	Rat (Charles River) 6 M	8 weeks (G)	0, 1.6	HP	Neuro			1.6	Extensive degeneration of dorsal root fibers
Methylmercuric chloride Yip and Chang 1981									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
112	Mouse (CD-1) 12 M	60 days (G)	0, 0.25, 1, 4	CS, BW, FI, HP	Neuro		0.25	1	LOAEL: hindleg weakness Serious LOAEL: motor incoordination and neuronal degeneration and microgliocytosis in subcortical regions of the brain
Methylmercuric chloride Berthoud et al. 1976									
113	Mouse (ICR) 9–10 M	3 weeks (W)	0, 0.08, 0.35, 1.7	BW, WI, GN, IX	Bd wt	1.7			
					Immuno		0.08		Suppressed immune response to antigens
Methylmercuric chloride Blakley et al. 1980									
114	Mouse (C57Bl/6) 12 M	2 months (F)	0, 0.00046, 0.0073	BW, NX	Bd wt	0.0073			
					Neuro	0.00046	0.0073		Impaired memory
Methylmercury Bourdineaud et al. 2011									
115	Mouse (ICR) 16 M	4 or 6 weeks (GW)	0, 1.6	BC	Endocr		1.6		~80–95% decrease in plasma insulin; ~25–40% increase in serum glucose
Methylmercuric chloride Chen et al. 2012									
116	Mouse (Swiss) 13–14 M	21 days (W)	0, 4.7, 8.7	LE, CS, BW, WI, NX	Death			8.7	100% mortality
					Bd wt			4.7	>10% body weight loss
					Neuro		4.7		Impaired motor coordination, hypoactivity, altered gait
Methylmercuric chloride Dietrich et al. 2005									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
117	Mouse (albino) 7 F	21 days PNDs 1–21 (via dam) (W)	0, 4.7	BW, WI, DX	Bd wt	4.7			
					Develop[b]		4.7		Impaired motor coordination in PND 21 offspring
Methylmercuric chloride Franco et al. 2006									
118	Mouse (C57BL/6) 14–34 F	6 weeks GD 2–PND 21 (W)	0, 0.9, 1.3, 1.7	DX	Repro	1.3	1.7		18% decrease in number of pups/litter
					Develop[b]	1.7 F	0.9 M	1.7 M	Effects in male offspring: Reduced locomotor activity at ≥0.9 mg Hg/kg/day; impaired working memory at ≥1.3 mg Hg/kg/day; 14% reduction in postnatal survival at 1.7 mg/kg/day
Methylmercuric chloride Goulet et al. 2003 [Neurobehavior assessed in offspring on PNDs 35–70.]									
119	Mouse (A.SW) 5–7 F	30 days (W)	0, 0.420	BC, BI, IX	Immuno		0.42		Positive ANoA and ACA; elevated serum IgG1, IgG2a; polyclonal B-cell activation
Methylmercuric chloride Havarinasab et al. 2007 [autoimmune susceptible mice]									
120	Mouse (ICR) 6 M, 6 F	26 weeks (F)	M: 0, 0.0300, 0.150, 0.724 F: 0, 0.0254, 0.115, 0.627	CS, BW, GN, HP	Bd wt	0.724			
					Resp	0.724			
					Cardio	0.724			
					Gastro	0.724			
					Musc/skel	0.724			
					Hepatic	0.724			
					Renal	0.115	0.627		Epithelial degeneration and regeneration of the renal proximal tubules
					Dermal	0.724			
					Ocular	0.724			
					Endocr	0.724			

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Immuno	0.724			
					Neuro	0.724			
					Repro	0.724			
Methylmercuric chloride									
Hirano et al. 1986 [interim sacrifice group]									
121	Mouse (ICR) 12–15 M	7 weeks PNDs 21–70 (GW)	0, 0.02	DX	Develop[b]		0.02		Hyperactivity, impaired motor coordination, and hearing impairment at PND 70
Methylmercury									
Huang et al. 2011									
122	Mouse (ICR) 12–15 F	10–17 weeks premating through PND 21 (via dam) Select pups: PNDs 21–70 (direct) (GW)	0, 0.02	RX, DX	Repro		0.02		16% decrease in litter size
					Develop[b]			0.02 M	Effects at PND 70: 19–32% decrease in pup weight, decreased motor activity and impaired hearing (both groups), impaired motor coordination (direct group only)
Methylmercury									
Huang et al. 2011									
123	Mouse (BALB/c CUM) 8 F	12 weeks (F)	0, 0.77	BW, BC, OW, IX	Bd wt	0.77			
					Immuno		0.77		Reduced natural killer T-cell activity, enhanced T-cell lymphoproliferative response, 22% decrease in absolute thymus weight, and ~50% decrease in thymic cell number
Methylmercury									
Ilback 1991									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
124	Mouse (C57BL/6N) NS M	21–28 days (IN)	0, 4.6	BI, NX	Bd wt	4.6			
					Neuro		4.6		Impaired motor coordination at 4 weeks
Methylmercury **Kirkpatrick et al. 2015** [Mice were given methylmercury-dosed cookies.]									
125	Mouse (Swiss) 35–40 M	28 weeks (W)	0, 0.89, 9.5	CS, BW, WI, HP	Death			9.5	100% mortality by 4–5 weeks
					Bd wt	0.89		9.5	Body weight loss
					Gastro	9.5			
					Hepatic	9.5			
					Renal	0.89	9.5		Slight degenerative changes in proximal tubular epithelial cells
					Neuro			0.89	Severe neurotoxicity (clinical signs, behavioral signs, histopathologic cerebellar changes)
Methylmercuric chloride **MacDonald and Harbison 1977**									
126	Mouse (ICR) 60 M, 60 F	26 weeks (F)	0, 2.3, 4.5	LE, CS, HP	Death			4.5	51/60 males and 59/60 females died or were sacrificed moribund by study week 26
					Neuro			4.5	Clinical signs of neurotoxicity prior to death or sacrifice
Methylmercuric chloride **Mitsumori et al. 1981**									
127	Mouse (C57BL/6) 8 M	21 days (W)	0, 5.6	BC, BI, NX	Hepatic		5.6		Elevated plasma total cholesterol
					Neuro		5.6		Decreased motor activity
Methylmercury **Moreira et al. 2012**									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
128	Mouse (C57BL/6) 6 M	21 days (W)	0, 5.6	BC, HP	Hepatic		5.6		Elevated plasma total cholesterol
					Renal		5.6		Glomerular shrinkage and tubular vacuolization
Methylmercury Moreira et al. 2012									
129	Mouse (Swiss Albino) NS M	28 days (W)	0, 5.6	BC	Hepatic		5.6		Elevated plasma total cholesterol, HDL cholesterol, non-HDL cholesterol, and triglycerides
Methylmercury Moreira et al. 2012									
130	Mouse (BALB/c) 27–72 F	15–16 weeks 10 weeks premating through PND 15 (F)	0, 0.098, 0.98	CS, BW, RX, DX	Bd wt	0.98			
					Repro	0.98			
					Develop[c]		0.098		Alterations in functional immune endpoints and thymocyte cell populations in offspring at ≥0.098 mg Hg/kg/day; 8% decrease in pup body weight at 0.98 mg Hg/kg/day
Methylmercuric chloride Thuvander et al. 1996									
131	Mouse (B6C3F1/HSD) 15–18 F	9–10 weeks Premating through PND 13 (W)	0, 0.2, 0.6	BW, RX, DX	Bd wt	0.6			
					Repro	0.6			
					Develop[b]		0.2		Impaired spatial learning and increased hindlimb splay at 5 and/or 15 months
Methylmercuric chloride Weiss et al. 2005									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
132	Mouse (C57BL/6) NS F	19 days GDs 0–18 (F)	0, 0.9	DX	Develop[b]		0.9		Male offspring: increased activity, decreased anxiety, and impaired spatial learning at PND 56 Female offspring: decreased activity at PND 56
Methylmercury **Yoshida et al. 2011**									
133	Mouse (C57BL/6J) 7–8 F	27 days PNDs 2–28 (F)	0, 0.9	DX	Develop[b]		0.9		Decreased motor activity at PND 77
Methylmercuric chloride **Yoshida et al. 2018**									
134	Mouse (A.SW) 2–7 F	5 weeks GD 8–PND 21 (W)	0, 0.03, 0.06, 0.13	DX	Develop	0.06		0.13	Complete litter loss in 6/7 dams
Methylmercury **Zhang et al. 2011** [Autoimmune susceptible mouse strain]									
135	Mouse (A.SW) 3–5 F	5 weeks GD 8–PND 21 (W)	0, 0.06	DX, IX	Immuno Develop[b,c]	0.06 0.06 M	0.06 F		Hyperactivity, cerebellar inflammation
Methylmercury **Zhang et al. 2011** [Autoimmune susceptible mouse strain; offspring immune and behavioral endpoints were evaluated at PNDs 21 and 70.]									
136	Mouse (A/WySnJ) 3–5 F	5 weeks GD 8–PND 21 (W)	0, 0.06	DX, IX	Immuno Develop[b,c]	0.06 0.06			
Methylmercury **Zhang et al. 2011** [Offspring immune and behavioral endpoints were evaluated at PNDs 21 and 70.]									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
137	Rabbit (New Zealand) 10 M, 10 F	14 weeks (F)	M: 0, 0.05, 0.53, 1.1 F: 0, 0.05, 0.49, 1.0	LE, CS, BW, BC, HE, HP, IX	Death			1	100% mortality
					Bd wt	0.05	0.49 F	0.53 M	Decreased body weight gain (13% in females, 43% in males)
					Hemato	0.53			
					Renal	0.49	1		Mild-to-moderate proximal tubule necrosis
					Immuno	0.05	0.49		Decreased immune response to influenza infection
					Neuro	0.05		0.49	Ataxia and intermittent convulsions at ≥0.49 mg Hg/kg/day; cerebellar degeneration at ≥1.0 mg Hg/kg/day
Methylmercuric chloride Koller et al. 1977									
138	Cat 15–16 B	11 months (F)	0, 0.012	CS, BW, HP	Neuro			0.012	Serious clinical signs of neurotoxicity, degenerative brain lesions
Methylmercury Chang et al. 1974									
139	Cat 4–5 M, 4–5 F	Up to 1 year (F)	0.003, 0.0084, 0.020, 0.046, 0.074, 0.176	LE, CS, GN, HP	Death			0.176	100% sacrificed moribund by ~16 weeks
					Bd wt	0.176			
					Resp	0.176			
					Cardio	0.176			
					Gastro	0.176			
					Hemato	0.176			
					Hepatic	0.176			
					Renal	0.176			
					Endocr	0.176			
					Immuno	0.176			

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro	0.046	0.074	0.176	Clinical signs of neurotoxicity first observed at ~40 weeks at 0.074 mg Hg/kg/day and ~14 weeks at 0.176 mg Hg/kg/day; serious clinical signs and degeneration in cerebral cortex, cerebellum, and dorsal root ganglia observed by ~16 weeks at 0.176 mg Hg/kg/day
Methylmercuric chloride Charbonneau et al. 1976									
140	Cat 3 or 5 M, 2 or 6 F	44–243 days (G)	0, 0.25, 0.37, 0.5, 0.75, 1.0	CS, HP	Neuro			0.25	Degeneration in granule cells, Purkinje cells, and cerebral neurons; distorted myelination in cortical hemispheres
Methylmercuric chloride Khera et al. 1974									
CHRONIC EXPOSURE									
141	Human 238–917 per study	Chronic dietary intake; high fish consumers	0.34–0.62	DX	Develop[b]	0.00041[d]			NAEL is based on estimated mercury dose associated with a 1-point decrease in IQ (calculated from -0.18 IQ points per µg Hg/g hair)
Methylmercury Axelrad et al. 2007a, 2007b [meta-analysis of three prospective birth cohorts]									
142	Monkey (*M. fascicularis*) 7–8 F	up to 395 days (4 menstrual cycles, mating, gestation) (IN)	0, 0.04, 0.08	CS, BW, NX, RX, DX	Bd wt	0.08			
					Neuro	0.04		0.08	Gross motor incoordination, decreased sucking responses, intention tremors, blindness
					Repro	0.04		0.08	Decreased number of viable pregnancies
					Develop	0.04			
Methylmercury hydroxide Burbacher et al. 1984									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
143	Monkey (*M. fascicularis*) 7–16 F	Up to ~4 years (2 breeding cycles) (IN)	0, 0.04, 0.06, 0.08	BW, BC, NX, RX, DX	Bd wt	0.08			
					Neuro	0.06		0.08	Slight tremors, decreased sucking response, gross motor incoordination, apparent blindness
					Repro	0.04		0.06	54% decrease in number of viable pregnancies
Methylmercury hydroxide Burbacher and Mottet 1988, Burbacher et al. 2005									
144	Monkey (*M. fascicularis*) 4–5 F	12 or 18 months (IN)	0, 0.05	CS, OW, HP	Neuro		0.05		Up to 152% increase in number of reactive glia in the brain
Methylmercury hydroxide Charleston et al. 1994									
145	Monkey (*M. fascicularis*) NS F	12 or 18 months (IN)	0, 0.05	HP	Neuro		0.05		89–152% increased number of reactive glia
Methylmercury Charleston et al. 1995									
146	Monkey (*M. fascicularis*) 4–5 F	12 or 18 months (IN)	0, 0.05	BC, BW, CS, GN, HE, HP, OW	Bd wt	0.05			
					Hemato	0.05			
					Neuro		0.05		Increased microglia and decreased astrocytes in thalamus
Methylmercury hydroxide Charleston et al. 1996; Vahter et al. 1994									
147	Monkey (*M. fascicularis*) 1–2 B	Gestation–4 years of age 5 days/week (IN)	0, 0.010, 0.025, 0.050	DX	Develop[b]		0.01		Impaired auditory function and visual spatial discrimination in offspring at 10–19 years
Methylmercuric chloride Rice 1998a; Rice and Hayward 1999									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
148	Monkey (*M. fascicularis*) 2–4 M, 1–2 F	7 years 5 days/week (C)	0, 0.050	NX	Neuro	0.05			
Methylmercuric chloride **Rice 1998b; Rice and Hayward 1999** [Visual function and operant training were assessed at 10–20 years.]									
149	Monkey (*M. fascicularis*) 4 M, 1 F	6.5–7 years (starting at birth) (IN)	0, 0.05	CS, NX	Neuro		0.05		Clumsiness, impaired fine motor skills, and diminished touch and pinprick sensitivity at 13–14 years
Methylmercuric chloride **Rice 1989c**									
150	Monkey (*M. fascicularis*) 5 treated, 2 controls, NS	3–4 years (starting at birth) (IN)	0, 0.05	DX	Develop[b]		0.05		Spatial visual impairment at 4–5.5 years
Methylmercuric chloride **Rice and Gilbert 1982, 1990**									
151	Monkey (*M. fascicularis*) 1–5 NS	Gestation–4–4.5 years of age 3 days/week during gestation; 5 days/week postnatally (IN)	0, 0.01, 0.025, 0.05	DX	Develop[b]	0.025		0.05	Overt neurotoxicity in 2/5 offspring
Methylmercuric chloride **Rice and Gilbert 1990**									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
152	Monkey (*M. fascicularis*) 3–5 NS	7 years (starting at birth) (C)	0, 0.05	CS, NX	Neuro		0.05		Clumsiness and impaired high-frequency hearing at 13–14 years
Methylmercuric chloride Rice and Gilbert 1992									
153	Rat (Wistar) 20 M	103 weeks (W)	0, 0.37, 3.7	LE, BW, HE, HP	Death			3.7	14/20 treated died, compared to 7/20 control
					Bd wt		0.37		Approximately 10% decrease in body weight gain
					Gastro	0.37	3.7		Ulcerative cecitis
					Hemato	0.37	3.7		Increased leukocytes; decreased erythrocytes, hemoglobin, and hematocrit
					Renal		0.37		Increased severity of chronic renal nephrosis
					Endocr	3.7			
					Cancer			3.7	CEL: renal cell adenoma
Phenylmercuric acetate Solecki et al. 1991									
154	Rat (NS) 25 M, 25 F	2 years (F)	M: 0, 0.006, 0.03, 0.16 F: 0, 0.007, 0.04, 0.18	LE, CS, BW, FI, BC, BI, UR, HE, OW, HP, NX	Bd wt	0.16 M 0.18 F			
					Resp	0.16 M 0.18 F			
					Cardio	0.16 M 0.18 F			
					Gastro	0.16 M 0.18 F			
					Hemato	0.16 M 0.18 F			
					Musc/skel	0.16 M 0.18 F			

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hepatic	0.16 M 0.18 F			
					Renal	0.03 M 0.04 F	0.16 M 0.18 F		30–36% increase in relative kidney weight, decreased kidney enzyme activity
					Dermal	0.16 M 0.18 F			
					Ocular	0.16 M 0.18 F			
					Endocr	0.16 M 0.18 F			
					Immuno	0.16 M 0.18 F			
					Neuro	0.16 M 0.18 F			
					Repro	0.16 M 0.18 F			
Methylmercuric chloride Verschuuren et al. 1976									
155	Mouse (ICR) 54 M, 54 F	104 weeks (F)	M: 0, 0.0300, 0.150, 0.724 F: 0, 0.0254, 0.115, 0.627	LE, CS, BW, GN, HP	Bd wt	0.724			
					Resp	0.724			
					Cardio	0.724			
					Gastro	0.724			
					Musc/skel	0.724			
					Hepatic	0.724			
					Renal	0.03 M	0.15 M		

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
						0.115 F	0.627 F		Effects in males: epithelial degeneration and regeneration of the renal proximal tubules, urinary casts, and pelvic dilation at ≥0.15 mg Hg/kg/day; cystic kidney and epithelial regeneration and focal hyperplasia at 0.724 mg Hg/kg/day Effects in females: epithelial degeneration and regeneration of the renal proximal tubules at 0.627 mg Hg/kg/day
					Dermal	0.724			
					Ocular	0.724			
					Endocr	0.724			
					Immuno	0.724			
					Neuro	0.724 M 0.115 F		0.627 F	Degeneration or fibrosis of sciatic nerve
					Repro	0.627 F 0.15 M	0.724 M		Decreased sperm in testes
					Cancer			0.724 M	CEL: renal epithelial adenocarcinoma in males
Methylmercuric chloride Hirano et al. 1986									
156	Mouse (ICR) 60 M, 60 F	78 weeks (F)	0, 2.1, 4.1	CS, HP	Neuro		2.1		Clinical signs of neurotoxicity
					Cancer			2.1 M	CEL: kidney tumors (11 adenocarcinomas, 5 adenomas)
Methylmercuric chloride Mitsumori et al. 1981									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
157	Mouse (B6C3F1) 60 M, 60 F	104 weeks (F)	M: 0, 0.0305, 0.139, 0.686 F: 0, 0.0265, 0.133, 0.601	LE, CS, BW, GN, HP	Death			0.686 M	50/60 males died versus 31/60 controls
					Bd wt	0.133 F	0.601 F		~10% decrease in body weight gain
					Resp	0.686			
					Cardio	0.686			
					Gastro	0.139 M 0.601 F	0.686 M		Stomach ulceration
					Musc/skel	0.686			
					Hepatic	0.686			
					Renal	0.0305 M 0.133 F	0.139 M 0.601 F		Increased chronic nephropathy with epithelial cell degeneration; regeneration of the proximal tubules; interstitial fibrosis
					Dermal	0.686			
					Ocular	0.686			
					Endocr	0.686			
					Immuno	0.686			
					Neuro	0.139 M 0.601 F		0.686 M	Sensory neuropathy; cerebral and cerebellar necrosis; posterior paresis/paralysis
					Repro	0.139 M 0.601 F		0.686 M	Tubule atrophy of testes
					Cancer			0.686 M	CEL: renal epithelial cell adenomas and carcinomas
Methylmercuric chloride Mitsumori et al. 1990									

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
158	Mouse (B6C3F1/HSD × CBA/J HSD) F0: 15–18 F F1: 16–28 M	Lifetime GD 0–PND 21 (via dam) PNDs 22–26 months (direct) (W)	0, 0.2, 0.6	NX	Neuro		0.2		Impaired spatial learning at ≥0.2 mg Hg/kg/day; impaired operant training and increased hindlimb splay at 0.6 mg Hg/kg/day
Methylmercuric chloride **Weiss et al. 2005** [Behavioral testing at 5, 15, and 26 months.]									
159	Cat 4–5 M, 4–5 F	2 years (F)	0.003, 0.0084, 0.020, 0.046, 0.074	LE, CS, BW, FI, WI, BC, UR, GN, HP	Death			0.074	100% sacrifice moribund by ~55 weeks
					Bd wt	0.074			
					Resp	0.074			
					Cardio	0.074			
					Gastro	0.074			
					Hemato	0.074			
					Hepatic	0.074			
					Renal	0.074			
					Endocr	0.074			
					Immuno	0.074			

Table 2-4. Levels of Significant Exposure to Organic Mercury – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro	0.02	0.046	0.074	LOAEL: decreased nociception and mild clinical signs Serious LOAEL: ataxia, incoordination, impaired reflexes, degeneration in cerebral cortex, cerebellum, and dorsal root ganglia
Methylmercuric chloride **Charbonneau et al. 1976**									

[a]The number corresponds to entries in Figure 2-8; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-8. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]The neurodevelopmental effects are discussed in Section 2.16 (Neurological).
[c]The immunodevelopmental effects are discussed in Section 2.15 (Immunological).
[d]Used to derive a provisional chronic-duration oral MRL of 0.1 µg Hg/kg/day for methylmercury; based on a NAEL of 0.00041 mg Hg/kg/day divided by a total uncertainty factor of 3 (for human variability). The NAEL represents an estimated mercury dose associated with a 1-point decrease in IQ, based on a meta-analysis of three prospective birth cohorts in populations with high fish consumption: Faroe Islands (Grandjean et al. 1997, 1999), Seychelles Islands (Myers et al. 2003), and New Zealand (Kjellstrom et al. 1989). See Appendix A for more detailed information regarding the provisional MRL.

Principal studies for the MRLs

ACA = antichromatin antibodies; ACTH = adrenocorticotrophic hormone; ANoA = antinucleolar antibodies; B = both sexes; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; CNS = central nervous system; Con-A = concanavalin-A; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; (F) = feed (dietary); F = female(s); FI = food intake; (G) = gavage; (GO) = gavage in oil; (GW) = gavage in water; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HDL = high-density lipoprotein; HE = hematology; Hemato = hematological; HP = histopathology; IgG = immunoglobulin G; IL-6 = interleukin-6; Immuno = immunological; IQ = intelligence quotient; (IN) = ingestion; IX = immune function; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; Neuro = neurological; NAEL = no-adverse-effect level (estimated no-effect level); NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; PHA = phytohemagglutinin; PND = postnatal day; Repro = reproductive; Resp = respiratory; RX = reproductive function; UR = urinalysis; (W) = drinking water; SBC = white blood cell; WI = water intake

Figure 2-8. Levels of Significant Exposure to Organic Mercury – Oral
Acute (≤14 days)

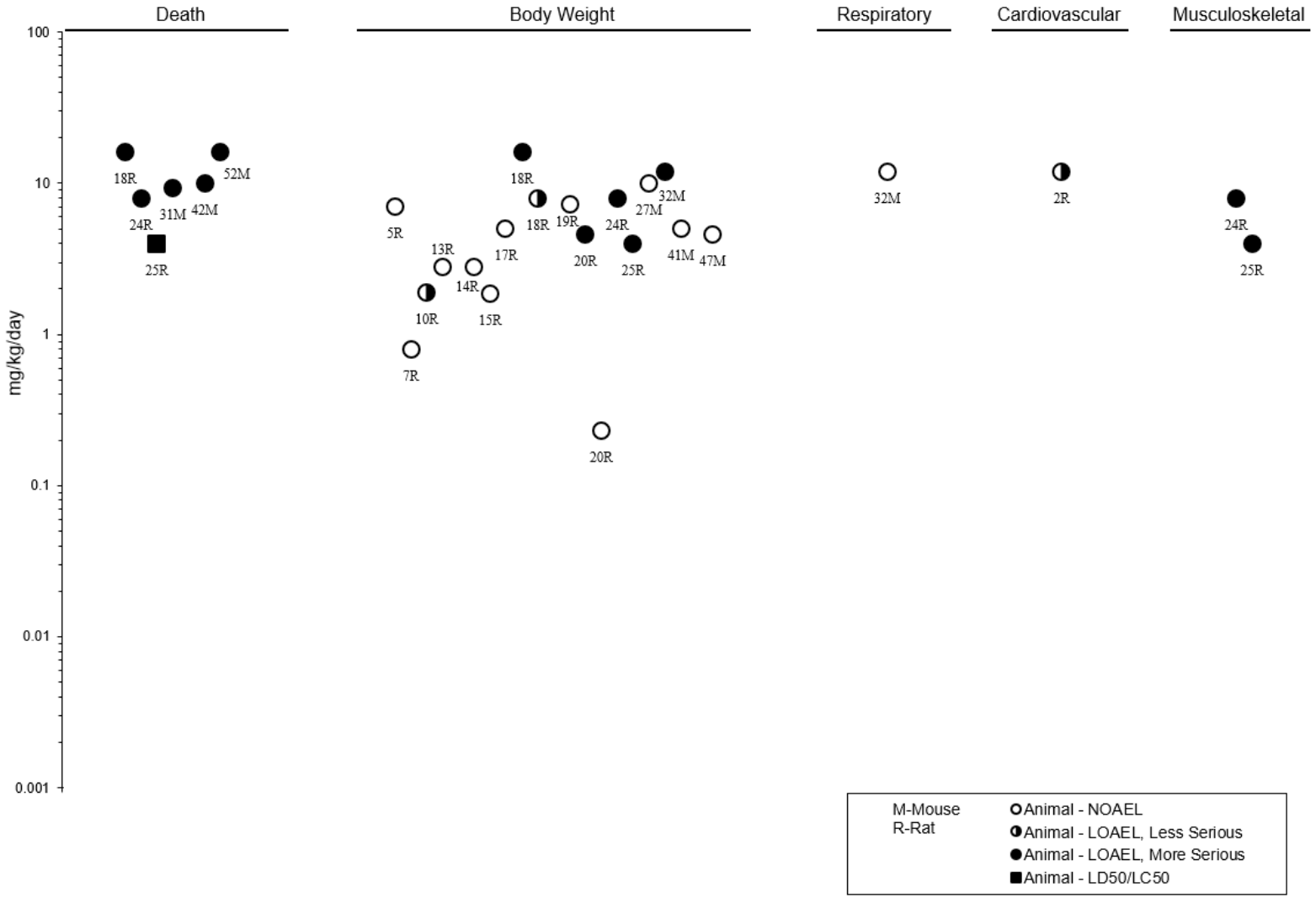


Figure 2-8. Levels of Significant Exposure to Organic Mercury – Oral
Acute (≤14 days)

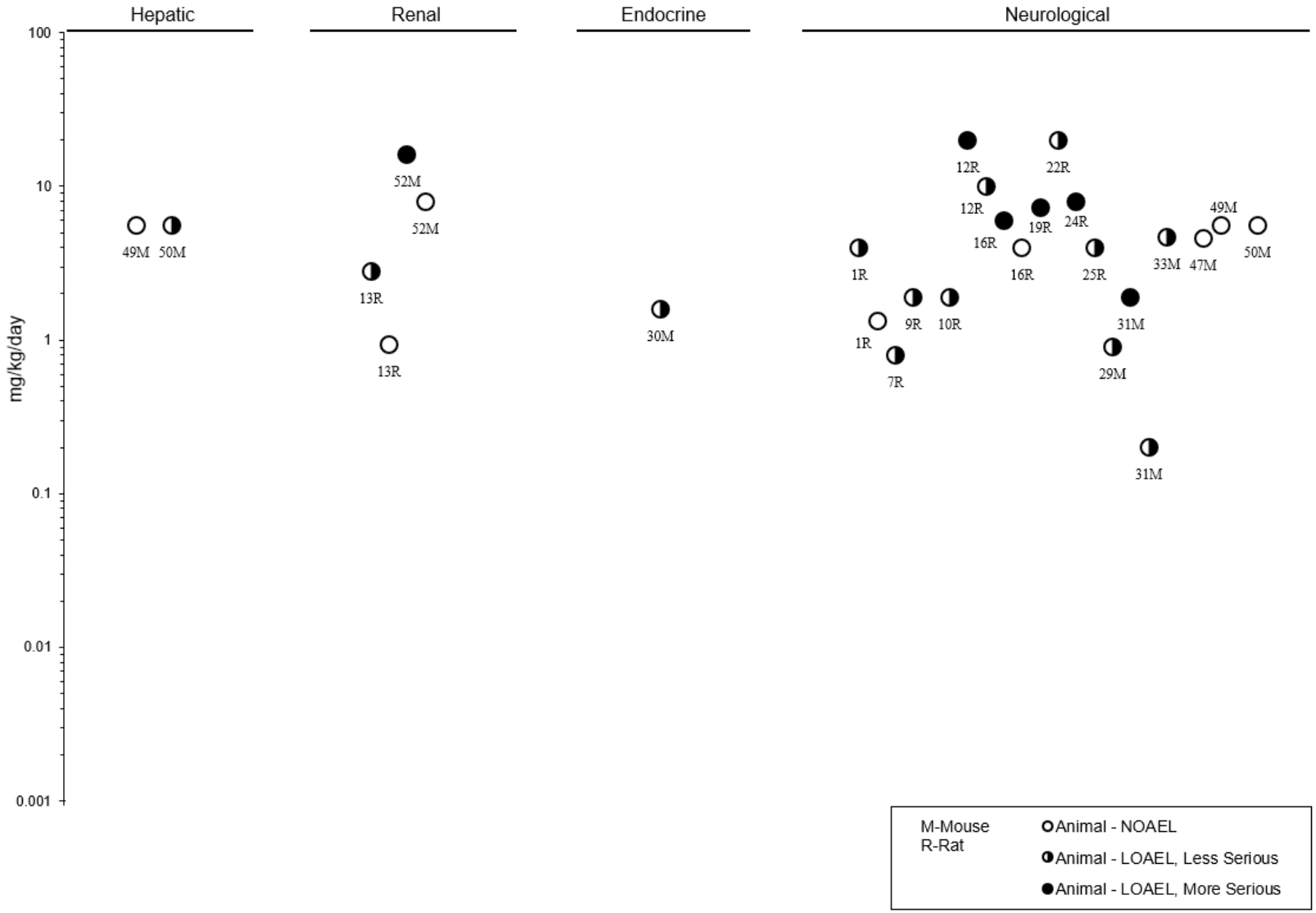


Figure 2-8. Levels of Significant Exposure to Organic Mercury – Oral
Acute (≤14 days)

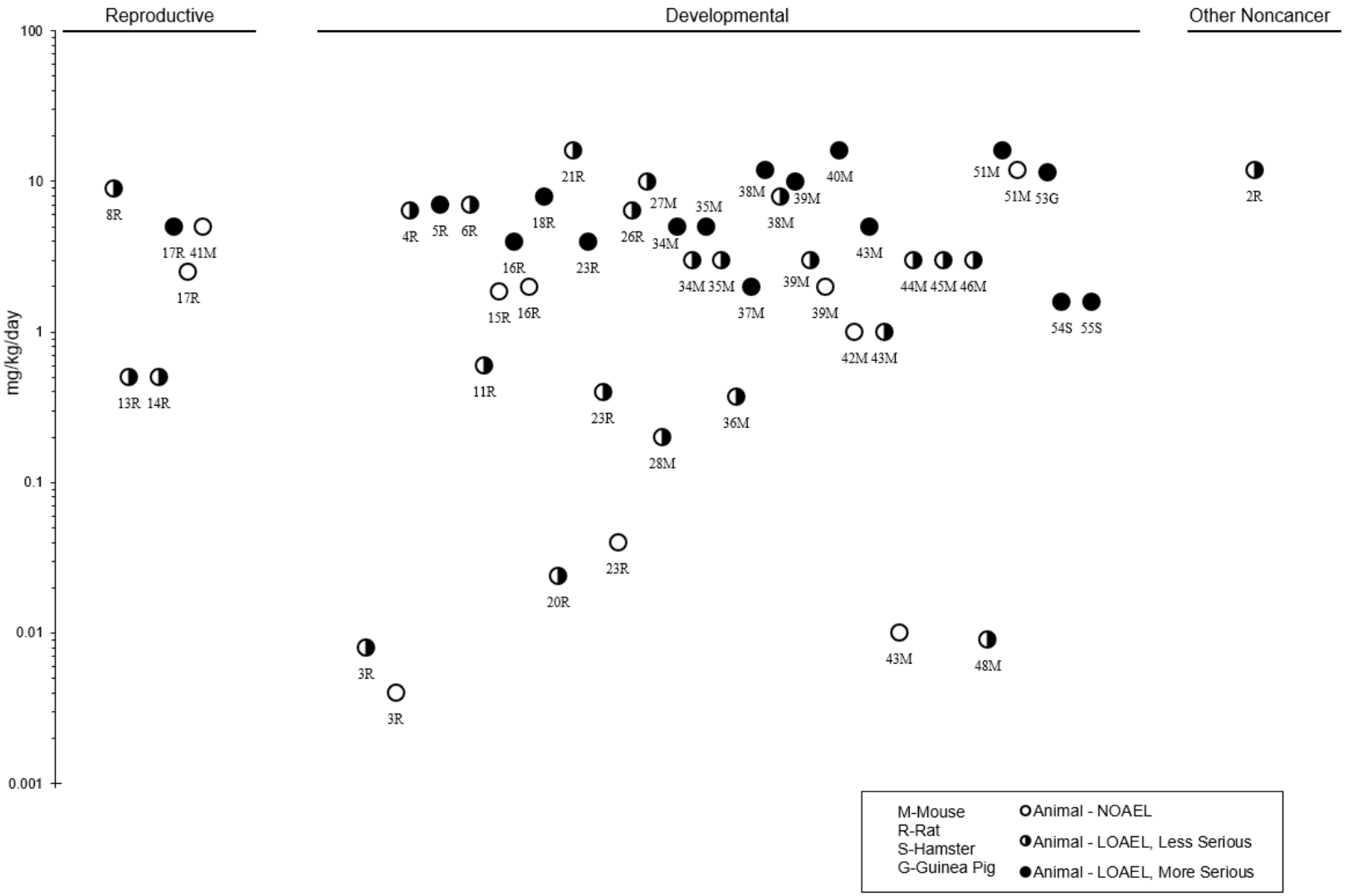


Figure 2-8. Levels of Significant Exposure to Organic Mercury – Oral
Intermediate (15–364 days)

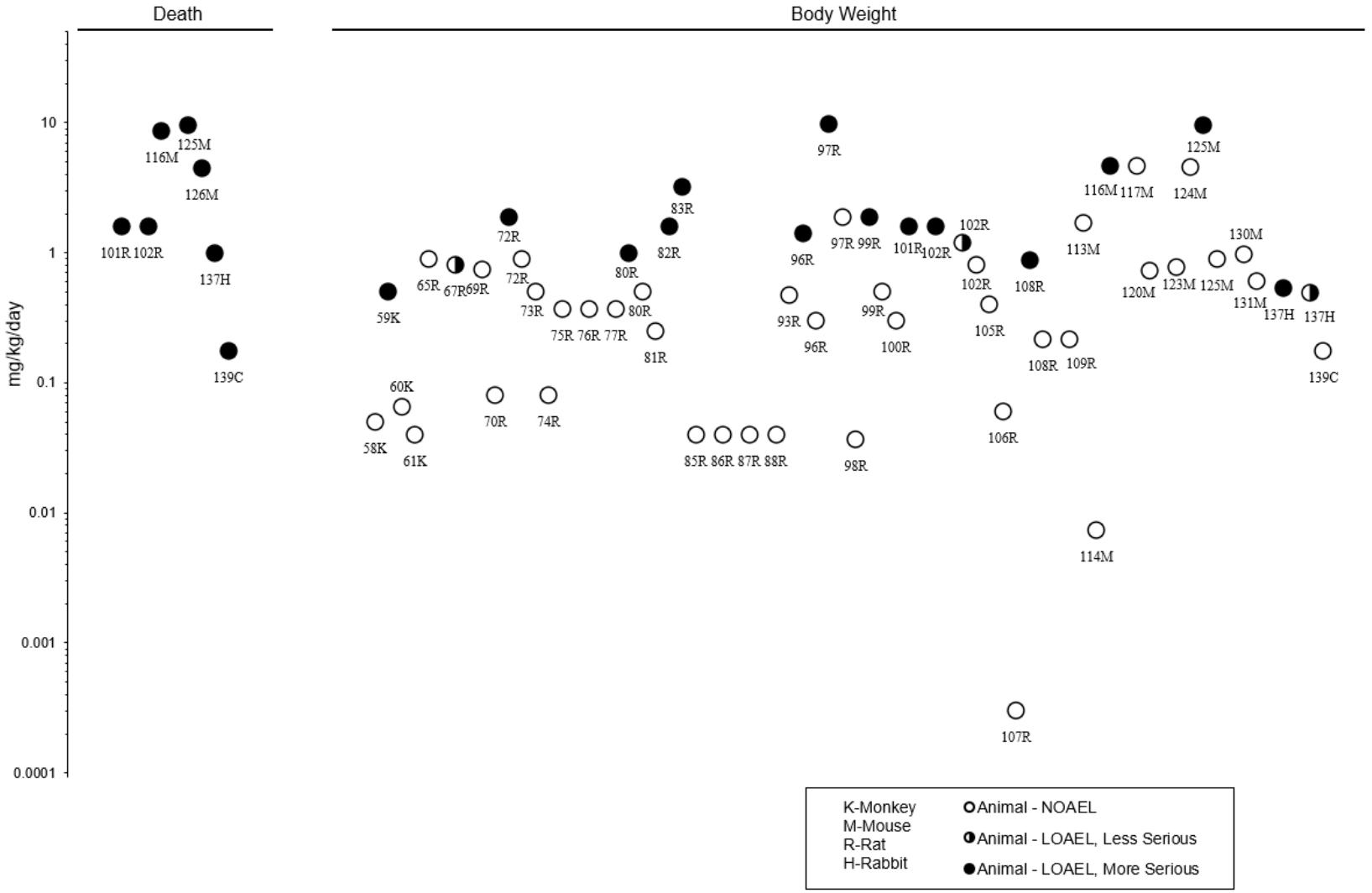


Figure 2-8. Levels of Significant Exposure to Organic Mercury – Oral
Intermediate (15–364 days)

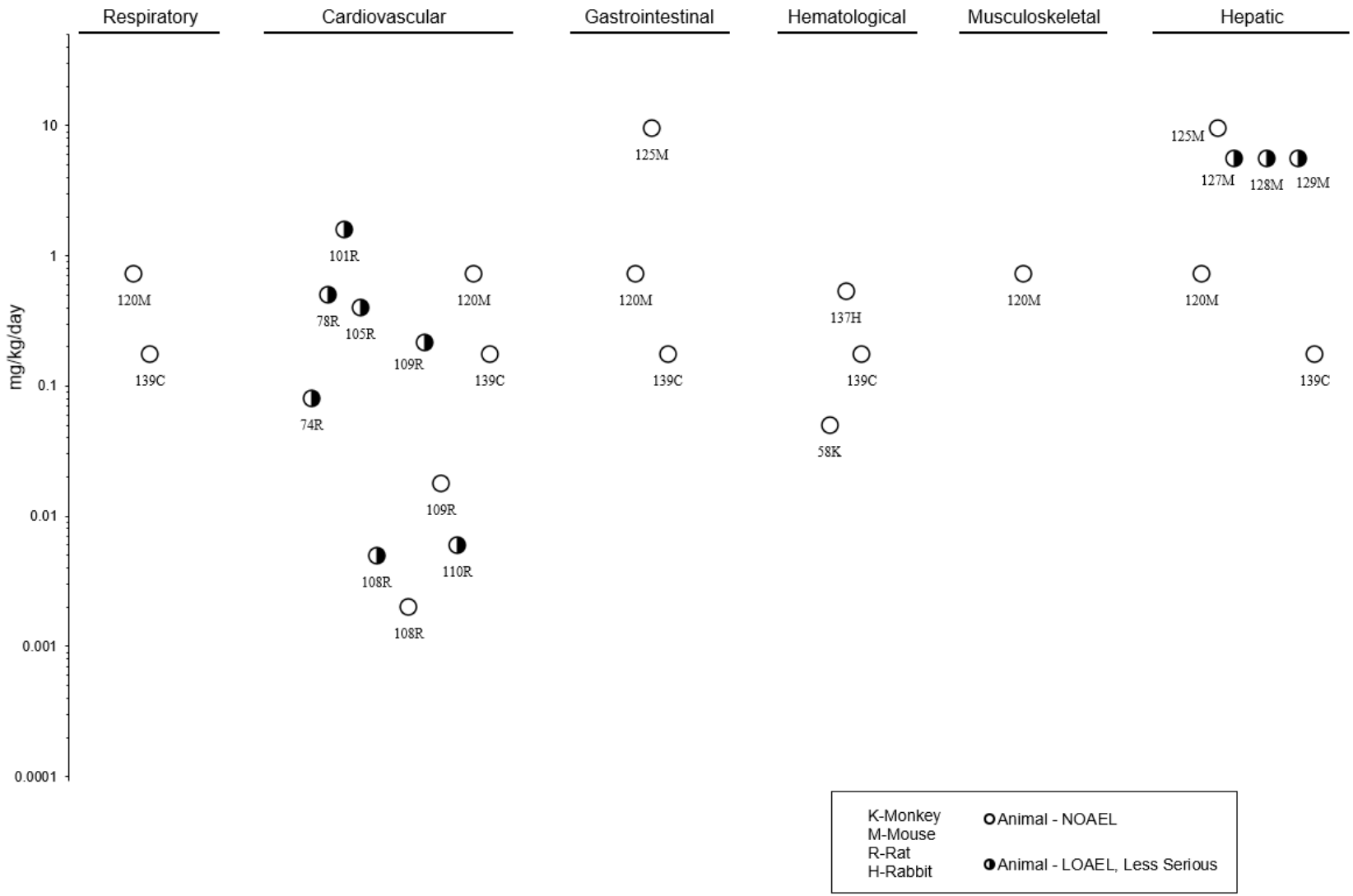


Figure 2-8. Levels of Significant Exposure to Organic Mercury – Oral
Intermediate (15–364 days)

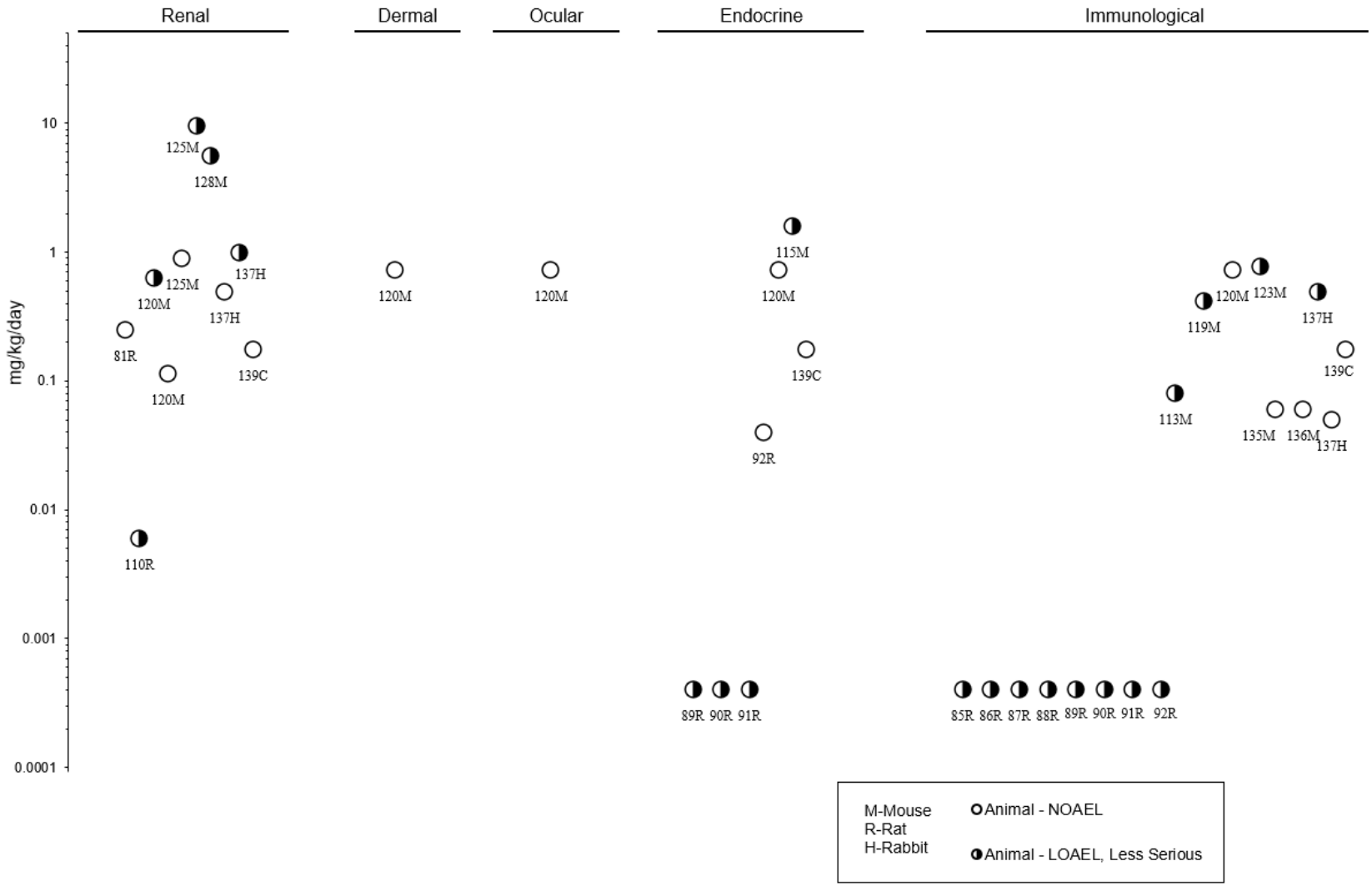


Figure 2-8. Levels of Significant Exposure to Organic Mercury – Oral
Intermediate (15–364 days)

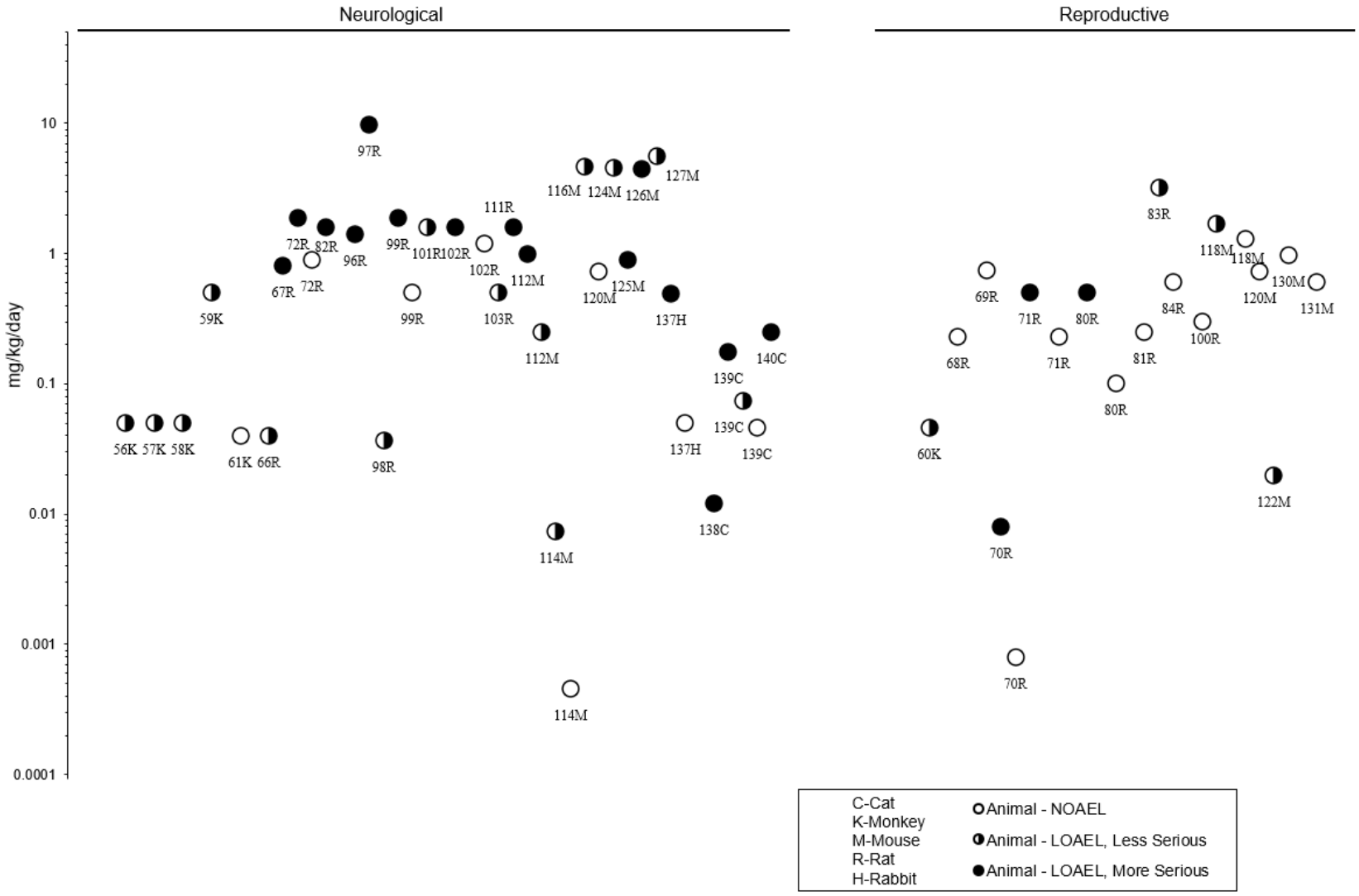


Figure 2-8. Levels of Significant Exposure to Organic Mercury – Oral
Intermediate (15–364 days)

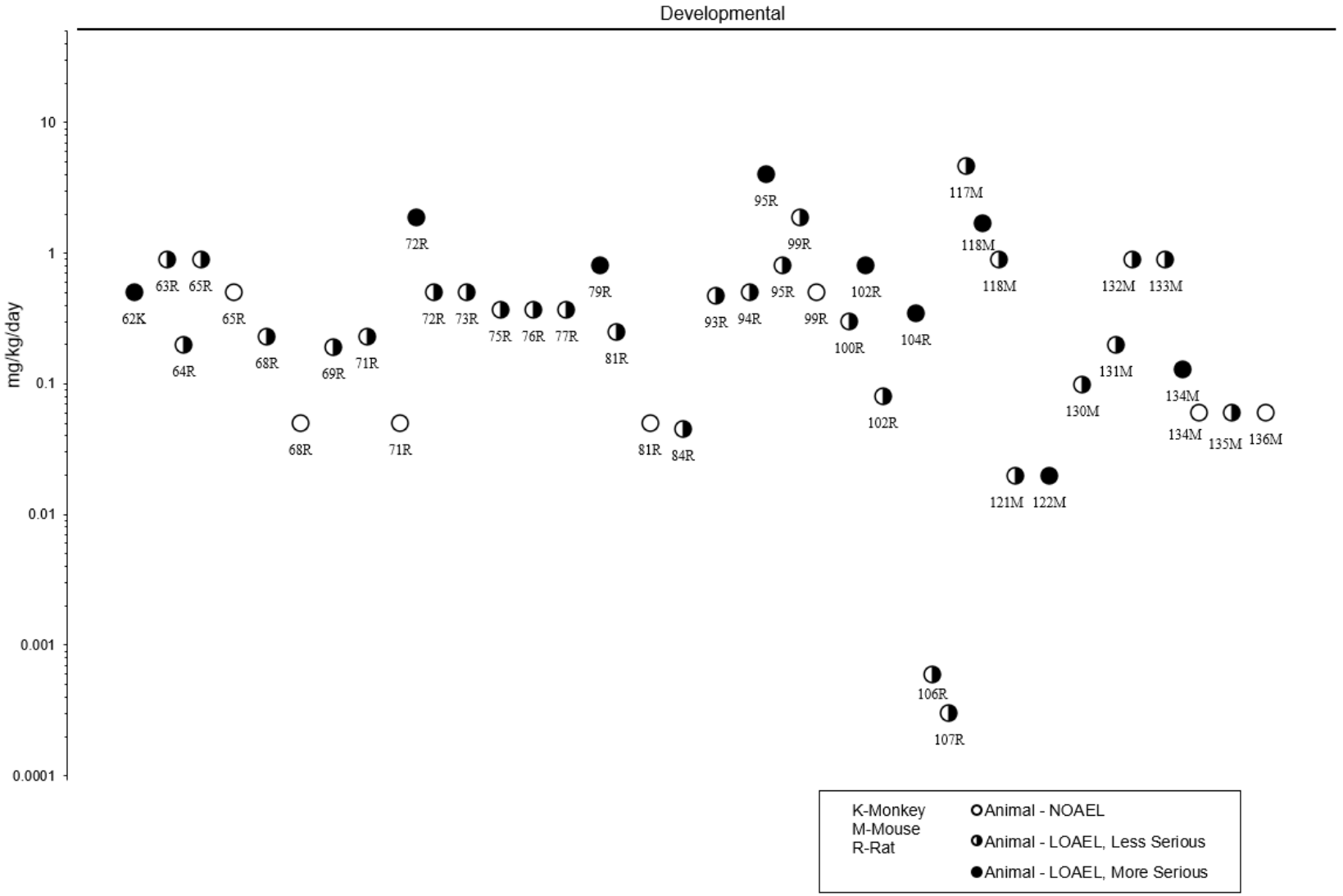


Figure 2-8. Levels of Significant Exposure to Organic Mercury – Oral
Chronic (≥365 days)

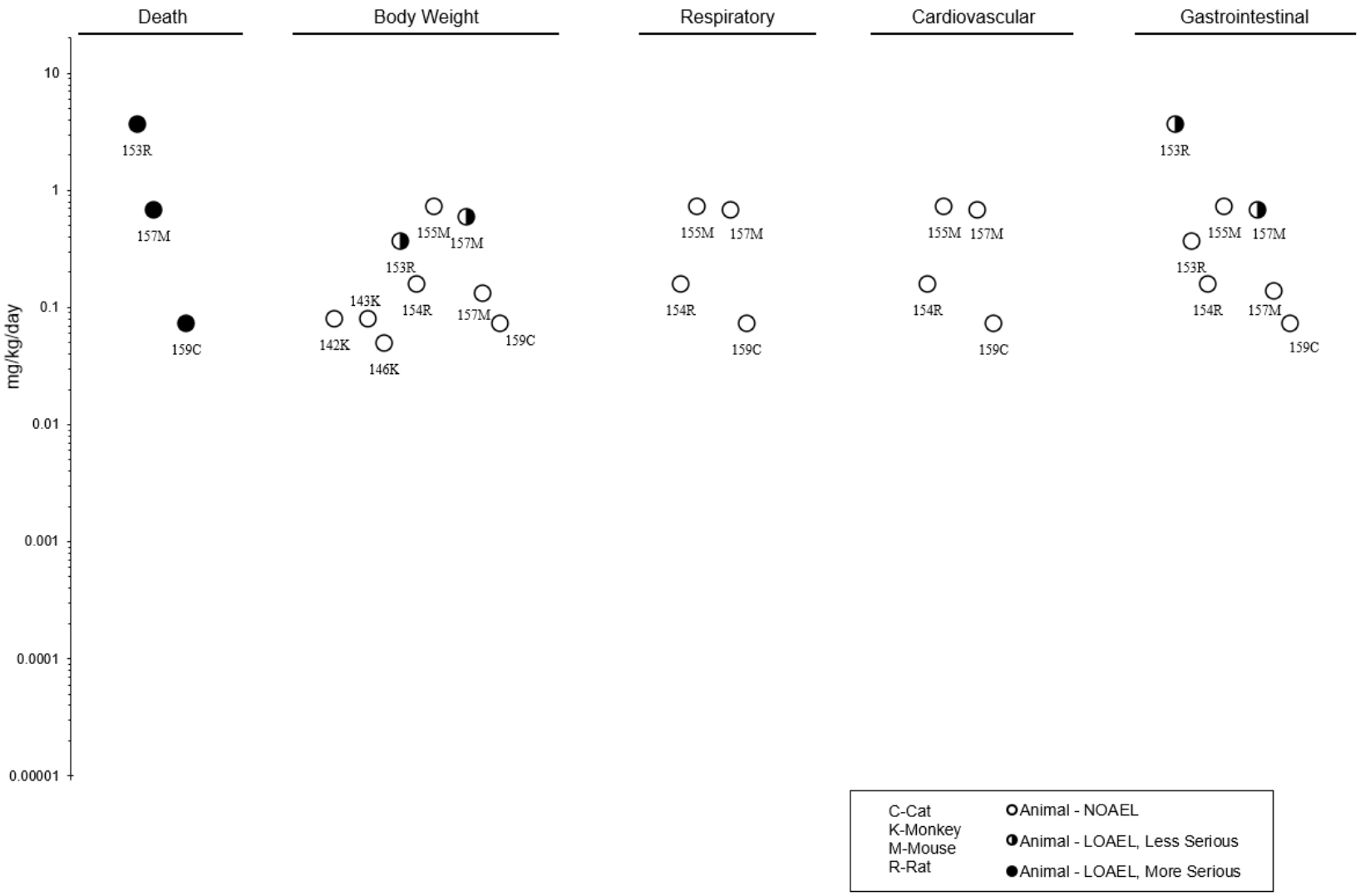


Figure 2-8. Levels of Significant Exposure to Organic Mercury – Oral
Chronic (≥365 days)

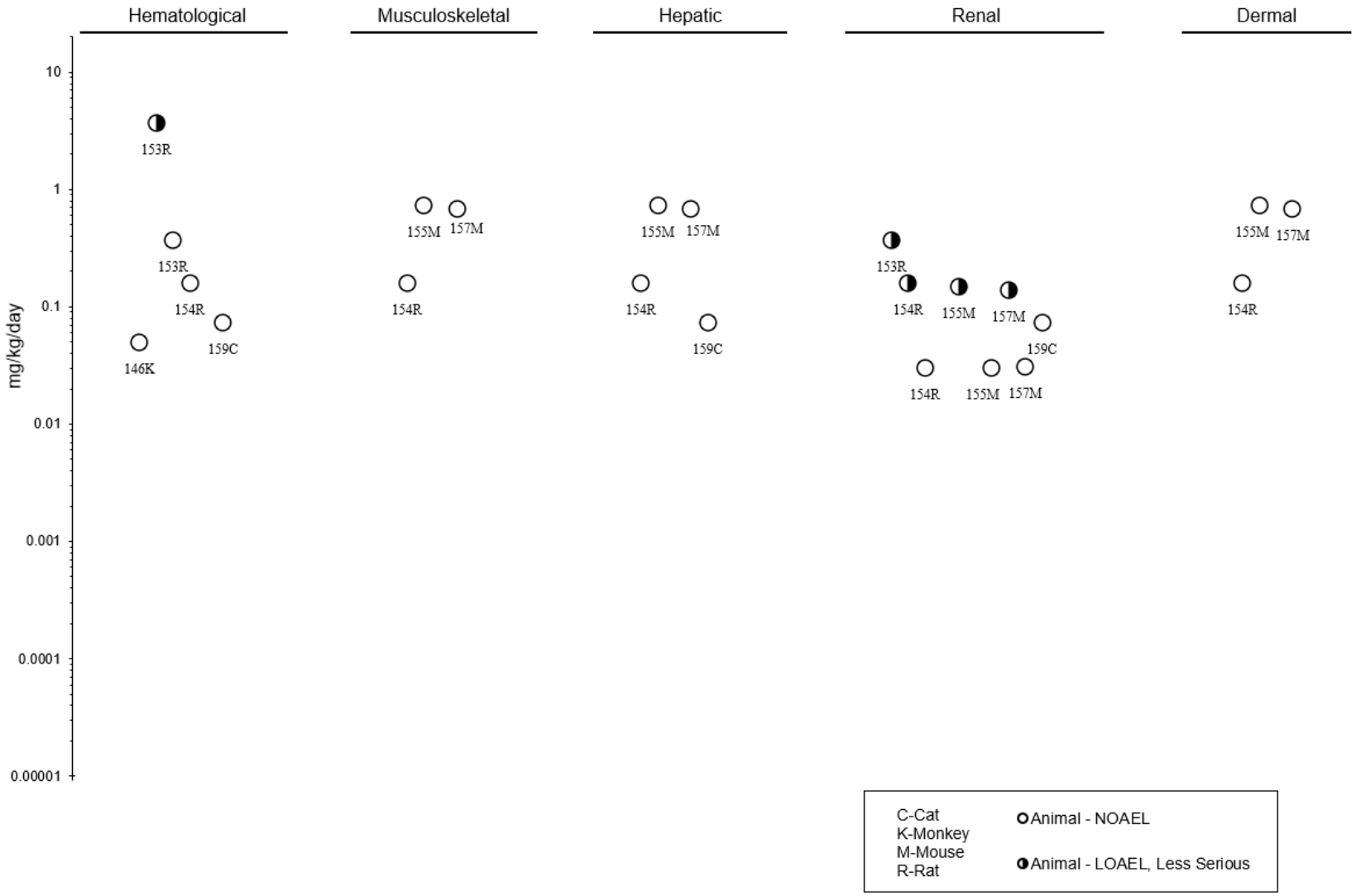


Figure 2-8. Levels of Significant Exposure to Organic Mercury – Oral
Chronic (≥365 days)

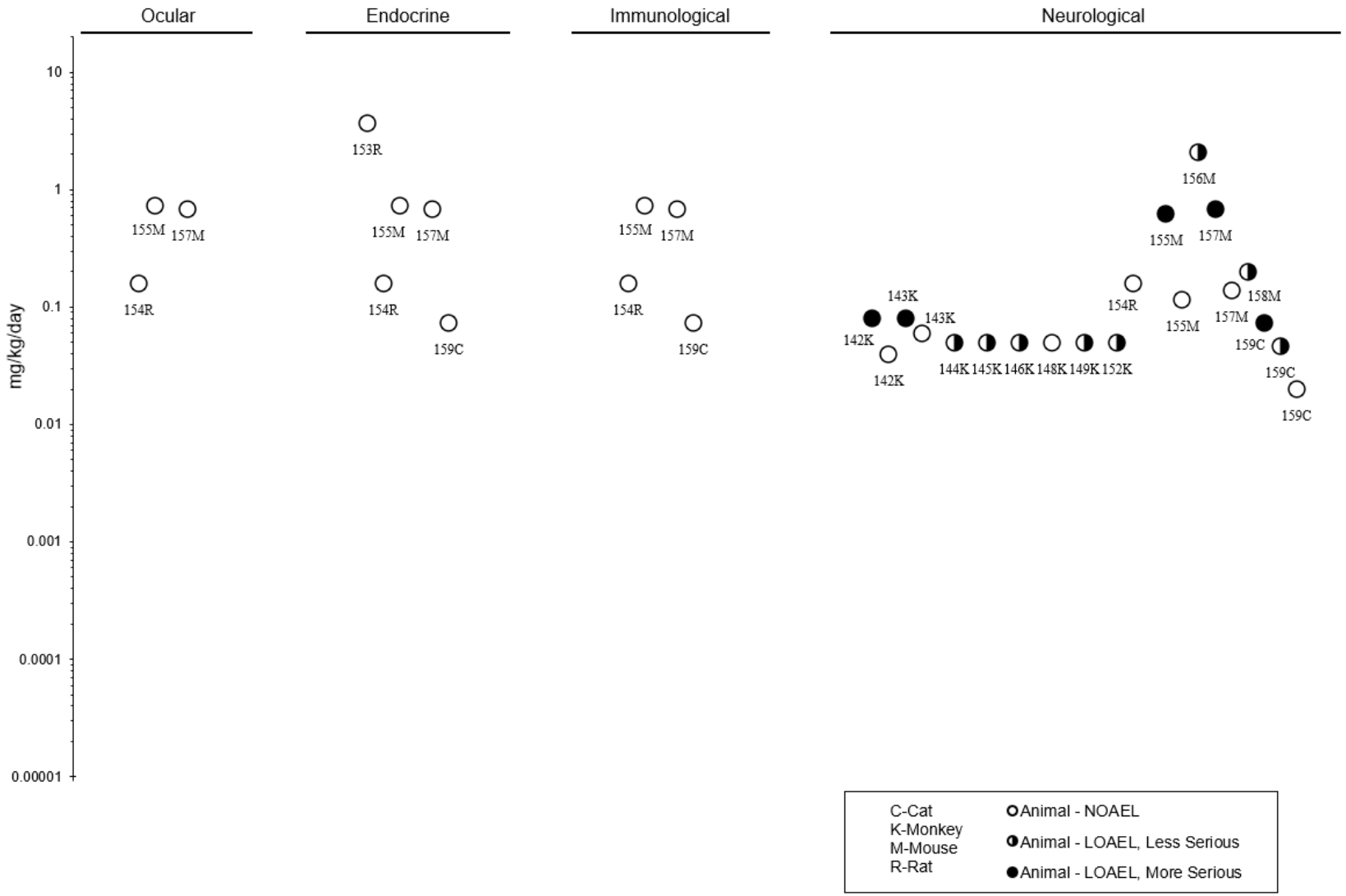
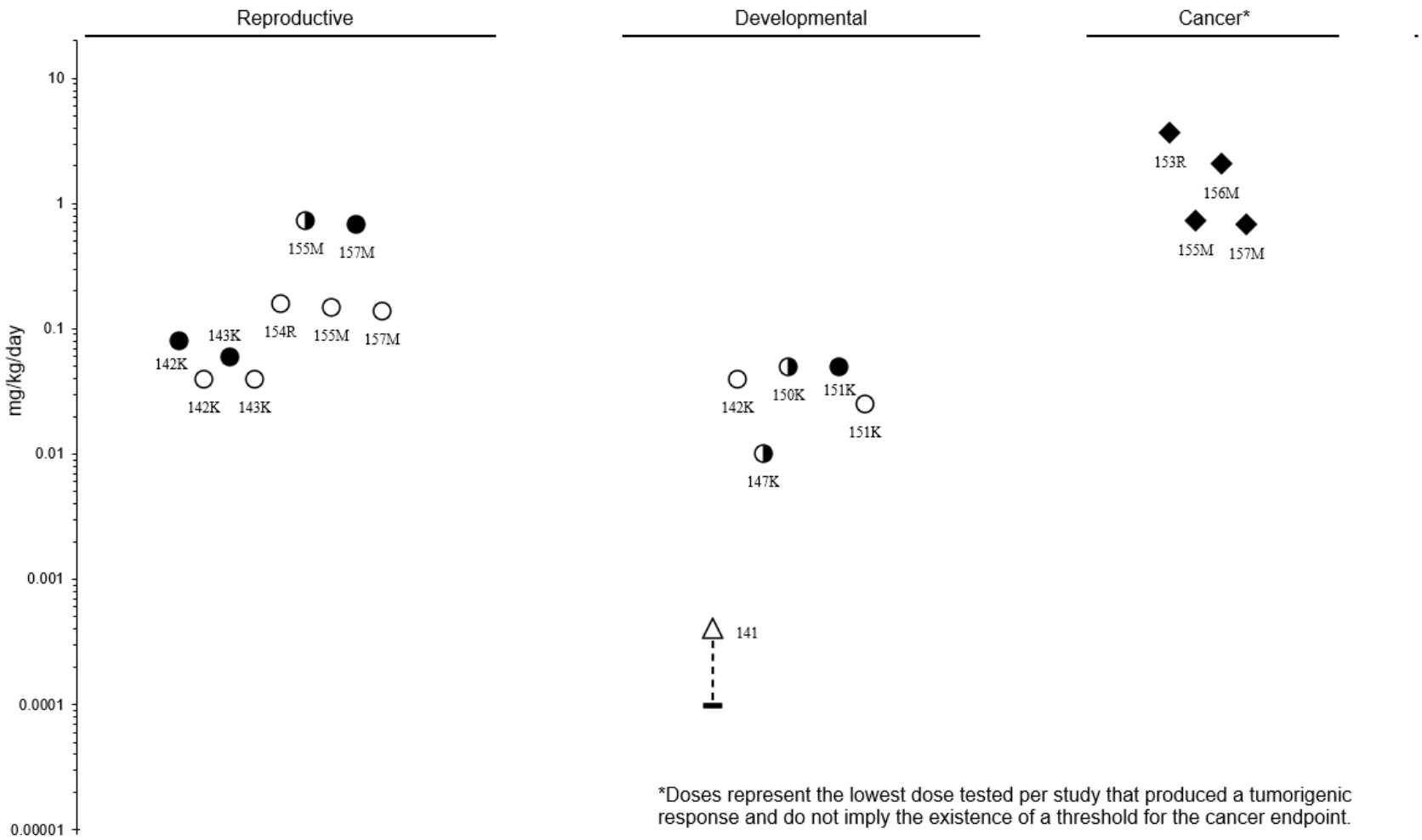


Figure 2-8. Levels of Significant Exposure to Organic Mercury – Oral
Chronic (≥365 days)



2.2 ACUTE POISONING IN HUMANS

Case reports of accidental or intentional poisonings provide information on acute-duration exposure effects in humans. These reports include acute-duration exposure poisonings from elemental mercury vapor, ingestion of mercuric chloride, and dermal exposure to dimethylmercury. In these cases, exposures are at near-lethal or lethal levels.

Elemental Mercury. Numerous cases of poisoning from acute-duration exposures to elemental mercury vapor have been reported. Symptoms of toxicity in lethal cases included chills, fever, dyspnea, headache, gastrointestinal disturbances (cramps, diarrhea), disturbances of hearing and vision, and pulmonary edema (Jung and Aaronson 1980; Kanluen and Gottlieb 1991; Rowens et al. 1991; Teng and Brennan 1959). Deaths were typically attributed to respiratory failure related to pulmonary edema.

Inorganic Mercuric Mercury. Numerous cases of poisoning from acute ingestion of mercuric chloride have been described. A review of 45 published cases of acute mercuric chloride poisoning indicated that the primary systems with symptoms were the gastrointestinal tract, kidney, and brain (Cappelletti et al. 2019). Gastrointestinal tract effects observed following acute poisoning have included abdominal pain, nausea, diarrhea, ulceration, and hemorrhages of the upper and lower tract. Kidney effects have included oliguria, proteinuria, hematuria, casts, nephritis, and acute renal failure; and, at autopsy, renal proximal tubular atrophy and glomerular pathology. Symptoms of neurological effects have included disturbances of vision and behavior and seizures; at autopsy, brain abscesses in the cerebrum have also been observed. In most cases of poisoning, the dose ingested was not known; however, for some cases, the dose was estimated to have been ≥1 g Hg (Cappelletti et al. 2019).

Organic Mercury. A lethal dose of dimethylmercury occurred following accidental contact to the dorsal surface of a latex gloved hand. The 48-year-old female chemistry professor reported the dose as “a few drops” of liquid dimethylmercury (Nierenberg et al. 1998; Siegler et al. 1999). Approximately 5 months after the exposure, the patient developed severe neurological symptoms that included deterioration of balance, gait and speech, paresthesia, and disturbances of vision and hearing (Nierenberg et al. 1998). The patient died 298 days following the exposure; autopsy revealed thinning of the cerebral cortex and atrophy of the cerebellum (Siegler et al. 1999). The applied dose was reconstructed based on measurements of blood mercury made approximately 5 months following the accident and the estimated half-time of 75 days for hair mercury in the subject (Nierenberg et al. 1998). The applied dose was

estimated to have been approximately 1,344 mg mercury contained in approximately 0.44 mL of liquid dimethylmercury (Nierenberg et al. 1998).

2.3 DEATH

Overview. Epidemiological studies evaluating associations between mercury exposure and specific causes of death are evaluated in subsequent sections of Chapter 2 when data are available (e.g., cardiovascular). This section reviews information on all-cause death or mortality (death not attributed to a specific underlying cause). Few epidemiological studies have assessed associations between mercury exposure and all-cause death. Most of the available studies did not provide biomarker data and did not adjust results for confounding factors. Available studies have evaluated all-cause death in workers exposed to elemental mercury, the Minamata population exposed to fish and shellfish with a high methylmercury content, the population in Iraq exposed to high levels of methylmercury in contaminated wheat, and general populations in Finland and Sweden. Studies show increases in all-cause death from exposure to methylmercury, but not for occupational exposures or in general populations.

Increased mortality in animals has been observed at high inhalation or oral exposure levels. Death following inhalation of high mercury vapor concentrations is associated with asphyxiation; no oral LC_{50} value is available. Oral LD_{50} values for mercuric chloride range from 25.9 to 77.7 mg Hg/kg/day, and death following chronic oral exposure is associated with renal nephropathy. Mortality following oral exposure to methylmercury at high doses is associated with overt neurotoxicity and/or renal nephropathy. Oral LD_{50} values for methylmercury are not available.

The following summarizes results of epidemiological and animal studies on mortality.

- ***Elemental mercury***
  - Few studies have evaluated all-cause mortality in workers exposed to elemental mercury. No increases in deaths in workers were observed. Biomarker data were not available.
  - *Animal studies*
    - Death due to asphyxiation has been reported following acute exposure to very high concentrations. No LC_{50} values were identified.
- ***Inorganic mercury salts***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to inorganic mercury salts and death were identified.

- *Animal studies*
  - Oral LD_{50} values for mercuric chloride in rats range from 25.9 to 77.7 mg Hg/kg/day.
  - Male rats are the most sensitive to lethal effects of mercuric chloride; with chronic duration, increased mortality is associated with increased severity of nephropathy.
  - Mercuric sulfide is not lethal to rats, mice, or guinea pigs at extremely high oral doses.

- ***Organic mercury***
  - Two long-term follow-up studies in populations with Minamata disease reported increases in all-cause mortality. Biomarker data are not available in this population.
  - All-cause death was elevated in the Iraq population exposed through methylmercury-contaminated wheat.
  - *Animal studies*
    - No LD_{50} values were identified.
    - Methylmercury is associated with increased mortality at high acute- and intermediate-duration doses associated with overt signs of neurotoxicity.
    - Following chronic exposure, male mice are the most sensitive to lethal effects of methylmercury. Increased mortality is associated with increased severity of nephropathy.
- ***Predominant mercury form unknown (general populations)***
  - Studies conducted in Finland and Sweden found inverse or no associations between mercury biomarkers and all-cause death.

Confounding Factors. Numerous factors can influence results of epidemiological studies evaluating associations between mercury exposure and mortality, including age, sex, body mass index (BMI), ethnicity, poverty level, education, alcohol consumption, smoking status, hypertension, diabetes, family history of diseases, activity level, total cholesterol, postmenopausal status, nutritional status, and co-exposure with other metals (i.e., arsenic or cadmium). Failure to account for these factors when they are associated with both mortality and exposure to mercury may reduce or strengthen the apparent associations between mercury exposure and the outcome.

Elemental Mercury—Epidemiological Studies. Few epidemiological studies have evaluated mortality due to all causes in workers exposed to elemental mercury, with the available studies showing no increases in all-cause death (Barregard et al. 1990; Cragle et al. 1984; Ellingsen et al. 1993). Cumulative exposure was reported in studies reporting an exposure metric. Extrapolation of these study results to other populations is highly uncertain due to reporting inadequacies and lack of adjustments for confounding factors.

Elemental Mercury—Animal Studies. Rats, guinea pigs, and mice died from severe pulmonary edema following a 24–48-hour exposure to an unspecified concentration of metallic mercury vapor resulting from spillage of mercury droplets on the floor of a static exposure chamber (Christensen et al. 1937). Death due to asphyxiation was reported in 20/32 rats exposed to 27.0 mg Hg/m^3 for 2 hours; all remaining animals died within 5 days of exposure (Livardjani et al. 1991). No deaths occurred in rats similarly exposed for 1 hour (Livardjani et al. 1991).

Inorganic Mercury Salts—Animal Studies. Oral LD_{50} values for mercuric chloride reported in female rats at 3, 6, 18, and 54 weeks of age are 77.7, 68.1, 37, and 37 mg Hg/kg/day, respectively. At 2 weeks of age, the oral LD_{50} in rats of unspecified sex was 25.9 mg Hg/kg/day (Kostial et al. 1978). However, in repeat-exposure studies, male rats appeared to be slightly more sensitive to the lethal effects of mercuric chloride, with 2/5 males and 0/5 females dying following gavage exposure to 15 mg Hg/kg/day for 4–5 days (NTP 1993). Mice showed slightly less toxicity, with no deaths at 14.8 mg Hg/kg, death in 1/5 males at 29 mg Hg/kg, and deaths in 5/5 males and 4/5 females at 59 mg Hg/kg when administered by gavage for up to 4 days (NTP 1993).

In intermediate-duration studies in rats and mice, no mortality was observed following exposure to gavage doses up to 4 or 15 mg Hg/kg/day, respectively (NTP 1993). Mortality was 100% in male rats exposed to mercuric chloride at drinking water doses of 5.91 mg Hg/kg/day for 4 weeks (Wildemann et al. 2015a). In a multigenerational study, 50% mortality was observed in F0 rat dams exposed to gavage doses of 1.98 mg Hg/kg/day for up to 81 days (Atkinson et al. 2001). Prior to death, rats showed signs of toxicity (e.g., significant decrease in body weight gain/weight loss, reduced food and water intake).

In a chronic gavage study, decreased survival until scheduled sacrifice was observed in male F344 rats exposed to 1.8 or 4 mg Hg/kg/day (21 or 10%, respectively), compared to controls (52%); increased mortality was associated with increased severity of nephropathy (Dieter et al. 1992; NTP 1993). Mortality was comparable to controls in similarly treated female rats. No effects on survival were observed in mice exposed to mercuric chloride at chronic-duration doses up to 7.4 mg Hg/kg/day, respectively (NTP 1993).

No exposure-related deaths following repeated oral exposure to mercuric sulfide at doses up to 860 mg Hg/kg/day in rats (Chuu et al. 2007), 1,700 mg Hg/kg/day in mice (Chuu et al. 2001a; Son et al. 2010), or 86 mg Hg/kg/day in guinea pigs (Chuu et al. 2001b).

Organic Mercury—Epidemiological Studies. Associations between methylmercury exposure and all-cause death in populations with high fish diets have been evaluated in long-term (≥20 years), follow-up studies in the Minamata population (Futatsuka et al. 2005; Tamashiro et al. 1985, 1986). Unfortunately, no biomarkers or adjustments for contributing factors were reported, limiting the interpretation of study results. Increased standardized mortality ratios (SMRs) for all-cause death were reported by Futatsuka et al. (2005) and Tamashiro et al. (1985). The Futatsuka et al. (2005) study, which evaluated 1,500 patients diagnosed with Minamata disease, reported SMRs ranging from 1.14 (95% CI 1.03, 1.26) to 1.27 (95% CI 1.15, 1.41), based on two different control groups. Tamashiro et al. (1985) evaluated 1,483 patients with Minamata disease; SMRs were 1.27 (95% CI 1.12, 1.44) in males and 1.30 (95% CI 1.10, 1.53) in females. In contrast, when not limiting deaths to patients with Minamata disease, this study did not find increased SMRs in a large population living in the Minamata area (n=36,782).

Information on mortality is available on the Iraq population exposed to methylmercury for approximately 3 months through widespread consumption of wheat that had been treated with a methylmercuric fungicide (Al-Mufti et al. 1976; Bakir et al. 1973; Clarkson et al. 1976). Based on measurements of methylmercury in flour used to bake contaminated bread and estimates of bread consumption, methylmercury intake was estimated to have ranged from 80 to 1,000 mg over a 3-month period (Al-Mufti et al. 1976). Approximately 6,500 cases of mercury poisoning occurred, with approximately 459 related deaths (Clarkson et al. 1976). Greenwood (1985) evaluated mortality by comparing death registries in the 2 years prior to exposure to death registries during exposure through 2 years after. Individuals were considered exposed if BHg >5 µg/g or HHg >5 µg/g. The number of deaths was significantly increased following exposure. The biggest increase in mortality (4-fold increase) was in age ranges 1–10 and 11–20 years. When limiting to 3 months after exposure cessation, there were no increase in deaths.

Organic Mercury—Animal Studies. No oral LD_{50} values were identified for organic mercury compounds; however, oral exposure has been associated with increased mortality at high doses.

In rats, a single exposure to 16 mg Hg/kg/day during gestation resulted in 17% maternal death (Lee and Han 1995). In repeat-dose studies, mortality was 41% in non-pregnant rats exposed to 8 mg Hg/kg/day for 10 days (Su et al. 1998) and 50% in male rats exposed to 4 mg Hg/kg/day for 12 days (Usuki et al. 1998). Furthermore, 100% mortality was observed in SHR/NCrj rats (spontaneously hypertensive strain) exposed to 1.6 mg Hg/kg/day for 26 days (Tamashiro et al. 1986), and 45% in pregnant rats exposed to

1.6 mg Hg/k/day during pregnancy and lactation (Tonk et al. 2010). Mortality in acute- and intermediate-duration studies was preceded by severe body weight effects and/or clinical signs of neurotoxicity. Mortality was comparable to controls in rats following chronic exposure to methylmercury at doses up to 0.18 mg Hg/kg/day (Verschuuren et al. 1976). A chronic study with phenylmercuric acetate reported a 50% increase in mortality associated with renal nephrosis in male rats at 3.7 mg Hg/kg/day (females not evaluated); no changes in survival were observed at doses up to 0.37 mg Hg/kg/day (Solecki et al. 1991).

In mice, a single oral dose exposure to methylmercury at 16 mg Hg/kg resulted in the death of 4/6 males but no deaths in females (Yasutake et al. 1991). No increase in mortality was observed in female mice until 40 mg Hg/kg was administered, at which dosage 4/6 females died (and 6/6 males died). Increased death in males was associated with impaired renal function. In other mouse studies, 100% mortality was observed in mice following acute exposure to ≥9.3 mg Hg/kg/day (Chuu et al. 2001a; Khera and Tabacova 1973) and or intermediate-duration exposure to ≥8.7 mg Hg/kg/day (Dietrich et al. 2005; MacDonald and Harbison 1977). Intermediate-duration doses of 4.5 mg Hg/kg/day were associated with 85 and 98% mortality in male and female mice, respectively (Mitsumori et al. 1981). Moderate-to-severe signs of clinical neurotoxicity were observed prior to death in the intermediate-duration studies. One chronic-duration study reported a 31% increase in male B6C3F1 mouse mortality at dietary doses of 0.686 mg Hg/kg/day (Mitsumori et al. 1990), but another chronic study reported survival comparable to controls in male ICR mice at dietary doses up to 0.724 mg Hg/kg/day (Hirano et al. 1986); both studies reported increased renal nephropathy and tumors in male mice. Female mouse survival in chronic dietary studies was comparable to controls in both studies at doses up to 0.627 mg Hg/kg/day (Hirano et al. 1986; Mitsumori et al. 1990).

In a study designed to evaluate immune function, 80% of rabbits exposed to 1 mg Hg/kg/day died within 4 weeks of exposure (prior to influenza inoculation); the remaining 20% of rabbits died between 4 and 12 weeks of exposure (post-inoculation) (Koller et al. 1977). As observed in rodents, body weight effects and severe neurotoxicity preceded death; however, deaths post-inoculation may be attributed (in part) to decreased immune response to influenza infection.

In a chronic study in cats, all animals exposed to 0.074 or 0.176 mg Hg/kg/day were sacrificed early due to overt signs of neurotoxicity after approximately 16 and 55 weeks of exposure, respectively (Charbonneau et al. 1976). One animal was similarly sacrificed at 0.046 mg Hg/kg/day after 38 weeks of exposure; the remaining animals in this group survived to terminal sacrifice.

Predominant Mercury Form Unknown (General Populations). Few studies of all-cause mortality in general populations exposed to mercury are available. Two prospective studies evaluated associations between mercury biomarkers and all-cause death in general populations of Finland and Sweden (Ahlqwist et al. 1999; Virtanen et al. 2005). Study results are summarized in Table 2-5. In men, no associations were observed between HHg and all-cause mortality (Virtanen et al. 2005). In women, an inverse relationship (increased death with decreasing SHg) was observed between SHg and all-cause death.

Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Mercury (Predominant Mercury Form Unknown) and Death in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Ahlqwist et al. 1999 Prospective; 1,397 women (ages 38–60 years at baseline in 1968–1969), followed for approximately 24 years 1974–1975, 1980–1981, and 1992–1993) (Sweden)	SHg mean: 17.0 µg/L	All-cause death	↓ (SHg)
Virtanen et al. 2005 Prospective; 1,871 men (42–60 years of age at baseline), followed for approximately 14 years (Finland)	HHg <2.03 µg/g ≥2.03 µg/g	All-cause death	0 (HHg, <2.03 µg/g) 0 (HHg, ≥2.03 µg/g)

↓ = inverse association; 0 = no association; HHg = hair mercury; SHg = serum mercury

Mechanisms of Action. Mortality is likely the result of effects on multiple organ systems.

2.4 BODY WEIGHT

Overview. Few epidemiological studies have evaluated effects of mercury on body weight. In humans, data are limited to studies of general populations, with no epidemiological studies identified for elemental mercury or in populations with high fish diets. Studies in general populations were conducted in children, adolescents, and adults. Positive associations were observed between mercury exposure and body weight outcomes in adults; findings were inconsistent in children and adolescents.

Body weight is a well-studied endpoint in animals following inhalation and oral exposure. Body weight effects have been noted following inhalation exposure to elemental mercury and oral exposure to

inorganic salts and organic mercury compounds. However, available data do not indicate that body weight is a sensitive effect of mercury toxicity since adverse effects are observed at exposure levels an order of magnitude higher than those associated with the most sensitive effects associated with exposure via the same route and duration. Following oral exposure to inorganic mercury salts or organic mercury, rats are more sensitive than mice. Limited data indicate that monkeys and rabbits may be more sensitive than rodents following oral exposure to organic mercury. It is not known whether there are more sensitive animals than rats following inhalation exposure, as rats are the only species that evaluated body weight via the inhalation route.

The following summarizes results of epidemiological and animal studies on body weight outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to elemental mercury and body weight were identified.
  - *Animal studies*
    - Body weight effects were reported in rats following acute- or intermediate-duration exposures ≥4 or 0.48 mg Hg/m^3, respectively.
    - Body weight data are not available in other species.
- ***Inorganic mercury salts***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to inorganic mercury salts and body weight were identified.
  - *Animal studies*
    - Body weight effects were consistently reported in rats at intermediate- or chronic-duration exposures ≥1.5 mg Hg/kg/day via gavage or drinking water, with inconsistent evidence for body weight effects at lower doses. In general, higher dietary doses were required to cause body weight effects.
    - Body weight effects in mice were only observed at high oral doses in males (>10 mg Hg/kg/day).
- ***Organic mercury***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to methylmercury in populations with high fish diets and body weight were identified.

- *Animal studies*
  - Decreases in body weight gain were observed in monkeys and rabbits after intermediate-duration exposure to ≥0.49 mg Hg/kg/day.
  - In rodents, body weight effects were noted in rats at acute-, intermediate-, and chronic-duration exposures ≥1.9, 0.8, and 0.37 mg Hg/kg/day, respectively. Mice are less sensitive, with body weight effects at acute-, intermediate-, and chronic-duration exposures ≥12, 4.7, and 0.6 mg Hg/kg/day, respectively.
- ***Predominant mercury form unknown (general populations)***
  - Epidemiological studies in adults reported positive associations between mercury exposure of general populations and body weight outcomes, including BMI, percent body fat, visceral adipose tissue, waist circumference, and overweight; however, data are limited.

Results of studies in children and adolescents are inconsistent, with one study reporting no associations between mercury exposure and body weight measures at low SHg, one study reporting positive associations at higher BHg, and one study reporting inverse associations in girls, but not in boys, at higher BHg.

Confounding Factors. Numerous factors contribute to body weight (or BMI), including age, sex, race, nutrition, diet, daily activity level, intercurrent illness, genetic pre-disposition for body type, income level, education, and alcohol and tobacco use. Failure to account for these factors when they are associated with both body weight and exposure may reduce or strengthen the apparent associations between mercury exposure and the outcome.

Elemental Mercury—Epidemiological Studies. No epidemiological studies evaluating associations between exposure to elemental mercury and body weight were identified.

Elemental Mercury—Animal Studies. Body weight effects have been reported in rats following acute exposure to high concentrations. Male rats exposed to a lethal concentration of 27.0 mg Hg/m^3 for 2 hours showed body weight loss; no body weight effects were noted in rats similarly exposed for 1 hour (Livardjani et al. 1991). Maternal body weight loss was observed in rat dams exposed to 8 mg Hg/m^3 on gestation days (GDs) 6–10 or 6–15 (Morgan et al. 2002). At lower exposure levels, maternal body weight was decreased approximately 10–20% from GD 13 to postnatal day (PND) 3 in dams exposed to 4 mg Hg/m^3 on GDs 6–15, but not GDs 6–10 (Morgan et al. 2002). No changes in maternal body weight were

observed in rat dams following gestational exposure to concentrations ≤8 mg Hg/m^3 for 1 day or ≤4 mg Hg/m^3 for 3–10 days (Danielsson et al. 1993; Fredriksson et al. 1996; Morgan et al. 2002). In non-pregnant female rats, a 17% decrease in body weight was observed following intermittent exposure to 4 mg Hg/m^3 for 11 days (Davis et al. 2001).

In intermediate-duration studies, a 17% decrease in body weight gain was observed in male rats intermittently exposed to 0.05 mg Hg/m^3 for 8 weeks (Sørensen et al. 2000) and body weight loss was observed in male rats intermittently exposed to 3 mg Hg/kg/day for 12–42 weeks (Kishi et al. 1978).

Inorganic Mercury Salts—Animal Studies. Body weight effects were not observed in rats exposed to mercuric chloride at gavage doses up to 9.24 mg Hg/kg/day for 1 day (Lecavalier et al. 1994) or 0.7 mg Hg/kg/day for 7–14 days (Chang and Hartmann 1972a). In intermediate- and chronic-duration studies, body weight and/or body weight gain decreases ≥10% were reported in rats exposed to mercuric chloride at doses ≥1.5 mg Hg/kg/day via gavage or drinking water, with serious decreases (≥20%) at intermediate- and chronic-duration doses ≥5.91 and 4 mg Hg/kg/day, respectively (Heath et al. 2012; NTP 1993; Perry and Erlanger 1974; Wildemann et al. 2015a). There is inconsistent evidence for body weight effects in rats at lower gavage and drinking water doses, including decreased body weight in female F344 rats exposed to ≥0.462 mg Hg/kg/day for 6 months (NTP 1993), F0 and F1 male Sprague-Dawley rats exposed to 1.31 or ≥0.37 mg Hg/kg/day, respectively, in a 2-generation study (Atkinson et al. 2001), and male Holtzman rats exposed to 0.7 mg Hg/kg/day for 11 weeks (Chang and Hartmann 1972a). Other studies reported no body weight effects in female Long-Evans rats exposed to 9.4 mg Hg/kg/day via gavage for 40 days (Goldman and Blackburn 1979), female Sprague-Dawley rats exposed to 1.5 mg Hg/kg/day for 60 days (Heath et al. 2009), or male Wistar rats exposed to intermediate-duration gavage or drinking water doses up to 0.4 mg Hg/kg/day (Agrawal et al. 2014; Teixeira et al. 2018, 2019; Wildemann et al. 2015b).

Body weight effects data in rats following intermediate-duration dietary exposure to mercuric chloride suggest differences between strains and sexes. In Sprague-Dawley rats, final body weight decreases of 37% were observed in females at 2.2 mg Hg/kg/day (Goldman and Blackburn 1979). In Wistar rats, body weight decreases >20% were observed in males at ≥11.4 mg Hg/kg/day and in females at 23.6 mg Hg/kg/day; no body weight effects were observed in Wistar rats at dietary doses up to 5.8 mg Hg/kg/day (Goldman and Blackburn 1979; Jonker et al. 1993; Takahashi et al. 2000a, 2000b).

In pregnant Wistar rats, no maternal body weight effects were noted following drinking water exposure to 0.6 mg Hg/kg/day for 1 week prior to mating through PND 21 (Szász et al. 2002). In a 2-generation study in Sprague-Dawley rats, transient body weight decreases up to approximately 21% during gestation were observed in F0 females at gavage doses ≥1.11 mg Hg/kg/day (Atkinson et al. 2001).

Body weight effects in mice orally exposed to mercuric chloride were limited to males exposed to high doses. Body weight decreases of 12–14% were reported in male mice following intermediate-duration exposure to gavage doses of 15 mg Hg/kg/day (NTP 1993) or drinking water doses of 11 mg Hg/kg/day (Dieter et al. 1983). No body weight effects were observed in mice exposed to gavage doses up to 30 mg Hg/kg/day for 16 days, 6 mg Hg/kg/day for 4 weeks, or 1.7 mg Hg/kg/day for up to 2 years (NTP 1993; Sin and Teh 1992). In a 1-generation study, no body weight effects were noted in F0 male or female rats at gavage doses up to 0.74 mg Hg/kg/day (Khan et al. 2004).

Gavage exposure to mercuric sulfide was not associated with body weight effects in rats exposed to 860 mg Hg/kg/day for 14 days (Chuu et al. 2007) or mice exposed to doses up to 1,700 mg Hg/kg/day for 28 days (Son et al. 2010).

Organic Mercury—Epidemiological Studies. No epidemiological studies evaluating associations between exposure to methylmercury in populations with high fish diets and body weight were identified.

Organic Mercury—Animal Studies. In primates, body weight loss was observed in marmoset monkeys exposed to methylmercury at 0.5 mg Hg/kg/day for up to 242 days (Eto et al. 2001). In macaque monkeys, no body weight effects were observed after intermediate- or chronic-duration exposure to methylmercury at doses up to 0.08 mg Hg/kg/day (Burbacher and Mottet 1988; Burbacher et al. 1984, 2005; Mohamed et al. 1987; Petruccioli and Turillazzi 1991).

In acute oral studies in rats, body weight effects were not noted in any strain exposed to methylmercury at doses up to 1 mg Hg/kg/day (Chang and Hartmann 1972a; Fossato da Silva et al. 2011, 2012; Khera 1973). Findings following methylmercury exposure at higher doses were inconsistent and differed between rat strains. In Sprague-Dawley rats, body weight decreases of approximately 10% were noted after a 14-day exposure to 1.9 mg Hg/kg/day (Chuu et al. 2007) and body weight loss was observed after a 10-day exposure to 8 mg Hg/kg/day (Su et al. 1998). In Wistar rats, a 37% decrease in body weight was observed after a 12-day exposure to 4 mg Hg/kg/day (Usuki et al. 1998); however, no body weight effects were observed after exposure to doses up to 5 mg Hg/kg/day for 7 days (Khera 1973) or 2.8 mg

Hg/kg/day for 14 days (Fossato da Silva et al. 2011, 2012). No body weight effects were observed in Wistar rats exposed to methylmercuric sulfide at doses up to 7 mg Hg/kg/day for 10 days (Miyakawa et al. 1974).

Thirteen intermediate-duration studies reported no exposure-related body weight effects in rats exposed to methylmercury compounds at doses up to 0.5 mg Hg/kg/day (see LSE Table 2-4 for references). With the exception of one study reporting no body weight effects following exposure to 1.9 mg Hg/kg/day for 5 weeks (Sakamoto et al. 2017), serious decreases in body weight or body weight gain (>20%) or body weight loss were consistently reported in all rat strains tested at intermediate-duration oral methylmercury doses ≥0.8 mg Hg/kg/day (Chang and Hartmann 1972a; Khera 1973; Larsen and Brændgaard 1995; Moussa et al. 2010; Sakamoto et al. 2017; Schiønning et al. 1998a; Tamashiro et al. 1986; Wildemann et al. 2015a). In chronic-duration studies, exposure to phenylmercuric acetate at doses of 0.37 mg Hg/kg/day resulted in an approximate 10% decrease in final body weight in male rats (Solecki et al. 1991); no body weight effects were noted in male or female rats chronically exposed to methyl mercuric chloride at doses up to 0.16 or 0.18 mg Hg/kg/day, respectively (Verschuuren et al. 1976).

In maternal rats, single methylmercury exposures during gestation were associated with body weight effects at doses ≥8 mg Hg/kg/day (Lee and Han 1995), but not 7 mg Hg/kg/day (Carratu et al. 2006). Following a 9-day exposure during gestation, a 55% decrease in maternal body weight gain was observed in rats exposed to 4.6 mg Hg/kg/day; no changes were observed in similarly exposed dams at 0.23 mg Hg/kg/day (Nolen et al. 1972). No maternal body weight effects were observed following exposure to doses up to 1.9 mg Hg/kg/day for 4 days during gestation (Fredriksson et al. 1996). Following intermediate-duration exposure during premating, gestation, and/or lactation periods, maternal body weight and/or body weight gain decreases ≥10% were observed at 1.2 mg Hg/kg/day with serious decreases (≥20%) at ≥1.6 mg Hg/kg/day (Gandhi et al. 2013; Tonk et al. 2010). Sitarek and Gralewicz (2009) also report a 30–40% decrease in maternal body weight after gestational and lactational exposure to 1.9 mg Hg/kg/day; however, findings were associated with a 10–20% decrease in food consumption. Body weight effects were observed at maternal doses up to 0.9 mg Hg/kg/day (see LSE Table 2-4 for references).

No body weight effects were observed in mice orally exposed to methylmercury at acute or intermediate-duration doses up to 4.6 mg Hg/kg/day (Blakley et al. 1980; Bourdineaud et al. 2011; Hirano et al. 1986; Ilback 1991; Khera 1973; Kirkpatrick et al. 2015; MacDonald and Harbison 1977). Acute exposure to 12 mg Hg/kg/day or intermediate-duration exposures ≥4.7 mg Hg/kg/day resulted in body weight loss in

mice (Das et al. 1997; Dietrich et al. 2005; MacDonald and Harbison 1977). In chronic-duration studies, female B6C3F1 mice showed an approximate 10% decrease in final body weight following dietary exposure to 0.601 mg Hg/kg/day for 2 years; male B6C3F1 mice also showed a decrease in body weight at 0.686 mg Hg/kg/day, but findings were associated with decreased food consumption (Mitsumori et al. 1990). In ICR mice, no body weight effects were noted at chronic doses up to 0.724 mg Hg/kg/day (Hirano et al. 1986). No body weight effects were noted in maternal mice following a single gestation exposure to 9.99 mg Hg/kg/day (Belles et al. 2002) or intermediate-duration exposure during premating, gestation, and/or lactation periods to doses up to 4.7 mg Hg/kg/day (Franco et al. 2006; Thuvander et al. 1996; Weiss et al. 2005).

Data in other species are limited. In an intermediate-duration oral study in rabbits, body weight gain was decreased by 13% in females at 0.48 mg Hg/kg/day and by 43% in males at 0.53 mg H/kg/day; no effects were observed in either sex at 0.05 mg Hg/kg/day (Koller et al. 1977). No body weight effects were noted in cats exposed to doses up to 0.176 mg Hg/kg/day approximately 16 weeks, 0.074 mg Hg/kg/day for approximately 55 weeks, or 0.046 mg Hg/kg/day for 2 years (Charbonneau et al. 1976).

Predominant Mercury Form Unknown (General Populations). Associations between mercury biomarkers and body weight have been evaluated in a prospective study and in several cross-sectional studies; results are summarized in Table 2-6. The prospective study was conducted in population of 2,277 mother-child pairs in the Norwegian Mother, Father and Child Cohort Study (Papadopoulou et al. 2021). All cross-sectional studies, except Park et al. (2017), examined large populations (n=1,567–11,159) in participants from NHANES (Fan et al. 2017) or KNHANES (Bae et al. 2016; Lee et al. 2016; Park and Lee 2013; Shin et al. 2018). Three studies evaluated body weight effects in children and adolescents (Fan et al. 2017; Papadopoulou et al. 2021; Shin et al. 2018), with the remaining studies conducted in adults. Studies used BHg and SHg as exposure biomarkers.

The prospective study of mother-child pairs assessed associations between maternal BHg and BMI in children from 1 month through 8 years of age (Papadopoulou et al. 2021). Inverse associations were observed between maternal BHg in the top 10th percentile and BMI in girls at ages 4, 5, 6, 7, and 8 years of age (range of top 10th percentile was not reported); no associations were observed for boys or for boys and girls combined at any assessment age. The cross-sectional studies in children and adolescents were conducted in NHANES (Fan et al. 2017) and KNHANES (Shin et al. 2018) participants. No association was observed between SHg and BMI in NHANES participants who had a mean SHg of 0.65 µg/L (Fan et al. 2017). In contrast, in the KNHANES population with higher mercury levels (4th BHg quartile: 4.08–

4.77 µg/L), positive associations were observed for overweight/obesity in males and females and abdominal obesity in males, but not females; no associations were observed at lower quartiles (Q1–Q3: 1.82–3.73 µg/L) (Shin et al. 2018). It is difficult to directly compare these studies because different biomarkers were used. Results of studies in adults consistently show positive associations between BHg and several body weight outcomes, including BMI, percent body fat, visceral adipose tissue, waist circumference, and overweight.

Table 2-6. Results of Epidemiological Studies Evaluating Body Weight Effects of Mercury Exposure (Predominant Mercury Form Unknown) in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Bae et al. 2016 Cross-sectional; 11,159 adults, 5,543 males and 5,616 females (KNHANES 2008–2012)	BHg mean Males: 5.07 µg/L Females: 3.59 µg/L	BMI	↑ (BHg, males) ↑ (BHg, females)
		Waist circumference	↑ (BHg, males) ↑ (BHg, females)
Fan et al. 2017 Cross-sectional; 5,404 children (2,734 males and 2,659 females), ages 6–19 years (NHANES 2011–2014)	SHg mean: 0.65 µg/L	BMI	0 (SHg)
Lee et al. 2016 Cross-sectional; 9,228 adults, 4,283 males and 4,945 females (KNHANES 2007–2013)	BHg quartiles, males Q1: <3.04 µg/L Q2: 3.04–4.52 µg/L Q3: 4.52–6.84 µg/L Q4: ≥6.84 µg/L BHg quartiles, females Q1: <2.24 µg/L Q2: 2.24–3.17 µg/L Q3: 3.17–4.55 µg/L Q4: ≥4.55 µg/L	Overweight	↑ (BHg, males, Q1–Q4) ↑ (BHg, females, Q1–Q4)
Park and Lee 2013 Cross-sectional; 4,522 adults, 2,217 males and 2,395 females (KNHANES 2008–2010)	BHg Gmean Males: 4.337 µg/L Females: 3.733 µg/L	Body fat (%)	↓ (BHg, males) 0 (BHg, females)
Park et al. 2017 Cross-sectional; 200 adults, 96 males and 104 females (Korea)	BHg tertiles T1: 1.06–2.66 µg/L T2: 2.69–4.43 µg/L T3: 4.46–7.16 µg/L	Visceral adipose tissue	↑ (BHg)

Table 2-6. Results of Epidemiological Studies Evaluating Body Weight Effects of Mercury Exposure (Predominant Mercury Form Unknown) in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Papadopoulou et al. 2021 Prospective study; 2,277 mother-child pairs (n=227 in the 90th percentile maternal BHg), assessed from 1 month to 8 years of age (Norway)	BHg (maternal) Median: 1.03 µg/L 90th percentile: 2.23 µg/L	BMI trajectory	↓ (BHg, 90th percentile, females) 0 (BHg, 90th percentile, males) 0 (BHg, 90th percentile, males and females combined)
Shin et al. 2018 Cross-sectional; 1,567 children and adolescents, 793 males and 774 females; ages 10–19 years (KNHANES 2010–2013)	BHg Gmean: 1.93 µg/L BHg quartiles boys Q1:<1.47 µg/L Q2: 1.47–1.93 µg/L Q3: 1.94–2.67 µg/L Q4: >2.67 µg/L BHg quartiles girls Q1: <1.39 µg/L Q2: 1.39–1.79 µg/L Q3: 1.80–2.41 µg/L Q4: >2.41 µg/L	Overweight/obesity	↑ (BHg, males and females, Q4)
		Abdominal obesity	↑ (BHg, males, Q4) 0 (BHg, females, Q4)

↑ = positive association; ↓ = inverse association; 0 = no association; BHg = blood mercury; BMI = body mass index; Gmean = geometric mean; KNHANES = Korean National Health and Nutrition Examination Survey; NHANES = National Health and Nutrition Examination Survey; SHg = serum mercury; Q = quartile; T = tertile

Mechanisms of Action. A recent review by Moon (2017) noted that "mercury has no known physiological role in human metabolism." However, proposed mechanisms for mercury-induced effects on body weight include the following: (1) mitochondrial dysfunction; (2) oxidative stress; (3) insulin resistance; and (4) pancreatic β-cell dysfunction and apoptosis (Moon et al. 2017). In addition, based on a study in adipocyte cell lines, mercuric chloride may influence signaling events and subsequent metabolic activity in adipose tissue (Barnes et al. 2003).

2.5 RESPIRATORY

Overview. Few epidemiological and animal studies have evaluated respiratory effects of mercury. However, based on the available data, the respiratory tract does not appear to be a sensitive target of environmental exposures to mercury. Most epidemiological studies were conducted in general populations of children and examined associations between biomarkers and asthma, with only one study reporting positive associations between biomarkers and asthma. Case studies of acute exposures to high

levels of elemental mercury vapor in confined occupational or residential spaces indicate that damage to the respiratory tract can occur.

Studies evaluating respiratory effects in animals are available for inhalation exposure to mercury vapor and oral exposure to mercuric chloride or methylmercury. Consistent with human data, respiratory distress and lung damage have been reported following exposure to acute lethal air concentrations of mercury vapor. Oral data do not indicate that the lung is a sensitive target of mercury toxicity in animal studies, although limited data indicate alveolar effects at high acute methylmercury doses. Nasal lesions have been reported in both mice and rats following chronic gavage exposure to mercuric chloride.

The following summarizes results of epidemiological and animal studies on respiratory outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - No epidemiological studies on respiratory effects of exposure to elemental mercury were identified.
    - Case studies show that acute exposure to high levels of mercury vapor in confined occupational or residential spaces produces adverse respiratory effects, which can be severe.
  - *Animal studies*
    - Respiratory distress and lung damage were reported at acute lethal air concentrations in one study.
    - Data are insufficient to determine if exposure to elemental mercury at nonlethal concentrations is associated with adverse respiratory effects.
- ***Inorganic mercury salts***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to inorganic mercury salts and respiratory effects were identified.
  - *Animal studies*
    - One study reported labored breathing in rats following intermediate-duration dietary exposure to mercuric chloride.
    - Chronic gavage exposure to mercuric chloride is associated with nasal lesions in both rats and mice.
    - There is no evidence of lung lesions following acute, intermediate, or chronic gavage exposure to mercuric chloride in rats or mice.

- ***Organic mercury***
  - *Epidemiology studies*
    - Data are insufficient to determine if exposure to organic mercury is associated with adverse respiratory effects. The only identified study did not show an association between cord BHg and asthma in children.
  - *Animal studies*
    - One acute study reported elevated lung weight and alveolar changes following oral exposure to high doses of methylmercury.
    - There is no evidence of lung lesions in cats, rats, or mice orally exposed to methylmercury for up to 2 years.
- ***Predominant mercury form unknown (general populations)***
    - Several studies evaluated outcomes related to asthma in children. Of the available studies, only one study found an association between biomarkers and asthma; no associations were observed in other studies.

Confounding Factors. The etiology for most respiratory diseases is multifactorial; therefore, several factors may contribute to clinical findings. These include poor housing conditions, exposure to allergens (e.g., pet dander, seasonal allergies), exposure to tobacco smoke and other respiratory irritants, and asthma compounded by obesity (Ali and Ulrik 2013). In addition, Aligne et al. (2000) reported that children living in urban settings have an increased risk of asthma. Failure to account for these factors when they are associated with both respiratory outcomes and exposure may attenuate or strengthen the apparent associations between mercury exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Elemental Mercury—Epidemiological Studies. Epidemiological studies evaluating effects of elemental mercury in respiratory effects meeting inclusion criteria were not identified (see inclusion criteria, Section 2.1). Several case studies of individuals reported adverse respiratory effects following acute exposure (a few hours) to near-fatal or fatal elemental mercury vapor generated from heating elemental mercury to high temperatures in confined spaces in occupational or residential settings. Findings include the following: cough, wheeze, and shortness of breath (Haddad and Stenberg 1963; Kanluen and Gottlieb 1991; Milne et al. 1970); decreased pulmonary function, including decreased vital capacity (VC), forced expiratory volume (FEV), and FEV in 1 second (FEV_1) (Gore and Harding 1987; Lilis et al. 1985); restrictive lung disease (Hallee 1969; Lilis et al. 1985); lung inflammation classified as bronchiolitis, bronchitis, or pneumonitis (Gore and Harding 1987; King 1954; Milne et al. 1970; Rowens et al. 1991;

Teng and Brennan 1959; Tennant et al. 1961); interstitial and alveolar fibrosis (Hallee 1969; Kanluen and Gottlieb 1991); and respiratory failure (Kanluen and Gottlieb 1991; Rowens et al. 1991; Teng and Brennan 1959). No information regarding respiratory effects at lower exposure levels (i.e., not near-fatal or fatal levels) of elemental mercury were identified.

Elemental Mercury—Animal Studies. Data on respiratory effects in animals following inhalation exposure to mercury vapor are limited. In rats, exposure to a lethal air concentration (27.0 mg Hg/m^3) for 2 hours resulted in dyspnea and asphyxiation. At necropsy, lung edema, necrosis of the alveolar epithelium and hyaline membranes, and occasional lung fibrosis were observed (Livardjani et al. 1991). In other studies, no evidence of respiratory distress or lung damage was observed in rats following nonlethal exposure to 26.6 mg Hg/m^3 for 1 hour (Livardjani et al. 1991), 8 mg Hg/m^3 for 2 hours/day for up to 10 days (Morgan et al. 2002), or 3 mg Hg/m^3 for 12–42 weeks (5 days/week; 3 hours/day) (Kishi et al. 1978).

Inorganic Mercury Salts—Animal Studies. The only study located regarding respiratory function in animals after oral exposure to inorganic mercury salts described forceful and labored breathing, bleeding from the nose, and other unspecified respiratory difficulties in rats after dietary exposure to 2.2 mg Hg/kg/day as mercuric chloride for 3 months (Goldman and Blackburn 1979).

Nasal lesions were observed in both rats and mice following chronic gavage exposure to mercuric chloride. Increased incidence of nasal mucosa inflammatory lesions was observed in rats at 4 mg Hg/kg/day and mice at 7.4 mg Hg/kg/day (NTP 1993). In mice, increased metaplasia in the olfactory epithelium was also observed in females at ≥4 mg/kg/day and in males at 7.4 mg/kg/day. No nasal lesions were observed in rats or mice following a 6-month exposure to gavage doses up to 4 or 15 mg/kg/day, respectively (NTP 1993).

No changes in lung histology were observed in rats exposed mercuric chloride via gavage at acute doses up to 9.24 mg Hg/kg/day, intermediate-duration doses up to 15 mg Hg/kg/day, or chronic-duration doses up to 4 mg Hg/kg/day (Lecavalier et al. 1994; NTP 1993). In mice, no changes in lung histology were observed following gavage exposure to intermediate-duration doses up to 59 mg Hg/kg/day or chronic-duration doses up to 7.4 mg Hg/kg/day (NTP 1993).

Organic Mercury—Epidemiological Studies. Data are not sufficient to determine if exposure to mercury in populations with high fish diets produces adverse respiratory effects, with only one study meeting

inclusion criteria (see inclusion criteria, Section 2.1). A prospective study of 656 singleton births in the Faroe Islands did not find an association between cord BHg (mean 11.3 µg/L) and asthma at ages 5 and 7 years (Grandjean et al. 2010). Adjustments included parental smoking in the home and PCB exposure.

Organic Mercury—Animal Studies. One acute study in mice reported a 22–23% increase in absolute and relative lung weight, reduced alveolar diameter, increased alveolar wall thickness, and increased minimal surface tension following gavage exposure to 12 mg Hg/kg/day as methylmercuric chloride for 4 days (Das et al. 1997).

No exposure-related changes in lung histology were observed following oral exposure to methylmercuric chloride in cats at doses up to 0.176 mg Hg/kg/day approximately 16 weeks, 0.074 mg Hg/kg/day for approximately 55 weeks, or 0.046 mg Hg/kg/day for 2 years (Charbonneau et al. 1976); rats at doses up to 0.18 mg Hg/kg/day for 2 years (Verschuuren et al. 1976), or mice at doses up to 0.724 mg Hg/kg/day for 2 years (Hirano et al. 1986; Mitsumori et al. 1990).

Predominant Mercury Form Unknown (General Populations). Respiratory effects of mercury in general populations have not been well studied. Available studies evaluated asthma and signs of respiratory effects in large populations (n≥582) of children using prospective, longitudinal, and cross-sectional designs. Except for one study, results did not find associations between mercury exposure and asthma or signs of respiratory effects; studies are summarized in Table 2-7. Results of both prospective studies did not find an association between HHg or cord BHg and wheeze (Miyake et al. 2011; Shaheen et al. 2004). A large longitudinal study that examined additional endpoints found positive associations between BHg and asthma and wheeze, but not asthma medication use or airway hyperresponsiveness (Kim et al. 2015a). Cross-sectional studies did not find associations between BHg and asthma, wheeze, or bronchial hyperresponsiveness (Heinrich et al. 2017; Wu et al. 2019). Given the small number of available studies and inconsistent results, evidence for effects of mercury on respiratory function is inconclusive.

Table 2-7. Results of Epidemiological Studies Evaluating Exposure to Mercury (Predominant Mercury Form Unknown) and Respiratory Effects in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Heinrich et al. 2017 Cross-sectional; 1,056 children 5–14 years of age (Germany)	BHg Gmean: 0.36 µg/L	Asthma	0 (BHg)
		Wheeze	0 (BHg)
		Bronchial hyper-responsiveness	0 (BHg)
Kim et al. 2015a Longitudinal; 4,350 children enrolled at 7–8 years of age, examined every 2 years through age 11–12 years (Korea 2005–2010)	BHg Gmean Ages 7–8: 2.02 µg/L Ages 9–10: 1.79 µg/L Ages 11–12: 1.96 µg/L	Asthma (age 9–10 years)	↑ (BHg at age 7–8 years) ↑ (BHg at age 9–10 years)
		Asthma (age 11–12 years)	↑ (BHg at age 7–8 years) 0 (BHg at age 9–10 years) 0 (BHg at age 11–12 years)
		Wheeze	↑ (BHg)[a]
		Asthma medication use (age 11–12 years)	0 (BHg)[a]
		Airway hyper-responsiveness (age 11–12 years)	↑ (BHg)[a]
Miyake et al. 2011 Prospective; mothers enrolled October 2002–March 2003; 582 mother-child; maternal and child exposure and child outcomes assessed at age 29–39 months (Japan)	HHg median Mother: 1.52 µg/g Child: 1.38 µg/g	Wheeze	0 (HHg, mother and child)
Shaheen et al. 2004 Prospective; mothers enrolled April 1991–December 1992; 1,755 newborns, assessed for wheeze at 18–30 months and 30–42 months of age (United Kingdom)	Cord BHg Gmean: 0.0127 µg/L	Wheeze	0 (BHg, cord, 18–30 months) 0 (BHg, cord, 30–42 months)
Wu et al. 2019 Cross-sectional; 5,866 children, 2–15 years of age (NHANES 2007–2012)	BHg mean: 0.54 µg/L	Asthma	0 (BHg)
		Wheeze	0 (BHg)

[a]Child age at time of BHg sampling not specified.

↑ = positive association; 0 = no association; BHg = blood mercury; Gmean = geometric mean; HHg = hair mercury; NNHANES = National Health and Nutrition Examination Survey

Mechanisms of Action. Epidemiological and animal studies do not provide strong evidence that exposure to mercury at environmental levels adversely affects the respiratory system, although exposure to near-fatal or fatal concentrations of mercury vapor produces respiratory damage. General mechanisms of toxicity of mercury (reviewed in Section 2.21) are likely involved in the development of toxicity to the respiratory system. In addition, immunomodulatory effects and subsequent cellular release of histamine and cytokines have been proposed as possible mechanisms of toxicity (Miyake et al. 2011).

2.6 CARDIOVASCULAR

Overview. Data on cardiovascular effects of mercury are available from studies in humans and animals. Numerous epidemiological studies have evaluated associations between biomarkers of mercury exposure and cardiovascular outcomes. Studies in humans are available for occupational exposures to elemental mercury, populations exposed primarily to methylmercury through high fish diets, and general populations with unspecified mercury exposures likely to be a combination of methylmercury in food and inorganic mercury from dental amalgams (elemental mercury) and other sources. Cardiovascular outcomes evaluated include blood pressure, cardiac function, or diagnosis of clinical hypertension or cardiovascular disease, and results are inconsistent for these outcomes. For blood pressure, the most studied outcome, evidence for effects is conflicting, and studies that do show positive associations indicate that the magnitude of changes is small. Taken together, results of current epidemiological studies do not provide conclusive evidence that the cardiovascular system is a highly sensitive target for mercury.

Studies evaluating functional cardiovascular endpoints in animals (blood pressure, baroreflex sensitivity, cardiac inotropism) are available for oral exposure to mercuric chloride or methylmercury. Overall, studies indicate that systolic and diastolic blood pressure are increased in a duration-dependent manner for mercuric chloride, and a dose- and duration-dependent manner for methylmercury. A limited number of studies indicate that both compounds also have positive inotropic effects and decreased baroreceptor reflex sensitivity. These data provide evidence that cardiovascular function in rats is altered following exposure to mercuric chloride and methylmercury.

The following summarizes results of epidemiological and animal studies on cardiovascular outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - Findings regarding effects on blood pressure are inconsistent, with no associations at the highest exposures and some positive associations at lower exposures.

        - Few studies investigated effects on cardiac function; data are insufficient to draw conclusions.
    - *Animal studies*
        - No adequate studies have evaluated cardiovascular effects of elemental mercury.
- ***Inorganic mercury salts***
    - *Epidemiology studies*
        - No studies on cardiovascular effects of exposure to inorganic mercury salts were identified.
    - *Animal studies*
        - Findings consistently show duration-dependent increases in systolic and diastolic blood pressure in rats.
        - A few studies have reported positive inotropism and decreased baroreflex sensitivity in rats.
        - No histopathological lesions have been identified in cardiovascular tissue following intermediate- or chronic-duration exposure in rats or mice.
- ***Organic mercury***
    - *Epidemiology studies*
        - Small increases in systolic and diastolic blood pressure have been reported in some studies; however, results are not consistent, and data do not provide clear evidence of a dose-response relationship between methylmercury exposure and increased blood pressure in populations with high fish diets. Associations between methylmercury exposure and prevalence of clinical hypertension are also inconsistent.
        - Data on effects of methylmercury on cardiac function are inconclusive, although some studies reported inverse associations for heart rate variability, which may lead to more serious cardiac effects.
        - No consistent evidence of associations between exposure and cardiovascular diseases has been reported.
    - *Animal studies*
        - Findings show dose- and duration-dependent increases in systolic and diastolic blood pressure in rats.
        - A few studies report positive inotropism and decreased baroreflex sensitivity in rats.
        - No histopathological lesions were identified in cardiovascular tissue following chronic-duration exposure in rats or mice.

- ***Predominant mercury form unknown (general populations)***
    - Evidence for effects of mercury exposure on blood pressure in general populations is inconclusive.
    - Most studies evaluating clinical hypertension reported no associations with mercury biomarkers, although a few studies reported increased risk of hypertension.
    - Evidence for associations between mercury exposure and cardiovascular disease is very limited, with most studies reporting no associations.

Confounding Factors. For epidemiological studies, numerous factors affect cardiovascular function, including age, body mass, race, smoking, alcohol consumption, ongoing family history of cardiovascular disease, low density lipoprotein (LDL) cholesterol levels, diet (including n-3 polyunsaturated fatty acids and selenium), other diseases (e.g., renal disease), and co-exposure to substances (lead, PCBs) that may affect the cardiovascular system either directly or indirectly through effects on other systems (e.g., renal, neurological). Failure to account for these factors when they are associated with both cardiovascular outcomes and exposure may attenuate or strengthen the apparent associations between mercury exposure and the outcome, depending on the direction of the effect of the variable on the outcome (e.g., Møller and Kristensen 1992). Although it is impractical to assess all possible confounders, epidemiological studies reviewed in this section include some of the adjustments listed above. No specific confounder or covariate was mandatory for the inclusion of the study into the profile; however, studies of cardiovascular outcomes that did not consider, at a minimum, age, body mass, race, smoking, alcohol consumption, and ongoing family history of cardiovascular disease are potentially more confounded than studies that did consider these variables.

In addition to potential confounding factors listed above, interpretation of study results is further complicated by the risks and benefits of fish consumption, particularly in populations with high fish diets. Fish contain high levels of n-3 polyunsaturated fatty acids and selenium, which are considered beneficial to cardiovascular health (Choi et al. 2008a, 2009; Hu et al. 2017). Therefore, cardiovascular effects of methylmercury may be offset by the beneficial effects of fatty acids and selenium (e.g., negative confounding) in high fish diets (Chan and Egeland 2004; Choi et al. 2008a; Guallar et al. 2002; Hu et al. 2017; Mozaffarian 2009; Smith et al. 2009; Virtanen et al. 2005). Several study authors noted that the balance between beneficial nutrients and methylmercury in high fish diets may contribute to the equivocal findings in some studies examining cardiovascular effects (Choi et al. 2008a; Guallar et al. 2002; Hu et al. 2017; Stern 2005; Virtanen et al. 2005).

Elemental Mercury—Epidemiological Studies. Studies evaluating effects of elemental mercury on cardiovascular function are summarized in Table 2-8. The database consists of several cross-sectional studies of dental professionals, miners, chloralkali workers, and adults with amalgam fillings. Population sizes in these studies are small (n=28–262), limiting the power to detect associations between elemental mercury and cardiovascular outcomes. All studies quantified exposure using UHg, with some studies also measuring BHg and/or HHg. Choice of biomarkers used in the studies may have impacted the strength and direction of the associations found. UHg has been shown to correlate with elemental mercury exposure in populations in which the main source of exposure was to elemental (e.g., workers in mercury production and processing) (see Section 3.3.1, Biomarkers of Exposure). UHg ranged from 0.94 µg/L in a study of U.S. dental professionals (Goodrich et al. 2013) to 51.4 µg/L in mercury-exposed Turkish adults, including dentists and "industrial" exposures (Yilmaz et al. 2016). Evidence for effects of elemental mercury on cardiovascular function is inconclusive.

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Effects on Cardiovascular Outcomes

Reference, study type, and population	Biomarker	Outcome evaluated	Result[a,b]
Goodrich et al. 2013 Cross-sectional; 262 dental professionals (Michigan)	HHg mean: 0.45 µg/g UHg mean: 0.94 µg/L	SBP	0 (HHg) ↓ (UHg)
		DBP	↑ (HHg) 0 (UHg)
Kobal et al. 2004 Cross-sectional; 54 male mercury miners, 58 male controls (Slovenia)	UHg mean Workers: 2.1 µg/L Controls: 1.4 µg/L	SBP	↑ (workers versus controls)
		DBP	↑ (workers versus controls)
Piikivi 1989 Retrospective, cross-sectional; 41 chloralkali male workers, 41 male referents (Finland)	Means for workers BMeHg: 3.8 µg/L BIHg: 7.8 µg/L UHg: 19.3 µg/L Means for referents BMeHg: 2.9 µg/L BIHg: 0.9 µg/L UHg: 1.8 µg/L	SBP	0 (workers versus referents)
		DBP	0 (workers versus referents)
Poreba et al. 2012 Cross-sectional; 115 adult chloralkali workers (Poland)	UHg mean: 4.11 µg/g Cr	LVF	↓ (UHg)
Rajaee et al. 2015	HHg mean: 1.11 µg/g UHg mean: 37.6 µg/L	SBP	0 (BHg, UHg)
		DBP	0 (BHg, UHg)

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Effects on Cardiovascular Outcomes

Reference, study type, and population	Biomarker	Outcome evaluated	Result[a,b]
Cross-sectional; 70 adult current and former mercury miners (Ghana)			
Siblerud 1990 Cross-sectional; 101 adults with amalgam fillings, 51 adults with no amalgam fillings (Colorado)	HHg mean Amalgam: 1.43 µg/g No amalgam: 1.13 µg/g UHg mean Amalgam: 3.70 µg/L No amalgam: 1.23 µg/L	SBP	↑ (amalgam versus no amalgam)
		DBP	↑ (amalgam versus no amalgam)
		HR	0 (amalgam versus no amalgam)
Yilmaz et al. 2016 Cross-sectional; 28 adults with exposure to Hg^0 (15 dentists, 10 workers with unspecified "industrial" exposure, and 3 individuals with chronic exposure in office or home after fluorescent light break) and 28 control adults (Turkey)	BHg mean Exposed: 14.8 µg/L Controls: 0.9 µg/L HHg mean Exposed: 2.1 µg/g Controls: 0.2 µg/g UHg mean Exposed: 51.4 µg/L Controls: 1.3 µg/L	SBP	0 (exposed versus controls)
		DBP	0 (exposed versus controls)
		HRR	↓ (exposed versus controls)

[a]Biomarkers are not considered in outcome analyses for studies that assess outcomes by comparisons between exposure groups.

↑ = positive association; ↓ = inverse association; 0 = no association; BHg = blood mercury; BIHg = blood inorganic mercury; BMeHg = blood methyl mercury; Cr = creatinine; DBP = diastolic blood pressure; HHg = hair mercury; HR = heart rate; HRR = heart rate recovery (post-exercise); LVF = left ventricular function; SBP = systolic blood pressure; UHg = urine mercury

Blood pressure. Results of studies evaluating associations between occupational exposure to elemental mercury and blood pressure are inconsistent, with no apparent relationship between level of exposure (as reflected by biomarkers) and outcomes (Table 2-8). At the highest mean UHg evaluated, no differences were observed for systolic or diastolic blood pressure in mercury-exposed subjects, including dentists, workers with "industrial" exposures, and individuals with chronic exposure in office or home after fluorescent light break (UHg: 51.4 µg/L), compared to controls (UHg: 1.3 µg/L) (Yilmaz et al. 2016). Similarly, no associations were observed between elemental mercury exposure and systolic or diastolic blood pressure in miners with mean UHg of 37.6 µg/L (Rajaee et al. 2015). However, increased blood pressure was observed at substantially lower UHg in a study of male miners with mean UHg of 2.1 µg/L, compared with controls with mean UHg of 1.4 µg/L (Kobal et al. 2004). This study found increases in both systolic (miners: 134.4 mm Hg; controls: 125.9 mm Hg) and diastolic (miners: 87.9 mm Hg; controls: 81.2 mm Hg;) blood pressure. In adults with amalgam fillings (mean UHg: 3.70 µg/L), average

systolic and diastolic blood pressure were increased by 5.73 and 4.37 mm Hg, respectively, compared to adults with no amalgam fillings (mean UHg: 1.23 µg/L) (Siblerud 1990). At the lowest UHg evaluated (0.94 µg/L) in U.S. dental professionals, an inverse association was reported for systolic blood pressure (decrease in blood pressure with increasing UHg), with no association for diastolic blood pressure (Goodrich et al. 2013). However, using HHg as the biomarker, associations between mercury and blood pressure showed different effects; no association was observed between HHg and systolic blood pressure and a positive association was observed for HHg and diastolic blood pressure (Goodrich et al. 2013). The difference between the associations observed with UHg and HHg may reflect a contribution of exposure to methylmercury, which may have contributed to HHg.

Cardiac function. Few studies have investigated effects of elemental mercury on cardiac function; however, studies have not evaluated the same endpoints and findings in single studies have not been corroborated (Table 2-8). For heart rate, no differences were observed in adults with amalgam fillings compared to adults with no amalgam fillings (Siblerud 1990). Heart rate recovery during the first 3 minutes post-exercise was decreased in mercury workers compared to controls (Yilmaz et al. 2016). An inverse association was observed between elemental mercury exposure and left ventricular diastolic function in chloralkali workers; the study authors noted that workers did not clinically present with cardiac dysfunction (Poreba et al. 2012).

Cardiovascular disease. No studies evaluating the relationships between cardiovascular diseases and exposure to elemental mercury that included biomarker data and assessed appropriate confounders were identified.

Elemental Mercury—Animal Studies. No adequate studies evaluating cardiovascular effects in animals following exposure to elemental mercury were identified.

Inorganic Mercury Salts—Animal Studies. Studies in laboratory animals have evaluated effects of inorganic mercuric mercury (e.g., mercuric chloride) on cardiovascular function following intermediate-duration oral exposure. Results indicate that exposure to mercuric chloride alters some cardiovascular functions, including systolic and diastolic blood pressure, ventricular pressure, baroreflex sensitivity, and cardiac inotropism.

Effects of mercuric chloride on blood pressure may exhibit duration-dependence following exposure via drinking water; however, there is no clear evidence for increased magnitude of effect with increasing dose

(see Table 2-9). In rats, blood pressure was generally unaffected at oral doses up to 5.91 mg Hg/kg/day for 28 days, with the exception of a spurious 15% increase in diastolic blood pressure at doses of 0.264 mg Hg/kg/day, up to 1.3 mg Hg/kg/day for 182 days (Jindal et al. 2011; Perry and Erlanger 1974; Wildemann et al. 2015a, 2015b, 2016), or 6 mg Hg/kg/day for 320 days (Carmignani and Boscolo 1984). However, systolic and diastolic blood pressures were increased in rats exposed to 24 mg Hg/kg/day for 180 days or 6 mg Hg/kg/day for 350 days, and systolic blood pressure was increased in rats exposed to 0.66 or 1.3 mg Hg/kg/day for 365 days; systolic blood pressure was not altered at 3.3 mg Hg/kg/day for 365 days, but this may have been due to poor general health at this dose (Carmignani and Boscolo 1984; Carmignani et al. 1992; Perry and Erlanger 1974). Aortic blood pressure was also increased in rats exposed to ≥6 mg Hg/kg/day for 350 days (Boscolo et al. 1989; Carmignani et al. 1989). No alterations in pulse pressure and/or heart rate were observed in these studies.

Table 2-9. Effects on Blood Pressure in Rats Exposed to Mercuric Chloride via Drinking Water Exposure

Duration; dose (mg Hg/kg/day)	ABP	SBP	DBP	Reference
28 days; dose: 0.005–0.244	–	0 (M)	0 (M)	Jindal et al. 2011; Wildemann et al. 2015a, 2015b
28 days; dose: 0.264	–	0	↑ (M) (15[a])	Wildemann et al. 2016
28 days; dose: 1.18–2.07	–	0 (M)	0 (M)	Wildemann et al. 2015a
28 days; dose: 2.955	–	0 (M)	0 (M)	Wildemann et al. 2016
28 days; dose: 5.91	–	0 (M)	0 (M)	Wildemann et al. 2015a
180 days; dose: 24	–	↑ (M) (15[b])	↑ (M) (28[b])	Carmignani et al. 1992
182 days; dose: 0.33–1.3	–	0 (F)	–	Perry and Erlanger 1974
320 days; dose: 6	–	0 (M)	0 (M)	Carmignani and Boscolo 1984
350 days; dose: 6	↑ (M) (32[b])	–	–	Boscolo et al. 1989; Carmignani et al. 1989
350 days; dose: 6	↑ (M) (43[b])	–	–	Boscolo et al. 1989
350 days; dose: 6	–	↑ (M) (35[b])	↑ (M) (32[b])	Carmignani and Boscolo 1984
350 days; dose: 24	↑ (M) (45[b])	–	–	Boscolo et al. 1989
365 days;	–	0 (F)	–	Perry and Erlanger 1974

Table 2-9. Effects on Blood Pressure in Rats Exposed to Mercuric Chloride via Drinking Water Exposure

Duration; dose (mg Hg/kg/day)	ABP	SBP	DBP	Reference
dose: 0.33				
365 days; dose: 0.66	–	↑ (F) (15[b])	–	Perry and Erlanger 1974
365 days; dose: 1.3	–	↑ (F) (13[b])	–	Perry and Erlanger 1974
365 days; dose: 3.3	–	0[c] (F)	–	Perry and Erlanger 1974

[a]Percent change compared to control, estimated from graphically presented data.
[b]Percent change compared to control, calculated from quantitative data.
[c]Lack of exposure-related effect may have been due to poor general health at this dose.

↑ = increased; 0 = no change; – = not assessed; ABP = aortic blood pressure; B = both; DBP = diastolic blood pressure; F = female; M = male; SBP = systolic blood pressure

In dietary studies, no alterations in systolic blood pressure were observed in normotensive Wistar rats exposed to doses up to 2.2 mg Hg/kg/day as mercuric chloride for 21 weeks (Takahashi et al. 2000a). In similarly exposed spontaneously hypertensive Wistar rats, systolic blood pressure was significantly increased by 6–10% following exposure to ≥0.1 mg Hg/kg/day for 4 or 5 weeks; however, no significant effects were noted following exposure to doses up to 3 mg Hg/kg/day for 6–12 weeks (Takahashi et al. 2000b). Findings in spontaneously hypertensive rats are difficult to interpret due to the transient nature of observed effects in a rat strain prone to hypertension.

Alterations in cardiac function in rats exposed to mercuric chloride include increased left ventricular end diastolic pressure (LvEDP), positive inotropic effects, and/or altered baroreceptor reflex sensitivity at daily doses of 0.012–24 mg Hg/kg/day for exposure durations of 1 month to 350 days. LvEDP was significantly increased by 3-fold and the maximum differential of LvEDP to the left ventricular end systolic pressure (LvESP) was decreased by 56–62% in rats administered 0.12 mg Hg/kg/day by gavage for 1 month (Jindal et al. 2011). Sprague-Dawley and Wistar rats showed a significant 25–32% increase in the maximum rate of rise in the left ventricular pressure after exposure to 6 mg Hg/kg/day for 350 days, indicating increased contractility (positive inotropic response); however, these effects were not observed in Wistar rats similarly exposed to 24 mg Hg/kg/day for 180 or 350 days (Boscolo et al. 1989; Carmignani et al. 1989, 1992). It is unknown if the lack of effects in Wistar rats indicates a difference in strain susceptibility or a non-monotonic dose-response. Increased cardiac inotropic responses to cardiac drugs (e.g., isoprenaline) were also observed after exposure for 350 days to 6 mg Hg/kg/day in Sprague-

Dawley rats (47–90% increase) and 24 mg Hg/kg/day in Wistar rats (87% increase); findings were not significant at 6 mg Hg/kg/day in Wistar rats (Boscolo et al. 1989; Carmignani et al. 1989). Decreased baroreceptor reflex sensitivity was also observed in Wistar and Sprague-Dawley rats after drinking water exposure to mercuric chloride, with ≥27% decrease in the change in aortic blood pressure at ≥6 mg Hg/kg/day following exposure to various vasoactive drugs (e.g., norepinephrine, phenylephrine) (Boscolo et al. 1989; Carmignani and Boscolo 1984; Carmignani et al. 1989). No exposure-related changes in electrocardiogram parameters, stroke volume, cardiac output, left ventricular wall thickness, or carotid artery diameter or thickness were observed in rats following drinking water exposure to mercuric chloride at doses up to 5.91 mg Hg/kg/day for 4 weeks (Wildemann et al. 2015a, 2015b, 2016).

Oral exposure to inorganic mercury salts has not been associated with histopathological lesions in the rodent heart. In an acute study, no treatment-related histopathological changes were observed in the hearts of rats exposed once to mercuric chloride at gavage doses up to 9.24 mg Hg/kg/day (Lecavalier et al. 1994). In intermediate-duration studies, no treatment-related histopathological changes were observed in the hearts of rats or mice exposed to mercuric chloride at gavage doses up to 4 or 15 mg Hg/kg/day, respectively (Dieter et al. 1992; NTP 1993). No treatment-related histopathological changes were observed in the hearts of mice exposed to mercuric chloride at gavage doses up to 7.4 mg Hg/kg/day for up to 2 years (NTP 1993). One chronic study in rats reported heart mineralization in males following exposure to mercuric chloride at gavage doses ≥1.8 mg Hg/kg/day for up to 2 years; however, this lesion was considered secondary to severely impaired renal function (Dieter et al. 1992; NTP 1993). Similarly exposed female rats, which did not show renal impairment, did not have heart mineralization at gavage doses up to 4 mg Hg/kg/day.

No exposure-related changes in heart histology were observed following oral exposure to methylmercuric chloride in cats at doses up to 0.176 mg Hg/kg/day for approximately 16 weeks, 0.074 mg Hg/kg/day for approximately 55 weeks, or 0.046 mg Hg/kg/day for 2 years (Charbonneau et al. 1976).

Organic Mercury—Epidemiological Studies. Studies evaluating effects of methylmercury exposure on cardiovascular function (blood pressure, heart rate, and heart rate variability) in populations with high fish diets are summarized in Table 2-10. Studies of high fish consumers are categorized as two types based on the timing of biomarker measurement: (1) cross-sectional studies of adults assessing outcomes based on current exposure measurements (biomarkers measured at the time outcome measures were assessed) and (2) prospective birth cohort studies assessing outcomes in children or adolescents based on prenatal exposure measurements. Cross-sectional studies based on current biomarker measurements include small

populations (n=42–732) of adults and adolescents, except for one larger population of 1,861 (Nielsen et al. 2012). The most common biomarker used to assess mercury exposure was BHg, although HHg and toenail mercury (NHg) have also been used in some studies (Choi et al. 2009; Fillion et al. 2006). Prospective birth studies include cohorts of children from the Faroe Islands and Seychelle Islands; population sizes ranged from 95 to 897. The main biomarkers to assess prenatal exposure were cord BHg and maternal HHg at parturition.

Table 2-10. Epidemiological Studies Evaluating Associations between Mercury and Blood Pressure and Cardiac Function in Populations with High Fish Diets

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Studies based on current mercury measurements			
Choi et al. 2009 Cross-sectional; 42 whaling men (Faroe Islands)	BHg Gmean: 29.5 µg/L HHg Gmean: 7.31 µg/g NHg Gmean: 2.04 µg/g	SBP	↑ (BHg) 0 (HHg, NHg)
		DBP	↑ (BHg, NHg) 0 (HHg)
		HR	0 (BHg, HHg, NHg)
		HRV	0 (BHg, HHg, NHg)[a]
Fillion et al. 2006 Cross-sectional; 251 adults (Brazilian Amazon community)	HHg: ≥10–77.2 µg/g	SBP	↑ (HHg)
		DBP	0 (HHg)
Hu et al. 2017 Cross-sectional study; 2,169 Inuit adults (Canada)	BHg Gmean: 7.0 µg/L 1st–99th percentile: 0.3–70 µg/L Low BHg: <20 µg/L High BHg: ≥20 µg/L Low BSe: <280 µg/L High BSe: ≥20 µg/L	Hypertension	0 (low BHg + low BSe) 0 (low BHg + high BSe) ↑ (high BHg + low BSe) ↑ (high BHg + high BSe)
Inoue et al. 2012 Cross sectional study; approximately 40,000 residents of Minamata, with approximately 1,000 with Minamata disease	Median HHg: 30 µg/g[b]	Hypertension	0 (HHg) in 1953–1957 0 (HHg) in 1958–1962 ↑ (HHg) in 1963–1967 0 (HHg) in 1998–1970
Miller et al. 2017 Cross-sectional; 94 adults, avid seafood consumers (Long Island, New York)	BHg mean: 8.4 µg/L	HRV	0 (BHg)
		QTc	0 (BHg)

Table 2-10. Epidemiological Studies Evaluating Associations between Mercury and Blood Pressure and Cardiac Function in Populations with High Fish Diets

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Nielsen et al. 2012 Cross-sectional; Inuit adults; 812 men and 1,049 women (Greenland)	BHg quintile ranges Men Q4: 27–49 µg/L Men Q5: 50–280 µg/L Women Q5: 36–170 µg/L	SBP	0 (Men, BHg Q5) 0 (Women BHg Q5)
		DBP	↓ (Men, BHg Q4) 0 (Women, BHg Q5)
		PP	0 (Men, BHg Q5) 0 (Women, BHg Q5)
		Hypertension	0 (Men, BHg Q5) 0 (Women, BHg Q5)
Valera et al. 2008 Cross-sectional; 205 Nunavik Inuit adults (Quebec)	BHg mean: 27 µg/L	SBP	↑ (BHg)
		DBP	0 (BHg)
		PP	↑ (BHg)
		HRV	↓ (BHg)
Valera et al. 2009 Cross-sectional; 732 Nunavik Inuit adults (Quebec)	BHg mean: 10 µg/L	SBP	↑ (BHg)
		DBP	0 (BHg)
		PP	↑ (BHg)
Valera et al. 2011a Cross-sectional; 180 adults (French Polynesia)	BHg mean: 14.5 µg/L	SBP	0 (BHg)
		DBP	0 (BHg)
		PP	0 (BHg)
		HR	0 (BHg)
		HRV	0 (BHg)
Valera et al. 2011a Cross-sectional; 101 adolescents (French Polynesia)	BHg mean: 8.1 µg/L	SBP	0 (BHg)
		DBP	0 (BHg)
		PP	0 (BHg)
		HRV	↓ (BHg)
Valera et al. 2011b [adjustments included Pb, PCBs, and 3-n polyunsaturated fatty acids] Cross-sectional; 724 Cree Inuit adults (Quebec)	BHg mean: 3.1 µg/L HHg mean: 0.47 µg/g	SBP	0 (BHg, HHg)
		DBP	0 (BHg, HHg)
		PP	0 (BHg, HHg)
		HRV	↓ (BHg, HHg)
Valera et al. 2013 Cross-sectional; 313 Inuit adults (Quebec) [adjustments included Pb, PCBs, and 3-n polyunsaturated fatty acids]	BHg mean: 15.4 µg/L BHg Q4: 28.4–112 µg/L	SBP	0 (BHg)
		DBP	0 (BHg)
		PP	0 (BHg)
		HR	↑ (BHg, Q4)
Yorifuji et al. 2010 Cross-sectional; 120 adults (Minamata, Japan)	HHg Q4: >28.3 µg/g Hair samples were analyzed in 1960[c]	Hypertension	0 (HHg, Q4)

Table 2-10. Epidemiological Studies Evaluating Associations between Mercury and Blood Pressure and Cardiac Function in Populations with High Fish Diets

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Studies based on prenatal exposure measurements			
Grandjean et al. 2004a (follow-up to Sørensen et al. 1999) Prospective birth cohort; 878 adolescents; blood pressure assessed at age 14 years (Faroe Islands)	BHg median (cord): 24.27 µg/L HHg median: Maternal at parturition[b]: 5.65 µg/g Child, age 14[c]: 0.96 µg/g	SBP	0 (BHg, HHg)
		DBP	0 (BHg, HHg)
		HR	0 (BHg, HHg)
		HRV	↓ (BHg) 0 (HHg)
Periard et al. 2015 Prospective birth cohort; 95 adults (age 19 years, 47 males, 48 females) (Seychelles Islands)	HHg mean Maternal during pregnancy: 6.7 µg/g Males, age 19: 11.2 µg/g Females, age 19: 7.9 µg/g	HRV	0 (HHg)
Sørensen et al. 1999 Prospective birth cohort; 894–897 children; blood pressure assessed at age 7 years (Faroe Islands)	BHg mean (cord): 31.8 µg/L HHg mean (maternal at parturition): 5.65 µg/g[b]	SBP	↑ (BHg, HHg)
		DBP	↑ (BHg) 0 (HHg)
Thurston et al. 2007 Prospective birth cohort; 644–559 children; blood pressure assessed at ages 12 and 15 years (Seychelles Islands)	HHg mean (maternal) for: Boys age 12: 6.6 µg/g Boys age 15: 6.5 µg/g Girls age 12: 7.0 µg/g Girls age 15: 7.0 µg/g	SBP	0 (HHg)
		DPB	0 (HHg, age 12 years) ↑ (HHg, boys, age 15 years) 0 (HHg, girls, age 15 years)
Valera et al. 2012 Prospective birth cohort; 226 Nunavik Inuit children (Quebec) assessed at age 11 years (adjustments included Pb and PCBs)	BHg mean (cord): 21.5 µg/L BHg mean (age 11 years): 4.5 µg/L HHg mean (age 11 years): 1.3 µg/g	SBP	0 (BHg, HHg)
		DBP	0 (BHg, HHg)
		HRV	0 (BHg, cord) ↓ (BHg, age 11 years) 0 (HHg, age 11 years)

[a]The study authors considered results for HRV to be equivocal, possibly due to the small study population size.
[b]Reported by Grandjean et al. (1992).
[c]Biomarkers were not measured in this population; for reference, the median HHg in a healthy Minamata fishermen measured in 1960 was 30 µg/g, compared to a median HHg of 2.1 µg/g in the control population in 1960.

↑ = positive association; ↓ = inverse association; 0 = no association; – = not reported; BHg = blood mercury; BSe = blood selenium; DBP = diastolic blood pressure; Gmean = geometric mean; HHg = hair mercury; HR = heart rate; HRV = heart rate variability; NHg = toenail mercury; Pb = lead; PCBs = polychlorinated biphenyls; PP = pulse pressure; Q = quartile or quintile; QTc = QT interval duration; SBP = systolic blood pressure

Blood pressure. Results of cross-sectional studies in adult populations using current biomarker measurements provide conflicting evidence regarding associations between methylmercury exposure

from fish consumption and blood pressure. For studies reporting positive associations, the mean or median BHg range was 10–29.5 µg/L, whereas the range for studies reporting no associations was 3.1–15.4 µg/L. However, results are not consistent and data do not provide clear evidence of a dose-response relationship between methylmercury exposure from fish and increased blood pressure. Furthermore, observed changes in blood pressure were small. The lowest mean BHg (10 µg/L) associated with increased blood pressure was reported in a study of Nunavik Inuit adults in Quebec, with positive associations between BHg and systolic blood pressure (Valera et al. 2009). Based on log transformed (base not reported) BHg, a 1% increase in BHg was associated with a 0.02 mmHg increase in systolic blood pressure. No association was observed for diastolic blood pressure. Similar results were observed in a smaller population of Nunavik Inuit adults (Valera et al. 2008).

For the highest mean BHg of 29.5 µg/L in a population of 42 whaling men from the Faroe Islands, BHg was positively associated with systolic and diastolic blood pressure (Choi et al. 2009). The magnitude of the association was reported in standardized beta coefficients (percent of standard deviation [SD] of outcome variable per 1 SD change in $\log_{10}$ BHg). The reported effect on systolic blood pressure was a 37.5% increase per 1 SD increase in $\log_{10}$ BHg. This would correspond to an increase of approximately 7 mmHg (0.375x18) in blood pressure per 1 SD increase in $\log_{10}$ BHg (approximately 90 µg/L). The reported effect on diastolic blood pressure was a 33.2% increase per 1 SD increase in $\log_{10}$ BHg. This would have corresponded to an increase in diastolic blood pressure of approximately 2.6 mmHg (0.332x8) per 1 SD increase in $\log_{10}$ BHg (approximately 90 µg/L increase in BHg; see legend of Table 2-10 for the basis for this estimate). No association between BHg and systolic or diastolic blood pressure was observed at mean BHg of 3.1–15.4 µg/L (Valera et al. 2011a, 2011b, 2013). Two of these studies adjusted for co-exposure to other chemicals that may also affect blood pressure (lead and PCBs) (Valera et al. 2011b, 2013). Using BHg data stratified by quintiles in a study of Inuit men and women, no association was observed for systolic blood pressure for the highest quintile in men and women; an inverse association was observed for diastolic blood pressure in men in the 4th and 5th quintiles, although no association was observed in women (Nielsen et al. 2012).

Prospective, prenatal exposure studies show inconsistent results regarding associations between methylmercury exposure from fish consumption and blood pressure in children and adolescents. Studies of the Faroe Island population evaluated blood pressure in children at 7 and 14 years of age (Grandjean et al. 2004a; Sørensen et al. 1999). The study in 7-year-olds found a positive association between cord BHg and maternal HHg for systolic blood pressure and between cord BHg and diastolic blood pressure, with increases in systolic blood pressure of 13.9 mmHg and diastolic blood pressure of 14.6 mmHg for an

increase in cord BHg from 1 to 10 μg/L (Sørensen et al. 1999). However, in the follow-up study assessing blood pressure at age 14 years, no association was observed between BHg, maternal HHg (at parturition), or child HHg (Grandjean et al. 2004a). In a population of children in the Seychelles Islands, no association was observed between prenatal exposure and systolic or diastolic blood pressure in girls at ages 12 and 15 years, or in boys at 12 years (Thurston et al. 2007). However, a positive association was observed between maternal HHg and diastolic blood pressure in boys at age 15; the study authors stated that biological significance of this finding is uncertain. No association between cord BHg and blood pressure was observed in a study of Nunavik Inuit children evaluated at age 11 years (Valera et al. 2012). This study also adjusted for exposure to lead and PCBs.

Hypertension. Associations between methylmercury exposure from fish consumption and clinical hypertension are inconsistent (see Table 2-10). In a cross-sectional study of an Arctic Inuit population, the prevalence of hypertension was increased at BHg ≥20 μg/L, but not <20 μg/L (Hu et al. 2017); the increase appeared to be attenuated at higher blood selenium levels (≥280 μg/L) compared to lower blood selenium levels (<280 μg/L). Some evidence that severe exposure to methylmercury is associated with hypertension mortality was reported in a large study of the Minamata population (Inoue et al. 2012). In a population of approximately 46,000 residents of Minamata, including approximately 1,000 Minamata disease patients, the age-standardized mortality ratio (AMSR) for hypertension (ASMR 1.38; 95% CI 1.06, 1.64) was increased compared to a control group during the period of 1963–1967; however, AMSRs were not elevated for the periods 1953–1957, 1959–1962, or 1969–1970. A small study of Minamata residents with HHg measured in 1960 did not find an association between HHg and prevalence of hypertension as assessed in 1971 (Yorifuji et al. 2010). A cross-sectional study of an Inuit population did not show associations between exposure and hypertension at the highest BHg reported (Nielsen et al. 2012).

Cardiac function. Associations between methylmercury exposure from fish consumption and cardiac function have been evaluated in cross-sectional and prospective birth cohort studies. Outcome variables include heart rate and heart rate variability. Cross-sectional studies reported conflicting results on heart rate. A positive association between BHg and resting heart rate was reported in a population of Inuit adults from Quebec, with resting heart rate increased by 6.9 beats per minute in the highest BHg quartile relative to lower BHg quartiles (Valera et al. 2013); potential confounders considered in this study included co-exposure to other contaminants (lead and PCBs) and n-3 polyunsaturated fatty acids levels. No associations between methylmercury exposure and heart rate were observed for mean BHg in French Polynesian adults and Faroe Island whalers, respectively (Choi et al. 2009; Valera et al. 2011a). In

addition, a prospective birth cohort study of the Faroe Island population did not find an association between cord BHg or maternal HHg and heart rate assessed at age 14 years (Grandjean et al. 2004a).

Several studies have evaluated the effects of methylmercury exposure and heart rate variability. Heart rate variability, which is mediated through the autonomic nervous system, reflects a balance between sympathetic and parasympathetic control (Gribble et al. 2015; Karita et al. 2018). Decreased heart rate variability may lead to cardiac arrhythmias and increased risk of ventricular fibrillation and sudden cardiac death (Karita et al. 2018; Valera et al. 2011a, 2012). Taken together, results of cross-sectional and prospective birth cohort studies do not provide compelling evidence that methylmercury exposure is associated with heart rate variability. Results of cross-sectional studies report conflicting results, with some studies showing inverse associations between exposure biomarkers and heart rate variability (Valera et al. 2008, 2011a, 2011b) and other studies reporting no associations (Choi et al. 2009; Miller et al. 2017; Valera et al. 2011a). The range of mean BHg for studies showing decreased heart rate variability (3.1–27 µg/L) is similar to the range for studies showing no change (8.4–29.5 µg/L); thus, results indicate that there is no apparent relationship between exposure level and outcome. In Faroe Island whalers with the highest reported mean BHg of 29.5 µg/L, study authors considered results on heart rate variability to be unclear; however, study power is limited by the small population size (n=42) (Choi et al. 2009). One study of Faroe Island adolescents and adults showed no association in between BHg (mean 14.5 µg/L) and heart rate variability in adults, but an inverse association in adolescents at lower BHg (mean: 8.1 µg/L) (Valera et al. 2011a). Retrospective birth cohort studies also report inconsistent results on effects of methylmercury exposure and heart rate variability. Heart rate variability was inversely associated with current BHg, but not cord BHg or current HHg in 11-year-old Nunavik children (Valera et al. 2012). In a Faroe Island birth cohort with outcomes assessed at age 14 years, an inverse association was observed between cord BHg and heart rate variability, but not for maternal HHg at parturition or age 14 years child HHg (Grandjean et al. 2004a). Similarly, follow-up of the Seychelles Islands prospective cohort at age 19 years showed no association between maternal HHg during pregnancy or current HHg in males or females; cord BHg was not reported (Periard et al. 2015).

Cardiovascular disease. Few studies reporting biomarker data and confounding factors have evaluated associations between methylmercury exposure in populations with high fish diets and cardiovascular disease morbidity and mortality. However, results do not provide evidence that exposure to methylmercury is associated with cardiovascular disease. Studies of various Inuit populations have not found associations for myocardial infarction (Hu et al. 2017), stroke (Hu et al. 2017), or non-specific cardiovascular disease (Larsen et al. 2018).

Organic Mercury—Animal Studies. Alterations in cardiovascular function have been reported in rats following acute- and intermediate-duration oral exposure to methylmercuric chloride, with blood pressure as the most studied cardiovascular endpoint. Generally, results show that exposure to methylmercuric chloride increases systolic and diastolic blood pressure in a dose- and duration-dependent manner; pulse pressure is also increased in some studies, but with no apparent dose-related effect (Table 2-11). In rats, systolic blood pressure was increased by 10–30% after exposure to doses of 0.005–1.6 mg Hg/kg/day for 26–28 days, and 40% after exposure to 0.08 mg Hg/kg/day for 100 days (Grotto et al. 2009a; Tamashiro et al. 1986; Wakita 1987; Wildemann et al. 2015a, 2015b, 2016). Diastolic blood pressure was slightly less sensitive, with significant increases of 22–31% with exposures to doses ≥0.009–0.879 mg Hg/kg/day for 28 days (not tested at other durations) (Wildemann et al. 2015a, 2015b, 2016). Pulse pressure increases of 10–20% were observed in a non-dose-related fashion in rats exposed to 0.005–0.216 mg Hg/kg/day, but not 0.879 mg Hg/kg/day (Wildemann et al. 2015a, 2015b, 2016). One study, however, did not observe changes in systolic or diastolic blood pressure or pulse pressure in rats exposed to 0.5 mg Hg/kg/day for 28 days (Jindal et al. 2011). No alterations in heart rate were observed in any of these studies.

Table 2-11. Effects on Blood Pressure in Rats Exposed to Methylmercuric Chloride via Oral Exposure

Strain (sex)	Duration (days)	Route	Dose (mg Hg/kg/day)	SBP	DBP	PP	Reference
SHR/NCrj[a] (F)	26	Oral NS	1.6	↑ (10%[b,c])	–	–	Tamashiro et al. 1986
Wistar (M)	28	DW	0.002	0	0	0	Wildemann et al. 2015a
Wistar (M)	28	DW	0.005	↑ (14%[b])	0	↑ (17%[b])	Wildemann et al. 2015a
Wistar (M)	28	DW	0.006	↑ (17%[b])	0	–	Wildemann et al. 2016
Wistar (M)	28	DW	0.009	↑ (20%[b])	↑ (22%[b])	↑ (20%[b])	Wildemann et al. 2015a
Wistar (M)	28	DW	0.018	↑ (19%[b])	↑ (21%[b])	↑ (18%[b])	Wildemann et al. 2015a
Wistar (M)	28	DW	0.018	0	0	0	Wildemann et al. 2015b
Wistar (M)	28	DW	0.036	0	0	↑ (16%[b])	Wildemann et al. 2015a

Table 2-11. Effects on Blood Pressure in Rats Exposed to Methylmercuric Chloride via Oral Exposure

Strain (sex)	Duration (days)	Route	Dose (mg Hg/kg/day)	SBP	DBP	PP	Reference
Wistar (M)	28	G	0.08	↑ (10%[b])	–	–	Grotto et al. 2009a
Wistar (M)	28	DW	0.216	↑ (21%[b])	↑ (24%[a])	↑ (17%[a])	Wildemann et al. 2015a
Wistar (M)	28	DW	0.216	↑ (10%[b])	0	↑ (10%[a])	Wildemann et al. 2015b
Wistar (M)	28	DW	0.285	↑ (30%[b])	↑ (30%[b])	–	Wildemann et al. 2016
Wistar (M)	28	G	0.4	↑ (20%[b,d])	–	–	Wakita 1987
Wistar (B)	28	G	0.5	0	0	0	Jindal et al. 2011
Wistar (M)	28	DW	0.879	↑ (23%[b])	↑ (31%[b])	0	Wildemann et al. 2015a
Wistar (M)	100	G	0.08	↑ (40%[b])	–	–	Grotto et al. 2009a

[a]Spontaneously hypertensive rat strain; blood pressure could not be adequately assessed in similarly exposed males due to 100% mortality.
[b]Percent change compared to control, estimated from graphically presented data.
[c]Blood pressure elevated after 21 days of exposure and 9 days post-exposure.
[d]Blood pressure elevations observed 42 days to ~1 year post-exposure.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; B = both; DBP = diastolic blood pressure; DW = drinking water; F = female; G = gavage; M = male; NS = not specified PP = pulse pressure; SBP = systolic blood pressure

The effects of methylmercuric chloride on other cardiovascular functions have not been well-studied. LvEDP was significantly increased 3.7-fold with the maximum differential of LvEDP to LvESP decreased by 46–53% in rats administered gavage doses of 0.5 mg Hg/kg/day for 1 month (Jindal et al. 2011). Additionally, these rats showed a 46–53% attenuation of baroreceptor reflex sensitivity at 0.5 mg Hg/kg/day. Heart rate was decreased by 10–18% for up to 16 days in male rats following exposure to two gavage doses of 12 mg Hg/kg (Arito and Takahashi 1991). Exposure to gavage doses of 0.5 mg Hg/kg/day for 1 month did not alter heart rate in male rats (Jindal et al. 2011), and no exposure-related changes in heart rate, stroke volume, cardiac output, electrocardiogram parameters, left ventricular wall thickness, or carotid artery diameter or thickness were observed.

Oral exposure to methylmercuric chloride has not been associated with histopathological lesions in the rodent heart. No treatment-related histopathological changes were observed in the hearts of rats or mice

exposed chronically to dietary doses up to 0.1 or 0.724 mg Hg/kg/day, respectively (Hirano et al. 1986; Mitsumori et al. 1990; Verschuuren et al. 1976).

Predominant Mercury Form Unknown (General Populations). Numerous studies have evaluated the relationship between mercury exposure and cardiovascular effects in general populations. Outcomes evaluated were blood pressure parameters, clinical hypertension, and cardiovascular disease. Study designs include meta- and pooled analyses, prospective studies, and cross-sectional studies. Many studies evaluated large populations (n=2,114–>33,000). The most common biomarkers were BHg and HHg, with some studies measuring mercury in toenails, serum, or erythrocytes. Mean BHg in these studies was <6 µg/L, which is lower than most studies evaluating exposures to methylmercury in populations with high fish diets (Table 2-10).

Blood pressure. Evidence for effects of mercury exposure on blood pressure in general populations is inconclusive. A few studies showed associations between biomarkers and small increases in systolic and/or diastolic blood pressure, although most studies did not show associations (Table 2-12). The largest study, a pooled analysis of 33,298 adults from 23 studies of various population types (general populations, populations with high fish diets, and workers), showed positive associations between HHg and systolic and diastolic blood pressure (Hu et al. 2018). Pooled weighted mean differences (PWMD) in systolic or diastolic blood pressure were calculated as the inverse-variance weighted mean of individual differences between the mean pressure in the lowest and highest mercury category in each study. PWMDs were calculated separately for groups of studies in which the mean HHg was <2 or ≥2 µg/g. For studies with HHg ≥2 µg/g, the PWMD for systolic blood pressure was an increase of 2.20 (95% CI 0.90, 3.49) mm Hg. A dose-response model suggested that systolic blood pressure increased with HHg concentrations above 2–3 µg/g. For diastolic blood pressure, the PWMD was increased by 0.96 mmHg (95% CI 0.08, 1.85) for combined study categories (HHg: 2 and ≥2 µg/g). Similar, small increases in blood pressure were observed in a large cross-sectional study of Korean adults (Park and Choi 2016), and in a small cross-sectional study of pregnant women showing a positive association between blood methylmercury levels, but not blood inorganic mercury levels, and systolic blood pressure (Wells et al. 2017). However, other studies did not find associations or found inverse associations between mercury biomarkers and blood pressure outcomes, including large prospective birth cohort studies in children (Gregory et al. 2016; Kalish et al. 2014) and cross-sectional studies in adults (Mordukhovich et al. 2012; Park et al. 2013; Vupputuri et al. 2005).

Table 2-12. Overview of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Blood Pressure in General Populations

Reference, study type, and population	Biomarker	Blood pressure outcome (biomarker)			
		SBP	DBP	PP	Hypertension
Al-Saleh et al. 2006 Case-control; 185 women (Saudi Arabia)	BHg mean Hypertensive: 3.5 µg/L Control: 3.7 µg/L	–	–	–	0 (BHg)
Bautista et al. 2009 Cross-sectional; 101 adults (Wisconsin)	BHg Gmean: 1.16 µg/L HHg Gmean: 0.27 µg/g	–	–	–	0 (BHg) ↑ (HHg)
Choi et al. 2015 Cross-sectional; 6,213 adults (KNHANES 2008–2010)	SHg mean Men: 5.7 µg/L Women: 4.0 µg/L	–	–	–	↑ (SHg, M, F)
Eom et al. 2014 Cross-sectional; 2,114 adults (South Korea)	BHg Gmean: 3.90 µg/L	–	–	–	0 (BHg)
Gregory et al. 2016 Prospective birth cohort; children assessed at age 7 years (n=1,754) and 17 years (n=1,102); mother enrollment with delivery expected between April 1991 and December 1992 (ALSPAC)	BHg median, maternal: 2.86 µg/L	0 (maternal BHg)[a]	0 (maternal BHg)[a]	–	–
Hu et al. 2018 Pooled analysis; 9 studies, 21,757 adults[a]	HHg stratified <2 µg/g ≥2 µg/g	–	–	–	0 (HHg)

Table 2-12. Overview of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Blood Pressure in General Populations

Reference, study type, and population	Biomarker	Blood pressure outcome (biomarker)			
		SBP	DBP	PP	Hypertension
Hu et al. 2018 Pooled analysis; 23 studies, 33,298 adults[b]	HHg stratified <2 µg/g ≥2 µg/g	↑ (HHg)	↑ (HHg)	–	–
Kalish et al. 2014 Prospective birth cohort; children assessed at early childhood (median age: 3.2 years; n=1,031) and mid-childhood (median age: 7.7 years; n=865); pregnant women enrolled between April 1999 and July 2002) (Massachusetts; Project Viva)[c]	ErHg mean, maternal (2nd trimester): 4.0 ng/g	0 (maternal ErHg)[d]	–	–	–
Kim et al. 2014 Cross-sectional; 3,800 adults (KNHANES 2008–2009)	BHg, mean: 5.44 µg/L	–	–	–	0 (BHg)
Mordukhovich et al. 2012 Cross-sectional; 639 men; samples and assessments conducted 1999–2009 (NAS)	NHg median: 0.22 µg/g	0 (NHg)	0 (NHg)	0 (NHg)	–
Mozaffarian et al. 2012 Prospective cohort; 1,624 male adults (HPFS cohort) and 4,421 female adults (NHS cohort) (United States)	NHg median Males: 0.30 µg/g Females: 0.21 µg/g	–	–	–	0 (NHg, M, F)

Table 2-12. Overview of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Blood Pressure in General Populations

Reference, study type, and population	Biomarker	Blood pressure outcome (biomarker)			
		SBP	DBP	PP	Hypertension
Park and Choi 2016 Cross-sectional; 8,371 adults (KNHANES 2008–2012)	BHg Gmean Males: 4.70 µg/L Females: 3.26 µg/L	↑ (BHg, M, F)	↑ (BHg, M, F)	–	–
Park et al. 2013 Cross-sectional; 6,607 adults (NHANES 2003–2006)	BHg Gmean: 1.03 µg/L BHg Q4: 1.84–32.8 UHg Gmean: 0.51 µg/L UHg Q4: 1.03–50.2	↓ (BHg) ↓ (UHg)	0 (BHg) 0 (UHg)	–	0 (BHg, Q4) 0 (UHg, Q4)
Virtanen et al. 2012b Cross-sectional; 1,757 adults (Finland)	HHg mean: 1.42 µg/g	0 (HHg)	0 (HHg)	0 (HHg)	–
Vupputuri et al. 2005 Cross-sectional; 1,240 women (NHANES 1999–2000)[d]	BHg median: 0.9 µg/L	0 (BHg)	0 (BHg)	–	–
Wells et al. 2017 Cross-sectional; 263 pregnant women (Baltimore, Maryland)	BMeHg Gmean: 0.95 µg/L BIHg Gmean: 0.13 µg/L	↑ (BMeHg) 0 (BIHg)	0 (BMeHg) 0 (BIHg)	↑ (BMeHg) 0 (BIHg)	–

[a]Includes nine studies (five studies of general populations and four studies of populations with high fish diets); BHg and NHg biomarkers were converted to HHg equivalents.
[b]Includes 23 studies (13 studies of general populations, 6 studies of populations with high fish diets, and 3 studies of populations with occupation exposure to elemental Hg); BHg, NHg, and UHg were converted to HHg equivalents.
[c]Child blood pressure assessed at ages 3.2 and 7.7 years; no association observed for either age.
[d]Fish consumers (n=759) and non-fish consumers (n=481).

↑ = positive association; ↓ = inverse association; 0 = no association; – = not reported; ALSPAC = Avon Longitudinal Study of Parents and Children (United Kingdom); BHg = blood mercury; BIHg = blood inorganic mercury; BMeHg = blood methyl mercury; DBP = diastolic blood pressure; ErHg = erythrocyte mercury; F = female(s); Gmean = geometric mean; HHg = hair mercury; HPFS = Health Professionals Follow-up Study; KNHANES = Korea National Health and Nutrition Examination Survey; M = male(s); NAS = Normative Aging Study; NHANES = United States National Health and Nutrition Examination Survey; NHg = toenail mercury; NHS = Nurses' Health Study; PP = pulse pressure; Q = quartile; SBP = systolic blood pressure; SHg = serum mercury; UHg = urine mercury

Hypertension. Of the several studies that have investigated associations between mercury exposure and clinical hypertension in general populations, two studies reported positive associations (Table 2-12). A small cross-sectional study in adults reported an increased risk of hypertension (adjusted odds ratio [OR] 4.19; 95% CI 1.28, 13.76) associated with HHg, but not with BHg (Bautista et al. 2009), and a large cross-sectional study of the KNHANES population showed an association between serum mercury levels and hypertension. Other studies, including a pooled analysis of 21,757 adults from nine studies (Hu et al. 2018) and a large prospective cohort study in 3,427 adults from the United States (Mozaffarian et al. 2012), did not find associations between mercury biomarkers and hypertension.

Cardiovascular disease. Results of numerous studies indicate that exposure of the general population to mercury is not associated with cardiovascular disease (myocardial infarction, stroke, angina, and other cardiovascular diseases); studies are summarized in Table 2-13. No associations between mercury biomarkers and myocardial infarction were found in most studies, including prospective studies, cohort studies, and cross-sectional studies. In contrast, two studies of Finnish men found an association between HHg and myocardial infarction (Salonen et al. 1995; Virtanen et al. 2005) and one case-control study found an association for NHg (Guallar et al. 2002). No studies reported associations between mercury biomarkers and stroke. No convincing evidence was obtained for associations with other cardiovascular diseases (coronary artery disease, coronary heart disease, or cardiovascular disease), with most studies reporting no associations. For example, two large meta-analyses (n=5,830–11,410) did not find associations between mercury biomarkers and cardiovascular disease or coronary heart disease (Chowdhury et al. 2018; Mozaffarian and Rimm 2006). However, a small cross-sectional study reported an association between serum mercury and coronary artery disease, and a prospective study in Finnish men found an association between HHg and atherosclerosis (Asgary et al. 2017; Salonen et al. 2000). Virtanen et al. (2005) found a positive association between HHg and increased risk of cardiovascular disease in a Finish population.

Table 2-13. Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Cardiovascular Disease and Mortality due to Cardiovascular Disease in General Populations

		Cardiovascular disease[a] (biomarker)			
Reference, study type, and population	Biomarker	MI	Stroke	Angina	CAD, CVD, or CHD[b]
Ahlqwist et al. 1999 Prospective; 1,397 women (Sweden)	SHg mean: 17.0 µg/L	0 (SHg)[c]	0 (SHg)	–	–
Asgary et al. 2017 Cross-sectional; 65 male cases, 65 controls (Iran)	SHg mean: 10.14 µg/L	–	–	–	↑ (SHg) CAD
Bergdahl et al. 2013 Cohort; 1,391 women (Sweden)	SHg median: 1.4 µg/L	0 (SHg)[c]	0 (SHg)[c]	–	–
Chen et al. 2018 Case-cohort; 662 cases; 2,494 controls (Southern United States)	SHg median Cases: 0.03 µg/L Controls: 0.03 µg/L	0 (SHg)	–	–	–
Chowdhury et al. 2018 Meta-analysis; 11,410 adults from four studies	Ranges of study means BHg: 0.0039–3.54 µg/L HHg: 1.9 µg/g NHg: 0.25–0.63 µg/g	–	–	–	0 (BHg, HHg, NHg)[d] CVD
Chowdhury et al. 2018 Meta-analysis; 9,169 adults from five studies		–	–	–	0 (BHg, HHg, NHg)[d] CHD
Daneshmand et al. 2016 Prospective; 1,828 men (Finland)	HHg mean: 1.90 µg/g	–	0 (HHg)	–	–
Downer et al. 2017 Nested case-control; 147 cases, 267 controls (Spain)	NHg mean Cases: 0.63 µg/g Controls: 0.67 µg/g	–	–	–	0 (NHg) CVD

Table 2-13. Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Cardiovascular Disease and Mortality due to Cardiovascular Disease in General Populations

		Cardiovascular disease[a] (biomarker)			
Reference, study type, and population	Biomarker	MI	Stroke	Angina	CAD, CVD, or CHD[b]
Guallar et al. 2002 Case-control; 684 male cases, 724 male controls (9 countries)	NHg mean: 0.26 µg/g[e]	↑ (NHg)	–	–	–
Hallgren et al. 2001 Prospective case-control; 78 cases, 156 controls (Sweden)	ErHg mean Cases: 4.44 µg/g Controls: 5.42 µg/g	0 (ErHg)	–	–	–
Kim et al. 2014 Cross-sectional; 3,800 adults (KNHANES 2008–2009)	BHg mean: 5.44 µg/L	0 (BHg)	0 (BHg)	0 (BHg)	–
Mozaffarian and Rimm 2006 Meta-analysis; 5,830 adults from five studies	SHg mean: 17.0 µg/L (one study) ErHg mean: 4.44 µg/g (one study) HHg: >2.03 µg/g (one study) NHg mean: 0.26–0.91 µg/g (range of means from two studies)	–	–	–	0 (SHg, ErHg, HHg, NHg)[d] CHD
Mozaffarian et al. 2011 Nested case-control from two cohorts: adult male cases (n=1,211) and controls (n=1,211) from HPFS cohort; female cases (n=2,216) and controls (n=2,166) from NHS cohort (United States)	NHg median Cases: 0.23 µg/g Controls: 0.25 µg/g	–	0 (NHg)	–	0 (NHg) CHD 0 (NHg) all CVD

Table 2-13. Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Cardiovascular Disease and Mortality due to Cardiovascular Disease in General Populations

		Cardiovascular disease[a] (biomarker)			
Reference, study type, and population	Biomarker	MI	Stroke	Angina	CAD, CVD, or CHD[b]
Raymond et al. 2016 Cross-sectional; 154 men (United States)	BHg median: 2.5 µg/L HHg median: 0.5 µg/g	↑ (BHg) 0 (HHg)	–	0 (BHg, HHg)	0 (BHg, HHg)
Salonen et al. 1995 Cohort; 1,833 men (Finland)	HHg mean: 1.92 µg/g	↑ (HHg)[c]	–	–	0 (HHg) CHD 0 (HHg) CVD
Salonen et al. 2000 Prospective; 1,014 men (Finland)	HHg mean: 1.8 µg/g	–	–	–	↑ (HHg) ATH
Virtanen et al. 2005 Prospective; 1,871 men (Finland)	HHg T3: ≥2.03 µg/g	↑ (HHg)[f]	–	–	↑ (HHg)[e] CVD 0 (HHg)[e] CHD
Virtanen et al. 2012a Prospective; 1,857 men (Finland)	HHg mean: 1.91 µg/g	0 (HHg)	–	–	–
Wennberg et al. 2011 Prospective, nested, case-control; 431 cases, 499 controls (Sweden)	ErHg median: 3.54 µg/L	0 (ErHg)	–	–	–
Wennberg et al. 2012 Prospective, nested case-control; 572 cases, 1,041 controls (Sweden and Finland)	HHg median Sweden: 0.57 µg/g Finland: 1.32 µg/g	↑ (HHg)	–	–	–

Table 2-13. Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Cardiovascular Disease and Mortality due to Cardiovascular Disease in General Populations

Reference, study type, and population	Biomarker	Cardiovascular disease[a] (biomarker)			
		MI	Stroke	Angina	CAD, CVD, or CHD[b]
Yoshizawa et al. 2002 Nested case-control; 470 cases; 464 controls (United States)	NHg mean Dentists: 0.91 µg/g Controls: 0.45 µg/g	–	–	–	0 (NHg) CHD

[a]Unless otherwise noted, associations are for nonfatal effects.
[b]Description as reported by the study authors.
[c]Fatal and nonfatal effects.
[d]Biomarkers in individual studies (BHg, HHg, or NHg) were not transformed to a single biomarker type. For example, BHg and NHg concentrations were not converted to an equivalent HHg concentration.
[e]Group mean HHg was not reported for separately for cases and controls.
[f]Fatal effects.

↑ = positive association; 0 = no association; – = not reported; ATH = carotid atherosclerosis; BHg = blood mercury; CAD = coronary artery disease; CHD = coronary heart disease; CVD = cardiovascular disease; ErHg = erythrocyte mercury; HHg = hair mercury; HPFS = Health Professionals Follow-up Study; KNHANES = Korea National Health and Nutrition Examination Survey; MI = myocardial infarction; NHg = toenail mercury; NHS = Nurses' Health Study; T = tertile; SHg = serum mercury

Mechanisms of Action. Possible mechanisms that may be involved in mercury-induced effects on cardiovascular function have been proposed (da Cunha Martins et al. 2018; Genchi et al. 2017; Grandjean et al. 2004a; Houston 2011; Omanwar and Fahim 2015; Roman et al. 2011; Virtanen et al. 2007). These include: (1) increased oxidative stress and lipid peroxidation due to an imbalance between production of reactive oxygen species (ROS) and anti-oxidative mechanisms; (2) endothelial cell damage and dysfunction resulting from impaired nitric oxide signaling, decreased enzymatic degradation of catecholamines, and increased intracellular levels of calcium, leading to altered coronary vascular reactivity; (3) altered function of the renin-angiotensin system by stimulation of angiotensin converting enzyme (ACE); (4) altered sodium channel function in cardiac muscle, vascular endothelium, or at other sites important for cardiovascular function; (5) inhibition of Na^+-K^+ ATPase on platelet membranes, leading to increased platelet aggregation and clotting disorders; (6) neurological damage, resulting in altered balance of sympathetic and parasympathetic control of heart rate; (7) increased formation of inflammatory mediators (e.g., prostaglandins and leukotrienes); and (8) decreased expression of genes involved in anti-inflammatory responses. Control of cardiovascular function is multi-factorial; therefore,

numerous mechanisms are likely involved. For additional information on general mechanisms of toxicity, see Section 2.21 (General Mechanisms of Action).

2.7 GASTROINTESTINAL

Overview. Gastrointestinal effects of mercury have not been well-studied in humans or animals. No epidemiological studies meeting inclusion criteria were identified for any form of mercury (see inclusion criteria, Section 2.1). Case studies and information from reviews indicate that adverse gastrointestinal effects occur following exposure to mercury vapor or from ingestion of high doses of mercury compounds at levels that were near fatal or fatal. However, the gastrointestinal tract does not appear to be a target of lower, environmental exposures to mercury.

Studies evaluating gastrointestinal effects in animals are available for oral exposure to mercuric chloride and methylmercury. Damage to the gastrointestinal tract (ulceration, hyperplasia) has been reported in rodents following exposure to inorganic salts or organic mercury at high oral doses associated with mortality. There is no evidence of gastrointestinal effects at nonlethal oral doses.

The following summarizes results of epidemiological and animal studies on the gastrointestinal system.

- ***Elemental mercury***
  - *Epidemiology studies*
    - No epidemiological studies on gastrointestinal effects from exposure to elemental mercury were identified.
    - Case studies of individuals acutely exposed to fatal or near-fatal levels of mercury vapor reported nausea and vomiting.
  - *Animal studies*
    - No adequate studies have evaluated gastrointestinal effects of elemental mercury.
- ***Inorganic mercury salts***
  - *Epidemiology studies*
    - No epidemiological studies on gastrointestinal effects from exposure to inorganic mercury salts were identified.
    - Case studies of individuals acutely exposed to fatal or near-fatal levels of inorganic mercuric compounds reported abdominal pain, nausea, diarrhea, ulceration, and hemorrhages of the upper and lower tract.

  - *Animal studies*
    - Gavage doses associated with increased mortality are associated with damage to the forestomach and glandular stomach in mice and with forestomach hyperplasia in rats.
    - No evidence of gastrointestinal effects at nonlethal oral doses was reported.
- ***Organic mercury***
  - *Epidemiology studies*
    - No epidemiological studies on gastrointestinal effects from exposure to organic mercury compounds were identified.
  - *Animal studies*
    - Irritative effects (ulceration) in rats and mice have been reported at chronic oral methylmercury doses associated with increased mortality.
    - No evidence of gastrointestinal effects at nonlethal oral doses was reported.
- ***Predominant mercury form unknown (general populations)***
    - No epidemiological studies on gastrointestinal effects from mercury exposure of general populations were identified.

Confounding Factors. The only studies that were identified regarding gastrointestinal effects of mercury are case reports. Confounding factors are not considered in case reports.

Elemental Mercury—Epidemiological Studies. Epidemiological studies evaluating gastrointestinal effects of elemental mercury and meeting inclusion criteria were not identified (see inclusion criteria, Section 2.1). Abdominal pain (classified by the study authors as a gastrointestinal effect) was observed in a population of gold miners in the Philippines (Cortes-Maramba et al. 2006); however, due to inadequate reporting, it is not possible to provide additional information on gastrointestinal findings. Several case reports of individuals exposed acutely to high levels of elemental mercury vapor generated from heating elemental mercury to high temperatures in confined spaces stated that exposed individuals had nausea, vomiting, and diarrhea (Bluhm et al. 1992; Gore and Harding 1987; Haddad and Stenberg 1963; Hallee 1969; King 1954; Teng and Brennan 1959). No information regarding gastrointestinal effects at low exposure levels of elemental mercury were identified.

Elemental Mercury—Animal Studies. No adequate studies evaluating gastrointestinal effects in animals following exposure to elemental mercury were identified.

Inorganic Mercury Salts—Human Studies. Studies evaluating gastrointestinal effects in populations exposed to inorganic mercury salts were not identified. However, as reviewed by Berlin et al. (2015), cases of accidental or intentional ingestion of near-fatal or fatal doses of mercuric salts indicate that the gastrointestinal tract is a target organ. Acute exposure to mercuric salts at near-fatal or fatal doses has corrosive effects on the gastrointestinal tract, causing gastric and abdominal pain, bloody diarrhea, and necrosis of the intestinal mucosa.

Inorganic Mercury Salts—Animal Studies. In rats, increased incidence of forestomach hyperplasia was observed in male rats exposed to mercuric chloride at chronic gavage doses associated with increased mortality (≥1.8 mg Hg/kg/day); findings were not observed in female rats at doses up to 4 mg Hg/kg/day (NTP 1993). No gross or microscopic changes in the gastrointestinal tract were observed in rats following acute- or intermediate-duration exposure to mercuric chloride at gavage doses up 15 mg Hg/kg/day (Lecavalier et al. 1994; NTP 1993).

In mice, inflammation of the forestomach and necrosis of the forestomach and glandular stomach were observed in mice exposed to mercuric chloride via gavage at a dose of 59 mg Hg/kg/day for 4–5 days; this dose was associated with increased mortality (NTP 1993). No gross or microscopic changes in the gastrointestinal tract were observed in mice at gavage doses up to 30 mg Hg/kg/day for 16 days, 15 mg Hg/kg/day for 6 months, or 7.4 mg Hg/kg/day for 2 years (NTP 1993).

Organic Mercury—Epidemiological Studies. Epidemiological studies evaluating gastrointestinal effects of exposures to methylmercury from high fish diets and meeting inclusion criteria were not identified (see inclusion criteria, Section 2.1). Nausea and diarrhea were observed in a gold mining community in the Philippines exposed to mercury through ingestion of methylmercury in fish (Cortes-Maramba et al. 2006); interpretation of study results is not possible due to inadequate reporting.

Organic Mercury—Animal Studies. Two chronic studies reported gastrointestinal effects consistent with local irritation at doses associated with increased mortality. The first study reported necrosis and ulceration of the cecum in rats following exposure to 3.7 mg Hg/kg/day via drinking water as phenylmercuric acetate (Solecki et al. 1991). The second study reported ulceration of the glandular stomach in male mice following dietary exposure to methylmercuric chloride at 0.686 mg Hg/kg/day; this was not observed in female mice at dietary doses up to 0.601 mg Hg/kg/day (Mitsumori et al. 1990).

In other studies, no exposure-related histopathological changes in the gastrointestinal tract were observed following oral exposure to methylmercuric chloride in cats at intermediate doses up to 0.176 mg or chronic doses up to 0.074 mg Hg/kg/day (Verschuuren et al. 1976), or mice at intermediate- or chronic-duration doses up to 9.5 or 0.724 mg Hg/kg/day, respectively (Hirano et al. 1986; MacDonald and Harbison 1977).

Predominant Mercury Form Unknown (General Populations). Studies evaluating gastrointestinal effects of mercury exposure in general populations were not identified.

Mechanisms of Action. Mercury has a direct caustic effect to the intestinal mucosa and causes extensive precipitation of proteins. Mercury ingestion can destroy and/or modify the composition of intestinal flora (Rice et al. 2014; Seki et al. 2021; Zhao et al. 2020). Mercury exposure biomarkers have been associated with changes in intestinal microflora profiles (Laue et al. 2020; Rothenberg et al. 2016a, 2019). Mercury biomarkers have also been associated with changes in microbiome profiles observed in certain disease states including autism, gestational diabetes, and autoimmune disease (Khan and Wang 2020; Zhai et al. 2019; Zhang et al. 2021). General mechanisms of toxicity of mercury (reviewed in Section 2.21) are likely involved in the development of toxicity to the gastrointestinal system.

2.8 HEMATOLOGICAL

Overview. Epidemiological and animal studies have evaluated hematological effects of mercury, although hematological effects have not been well-studied in humans. Furthermore, few epidemiological studies on hematological effects meet the inclusion criteria for this toxicological profile (see inclusion criteria, Section 2.1). Although there are plausible mechanisms for mercury to adversely affect erythrocytes, data from epidemiological studies are insufficient to determine if exposure to mercury produces adverse hematological effects in humans.

Effects of mercury on the hematological system in animals have been evaluated following acute- and intermediate-duration oral exposure to mercuric chloride and intermediate- and chronic-duration oral exposure to inorganic mercury salts. Available data suggesting impaired clotting, small decreases in RBC counts, and increased WBC counts in rodents exposed to mercuric chloride are of uncertain biological relevance. Available data are inadequate to determine if exposure to organic mercury is associated with adverse hematological effects.

The following summarizes results of epidemiological and animal studies on hematological outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - Inadequate data are available to determine if exposure to elemental mercury is associated with adverse effects to the hematological system. One study showed increased lipid peroxidation in erythrocytes, but erythrocyte function was not assessed.
  - *Animal studies*
    - No studies evaluating hematological effects following exposure to elemental mercury were identified.
- ***Inorganic mercury salts***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to inorganic mercury salts and hematological effects were identified.
  - *Animal studies*
    - A few studies reported impaired clotting in rats following oral exposure to mercuric chloride.
    - Some evidence of small decreases in RBC parameters (count, hemoglobin, hematocrit), but findings are of uncertain biological significance.
    - Inconsistent evidence for increased WBC counts in rodents following oral exposure to mercuric chloride.
- ***Organic mercury***
  - *Epidemiology studies*
    - Data are insufficient to determine if exposure to organic mercury is associated with adverse hematological effects. The only identified study showed an inverse association between hair mercury and blood hemoglobin; however, the study did not account for iron status, a major confounding factor.
  - *Animal studies*
    - Data are insufficient to determine if exposure to organic mercury is associated with adverse hematological effects. One study reported anemia in rats following chronic exposure to phenylmercuric acetate in rat, but this finding is attributed to ulceration in the gastrointestinal tract.

- ***Predominant mercury form unknown (general populations)***
    - Inadequate data are available to determine if exposure of the general population to mercury is associated with adverse effects to the hematological system. One study showed a positive association between BHg and hemoglobin.

Confounding Factors. Numerous factors can complicate interpretation of studies on hematological function. These include nutritional status, negative iron balance, infectious or chronic diseases (e.g., malaria, obesity), micronutrient balance (e.g., vitamin D, vitamin A, vitamin B12, zinc, folate), and other environmental exposures (e.g., lead, cadmium, PCBs) (Weinhouse et al. 2017), which may also vary by mercury exposure status. Few of these factors were considered in the epidemiological studies reviewed in this section and no studies assessed iron balance as a confounding factor for changes in blood hemoglobin.

Elemental Mercury—Epidemiological Studies. Little information is available regarding effects of elemental mercury on the hematological system in humans, with only two studies meeting inclusion criteria for this toxicological profile (see inclusion criteria, Section 2.1); study results are summarized in Table 2-14. A prospective study of women with amalgam fillings found a positive association between serum mercury and blood hemoglobin at the baseline assessment but no association at the 22-year follow-up assessment (Ahlqwist et al. 1999). The toxicological significance of this increased blood hemoglobin is unclear. No associations were observed between serum mercury and leukocyte or platelet counts at the enrollment or follow-up assessments. Due to high participant attrition between the enrollment (n=1,462) and follow-up assessments (n=135), effects on blood hemoglobin reported in this study are difficult to interpret. A cross-sectional study of chloralkali workers found increased erythrocyte activities of glutathione peroxidase (GPX), superoxide dismutase (SOD), and glucose-6-phosphate dehydrogenase (G6PDH), and increased erythrocyte levels of malondialdehyde, compared to controls (Bulat et al. 1998). The study authors stated that results are consistent with increased lipid peroxidation.

Table 2-14. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Hematological Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Ahlqwist et al. 1999 Prospective; 1,462 women with amalgam fillings, enrolled in 1968–1969, and followed through 1980–1981(n=135 at follow-up) (Sweden)	SHg mean: 3.4 µg/L	Blood hemoglobin	↑ (SHg, baseline) 0 (SHg, follow-up)
		Leukocyte count	0 (SHg, baseline) 0 (SHg, follow-up)
		Platelet count	0 (SHg, baseline) 0 (SHg, follow-up)
Bulat et al. 1998 Cross-sectional; 42 chloralkali workers and 75 controls (former Yugoslavia)	BHg mean Workers: 35.9 µg/L Controls: 4.6 µg/L UHg mean Workers: 41.1 µg/g Cr Controls: 4.8 µg/g Cr	Erythrocyte GPX	↓ (BHg, UHg, workers versus controls)
		Erythrocyte SOD	↓ (BHg, UHg, workers versus controls)
		Erythrocyte MDA	↑ (BHg, UHg, workers versus controls)
		Erythrocyte G6PDH	↓ (BHg, UHg, workers versus controls)

↑ = positive association; ↓ = inverse association; 0 = no association; BHg = blood mercury; Cr = creatinine; G6PDH = glucose-6-phosphate dehydrogenase; GPX = glutathione peroxidase; MDA = malondialdehyde; SHg = serum mercury; SOD = superoxide dismutase; UHg = urine mercury

Elemental Mercury—Animal Studies. No studies were located regarding hematological effects in animals after exposure to elemental mercury.

Inorganic Mercury Salts—Animal Studies. Hematological findings following oral exposure to mercuric chloride are shown in Table 2-15. Limited rat data suggest a potential for impaired clotting following acute- or intermediate-duration oral exposure to mercuric chloride, but the effects lessened in severity with increased duration of exposure. Data suggest small decreases in RBC parameters in rodents following acute or intermediate-duration oral exposure to mercuric chloride; however, the biological relevance of these small changes is unclear. There is inconsistent evidence for increased WBC counts in rodents following oral exposure to mercuric chloride.

Table 2-15. Hematological Effects in Rodents Orally Exposed to Mercuric Chloride

Strain (sex); duration; dose (mg Hg/kg/day)	Clotting measures[a]	RBC count[a]	Hemo-globin[a]	Hct[a]	WBC count[a]	Total lympho-cytes[a]	Reference
Rat (NS); 1 day; dose: 0.684	BT: ↑ (88) CT: ↑ (66)	↓ (3)	0	–	↑ (10)	–	Mahour and Saxena 2009
Rat (F); 1 day; dose: 7.4	–	↓ (10)	↓ (9)	↓ (10)	–	–	Lecavalier et al. 1994
Rat (F); 1 day; dose: 9.24	–	↓ (9)	0	↓ (8)	–	–	Lecavalier et al. 1994
Rat (NS); 7 days; dose: 0.033	BT: ↑ (21) CT: ↑ (26)	↓ (1)	↓ (7)	–	↑ (2)	–	Mahour and Saxena 2009
Rat (NS); 14 days; dose: 0.033	BT: ↑ (4) CT: ↑ (13)	↓ (2)	↓ (9)	–	↑ (13)	–	Mahour and Saxena 2009
Rat (NS); 21 days; dose: 0.033	BT: ↓ (2) CT: ↓ (18)	↓ (13)	↓ (5)	–	↑ (17)	–	Mahour and Saxena 2009
Rat (B); 28 days); dose: 0.61–0.76	–	0	0	–	0	–	Jonker et al. 1993
Rat (B); 28 days; dose: 5.1–5.5	–	0	0	–	0	–	Jonker et al. 1993
Rat (M); 90 days; dose: 5.5	–	↓ (5)	↓ (5)	↓ (4)	–	–	Boujbiha et al. 2012
Rat (M); 90 days; dose: 11	–	↓ (10)	↓ (10)	↓ (7)	–	–	Boujbiha et al. 2012
Rat (M); 182 days; dose: 0.04	0 PLT	0	0	0	↑ (140)	–	Agrawal et al. 2014
Mouse (M); 14 days; dose: 0.06	–	↓ (13)	–	–	0	–	Kim et al. 2003
Mouse (M); 14 days; Dose: 0.31	–	↓ (13)	–	–	0	–	Kim et al. 2003
Mouse (M); 14 days; dose: 1.39	–	↓ (11)	–	–	0	–	Kim et al. 2003

Table 2-15. Hematological Effects in Rodents Orally Exposed to Mercuric Chloride

Strain (sex); duration; dose (mg Hg/kg/day)	Clotting measures[a]	RBC count[a]	Hemo-globin[a]	Hct[a]	WBC count[a]	Total lympho-cytes[a]	Reference
Mouse (M); 14 days; dose: 4.81	–	↓ (19)	–	–	↑ (91)	–	Kim et al. 2003
Mouse (M); 49 days: dose: 0.4	–	0	–	–	↑ (35)	↑ (51)	Dieter et al. 1983
Mouse (M); 49 days; dose: 2	–	0	–	–	0	0	Dieter et al. 1983
Mouse (M); 49 days; dose: 11	–	↓ (8)	–	–	↓ (36)	↓ (35)	Dieter et al. 1983

[a]Numbers in ( ) are percent change compared to control, calculated from quantitative data.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; B = both sexes; BT = bleeding time; CT = clotting time; F = female; Hct = hematocrit; M = male; MCV = mean corpuscular volume; NS = not specified; PLT = platelet; RBC = red blood cell; WBC = white blood cell

Increased bleeding and clotting times were observed in rats following a single oral exposure to 0.684 mg Hg/kg or repeated exposure to 0.033 mg Hg/kg/day for 1–3 weeks (Mahour and Saxena 2009). However, biological relevance is unclear as findings became less pronounced with increased duration of exposure. Scanning electron microscopy data from another 4-week study also suggest impaired clotting, showing platelet activation (spreading of platelets, formation of pseudopods) and a poorly developed fibrin network in rats exposed to 0.848 mg Hg/kg/day; fibrin fiber thickness did not differ between groups (Arbi et al. 2017). Due to the qualitative nature of scanning electron microscopy data, Arbi et al. (2017) was not included in the LSE table. No other studies identified measured clotting, but Agrawal et al. (2014) indicated no exposure-related changes to the number of platelets in mice exposed to 0.04 mg Hg/kg/day for 6 months (Agrawal et al. 2014).

Several studies have reported changes in RBC parameters following oral exposure to mercuric chloride; however, the reported changes are small in magnitude and the toxicological relevance is unclear. In single exposure studies in rats, RBC counts were minimally (<5%) decreased at 0.684 mg Hg/kg and mildly (<20%) decreased at ≥7.4 mg Hg/kg (Lecavalier et al. 1994; Mahour and Saxena 2009). Hemoglobin and hematocrit were mildly decreased at ≥7.4 mg Hg/kg (Lecavalier et al. 1994). Following repeated exposure to 0.033 mg Hg/kg/day, RBC counts were minimally decreased after 1 or 2 weeks and

mildly decreased after 3 weeks; hemoglobin levels were mildly decreased at all time points (no duration-dependency) (Mahour and Saxena 2009). Other intermediate-duration studies in rats report no changes in RBC count, hemoglobin levels, or hematocrit following exposure to 0.04 mg Hg/kg/day for 6 months (Agrawal et al. 2014) or doses up to 5.5 mg Hg/kg/day for 28 days (Jonker et al. 1993), and mild decreases in RBC parameters at doses ≤5.5 mg Hg/kg/day for 90 days (Boujbiha et al. 2012). In mice, mild decreases in RBC counts were reported following exposure to ≥0.06 mg Hg/kg/day for 2 weeks (Kim et al. 2003). In contrast, no changes in RBC counts were observed in mice exposed to doses up to 2 mg Hg/kg/day for 7 weeks; similar exposure to 11 mg Hg/kg/day resulted in a mildly decreased RBC count (Dieter et al. 1983).

The evidence for elevated WBC counts in rodents following oral exposure to mercuric chloride is inconsistent. In rats, WBC counts were mildly increased following a single exposure to 0.684 mg Hg/kg or repeated exposure to 0.033 mg Hg/kg/day for 2 or 3 weeks; exposure to 0.033 mg Hg/kg/day for 1 week resulted in minimal increases in WBC count (Mahour and Saxena 2009). Larger elevations in WBC count (>2-fold) were observed in rats exposed to 0.04 mg Hg/kg/day for 6 months. However, other intermediate-duration studies in rats reported no changes in WBC counts at doses up to 5.5 mg Hg/kg/day for 28 days (Jonker et al. 1993). In mice, an increase in WBC count (~2-fold) was observed following exposure to 4.81 mg Hg/kg/day for 14 days; no changes were observed at ≤1.39 mg Hg/kg/day (Kim et al. 2003). A 7-week study in mice observed a non-monotonic response for WBC counts, with increases at 0.4 mg Hg/kg/day, no change at 2 mg Hg/kg/day and decreases at 11 mg Hg/kg/day (Dieter et al. 1983).

The erythrocyte sedimentation rate (ESR) was increased by 21, 10, and 41% in rats exposed to 0.033 mg Hg/kg/day for 7, 14, or 21 days, respectively (Mahour and Saxena 2009). This finding may be related to immune function, as elevated ESR is a marker for inflammation.

Organic Mercury—Epidemiological Studies. Data are not sufficient to determine if exposure to mercury in populations that consume high fish diets produces adverse hematological effects, with only one study meeting inclusion criteria for this toxicological profile (see inclusion criteria, Section 2.1). In a cross-sectional study, Weinhouse et al. (2017) evaluated the association between total HHg (median: 1.18 µg/g) and blood hemoglobin levels in a population of 83 children <12 years of age. This population, from the Peruvian Amazon, was primarily exposed through fish consumption. HHg was inversely associated with blood hemoglobin (β -0.18; 95% CI -0.31, -0.046). Several covariates, including age, sex, and micronutrients, were considered; however, iron status, a major confounding factor, was not assessed in this population.

Organic Mercury—Animal Studies. Hematological data following exposure to organic mercury compounds are very limited. Rats that received phenylmercuric acetate in their drinking water for 2 years showed decreases in hemoglobin, hematocrit, and RBC counts at a dose of 3.7 mg Hg/kg/day (Solecki et al. 1991). The anemia observed in this study may have been secondary to blood loss associated with the ulcerative lesions in the large intestine seen at this dose (see Section 2.7, Gastrointestinal). In other studies, no hematological effects were noted following dietary exposure to methylmercury in rats at doses up to 0.18 mg Hg/kg/day for 2 years (Verschuuren et al. 1976), rabbits at doses up to 0.53 mg Hg/kg/day for 14 weeks (Koller et al. 1977), or cats at doses up to 0.176 mg Hg/kg/day for approximately 16 weeks, 0.074 mg Hg/kg/day for approximately 55 weeks, or 0.046 mg Hg/kg/day for 2 years (Charbonneau et al. 1976).

Predominant Mercury Form Unknown (General Populations). One study evaluating hematological effects of mercury in general populations meeting inclusion criteria was identified (Park and Lee 2013). In a cross-sectional study of 4,522 adults from the 2008–2010 KNHANES population, positive associations were observed between BHg and hemoglobin in men and women. Mean BHg was 4.34 µg/L in men and 3.73 µg/L in women. The toxicological significance of this finding is unclear, and the study authors did not propose a mechanism for mercury-induced increases in hemoglobin.

Mechanisms of Action. Epidemiological and animal studies do not provide strong evidence that mercury adversely affects the hematological system. However, mercury is transported into erythrocytes and has a high affinity for hemoglobin and other protein and non-protein sulfhydryls (see Section 3.1, Toxicokinetics); therefore, there is the potential for mercury to adversely affect erythrocytes. Weinhouse et al. (2017) reviewed several possible mechanisms for mercury-induced adverse effects on erythrocytes, including: (1) oxidative damage and inflammatory effects; (2) erythrocyte apoptosis; (3) decreased erythrocyte production; (4) decreased heme biosynthesis; (5) dysregulation of iron homeostasis; and (6) exacerbation of vitamin B12 or folate deficiency.

2.9 MUSCULOSKELETAL

Overview. Few epidemiological and animal studies have evaluated musculoskeletal effects of mercury. However, based on the available data, the musculoskeletal system does not appear to be a sensitive target of mercury exposure. No epidemiological studies were identified for elemental and organic mercury. A few studies in general populations evaluated associations between mercury biomarkers and indicators of

bone mineral status, and risks of sarcopenia, and periodontitis. Results indicate mercury exposure does not adversely affect bone mineral. Data are inadequate to determine if mercury is associated with sarcopenia or periodontitis.

No primary musculoskeletal effects were observed in rodents following oral exposure to inorganic salts or organic mercury. Effects secondary to renal impairment (mercuric chloride) and neurological impairment (methylmercury) included fibrous osteodystrophy and muscle weakness/atrophy, respectively. No inhalation studies were available.

The following summarizes results of epidemiological and animal studies on musculoskeletal outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - No epidemiological studies on musculoskeletal effects from exposure to elemental mercury were identified.
  - *Animal studies*
    - No studies evaluating musculoskeletal effects following exposure to elemental mercury were identified.
- ***Inorganic mercury salts***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to inorganic mercury salts and musculoskeletal effects were identified.
  - *Animal studies*
    - No primary musculoskeletal effects were observed in rats or mice following acute, intermediate, or chronic oral exposure to mercuric chloride.
    - Fibrous osteodystrophy was reported in male rats following chronic exposure to mercuric chloride. This was considered secondary to marked renal impairment.
- ***Organic mercury***
  - *Epidemiology studies*
    - No epidemiological studies on musculoskeletal effects from exposure to organic mercury were identified.
  - *Animal studies*
    - No primary musculoskeletal effects were observed in rats or mice following intermediate or chronic oral exposure to mercuric chloride.

    - Muscle weakness and atrophy were reported in rats following acute exposure to methylmercury. This was considered secondary to neurological impairment.
- ***Predominant mercury form unknown (general populations)***
    - Based the limited data, exposure of the general population to mercury is not associated with adverse effects on bone.
    - Results of single studies found positive associations between mercury biomarkers and sarcopenia and periodontitis.

Confounding Factors. Factors associated with bone mineral status that may also be associated with mercury exposure status include nutrition, age, pregnancy, menopausal status, activity level, and exposure to other chemicals that act on bone mineral (e.g., cadmium).

Elemental Mercury—Epidemiological Studies. No studies on musculoskeletal effects from exposure to elemental mercury were identified.

Elemental Mercury—Animal Studies. No studies were located regarding musculoskeletal effects in animals after exposure to elemental mercury.

Inorganic Mercury Salts—Animal Studies. Fibrous osteodystrophy was reported in male rats following chronic exposure to mercuric chloride at gavage doses ≥1.8 mg Hg/kg/day; this finding is considered secondary to marked renal impairment observed at these doses (NTP 1993). Fibrous osteodystrophy was not observed in female rats at chronic doses up to 4 mg Hg/kg/day; renal impairment was also not observed in females. In shorter-duration exposure studies, no histopathological lesions in muscle or bone were observed in rats at acute doses up to 9.24 mg Hg/kg/day (Lecavalier et al. 194) or intermediate-doses up to 4 mg Hg/kg/day (NTP 1993). In mice, no histopathological lesions in muscle or bone were observed at intermediate- or chronic-duration doses up to 15 or 7.4 mg Hg/kg/day, respectively (NTP 1993).

Organic Mercury—Animal Studies. Skeletal muscle weakness and wasting/atrophy were observed in rats exposed to methylmercuric chloride at gavage doses of ≥4 mg Hg/kg/day for 10–12 days (Su et al. 1998; Usuki et al. 1998). These findings are considered neurogenic in nature, as opposed to a direct toxic action of methylmercury on skeletal muscle. Effects occurred at doses associated with overt signs of neurotoxicity and mortality.

No exposure-related changes in muscle or bone histology were observed following oral exposure to methylmercuric chloride in cats at doses up to 0.176 mg Hg/kg/day for approximately 16 weeks, 0.074 mg Hg/kg/day for approximately 55 weeks, or 0.046 mg Hg/kg/day for 2 years (Charbonneau et al. 1976); rats at doses up to 0.18 mg Hg/kg/day for 2 years (Verschuuren et al. 1976); or mice at doses up to 0.724 mg Hg/kg/day for 2 years (Hirano et al. 1986; Mitsumori et al. 1990).

Predominant Mercury Form Unknown (General Populations). Few studies on musculoskeletal effects of mercury in general populations were identified. Cross-sectional studies evaluated associations between mercury biomarkers and bone outcomes (bone mineral density, bone resorption, and risks of osteopenia, osteoporosis, and fracture), sarcopenia, and periodontitis; studies are summarized in Table 2-16. Several studies evaluated outcomes in KNHANES participants (Cho et al. 2012; Kim et al. 2016a; Lim et al. 2016; Yoo et al. 2016). BHg was used as the biomarker in all studies, except for one study that used HHg (Han et al. 2009).

Table 2-16. Results of Epidemiological Studies Evaluating Exposure to Mercury (Predominant Mercury Form Unknown) and Musculoskeletal Effects in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Callan et al. 2015 Cross-sectional; 77 women ≥50 years of age (Australia)	BHg median: 2.04 µg/L	Bone resorption	↓ (BHg, Q2−Q4)
Cho et al. 2012 Cross-sectional; 481 post-menopausal women (KNHANES)	BHg, quartiles Q1: <2.67 µg/L Q2: ≥2.67−<3.74 µg/L Q3: ≥3.74−<5.23 µg/L Q4: ≥5.23 µg/L	Risk of osteoporosis	↓ (BHg, Q2−Q4)
Han et al. 2009 Cross-sectional; 598 men and 730 women (Korea)	HHg, median With periodontitis: 1.11 µg/g No periodontitis: 0.97 µg/g	Risk of periodontitis	↑ (HHg, men) 0 (HHg, women)
Kim et al. 2016a Cross-sectional; 1,190 men ≥50 years of age (KNHANES)	BHg, quartiles Q1: <3.347 µg/L Q2: 3.347−5.337 µg/L Q3: 5.337−8.914 µg/L Q4: >8.014 µg/L	Bone mineral density Total hip Femur neck Lumbar spine	 0 (BHg) ↑ (BHg) 0 (BHg)
		Risk of osteopenia and osteoporosis Total hip Femur neck Lumbar spine	 ↓ (BHg, Q4) ↓ (BHg, Q4) 0 (BHg, Q4)
		Risk of facture	0 (BHg, Q4)

Table 2-16. Results of Epidemiological Studies Evaluating Exposure to Mercury (Predominant Mercury Form Unknown) and Musculoskeletal Effects in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Lim et al. 2016 Cross-sectional; 2,429 adults (KNHANES)	BHg, quartiles Q1: <2.549 µg/L Q2: 2.549−3.798 µg/L Q3: 3.798−5.710 µg/L Q4: >5.710 µg/L	Risk of osteopenia and osteoporosis	0 (BHg, Q4)
Pollack et al. 2013 Cross-sectional; 248 premenopausal women (Buffalo, New York)	BHg, mean: 1.51 µg/L	Bone mineral density Whole body Total hip Lumbar spine Wrist	 0 (BHg) 0 (BHg) 0 (BHg) 0 (BHg)
		Risk of low bone mineral density Whole body Total hip Lumbar spine Wrist	 0 (BHg) 0 (BHg) ↓ (BHg) 0 (BHg)
Yoo et al. 2016 Cross-sectional; 344 men and 360 women >65 years of age (KNHANES)	Men, BHg, quartile means Q1: 1.79 Q2: 2.95 Q3: 4.48 Q4: 9.69 Women, BHg, quartile means Q1: 1.79 Q2: 2.95 Q3: 4.41 Q4: 10.30	Risk of sarcopenia	↑ (BHg, Q4, men and women)

↑ = positive association; ↓ = inverse association; 0 = no association; BHg = blood mercury; HHg = hair mercury; KNHANES: Korean National Health and Nutrition Examination Survey; Q = quartile

Associations between mercury and bone outcomes were evaluated in postmenopausal women (≥50 years of age), pre-menopausal women, men ≥50 years of age, and adults ≥18 years of age. Results indicate that mercury exposure of general populations is not associated with adverse effects on bone; instead, mercury could possibly have a protective effect. In older women, inverse associations were observed between BHg and bone resorption and the risk of osteoporosis (Callan et al. 2015; Cho et al. 2012). In pre-menopausal women, no associations were observed between BHg and bone mineral density, and the risk of having a low bone mineral density of the lumbar spine was decreased (Pollack et al. 2013). In older men, an inverse association was observed between BHg and risk of osteopenia and osteoporosis of the hip and femur, and increasing BHg was associated with increasing bone mineral density of the femur (Kim et al. 2016a). However, no association was observed between BHg and the risk of fracture. In adults

≥18 years of age, no associations were observed between BHg and the risk of osteopenia and osteoporosis (Lim et al. 2016). Taken together, results of these studies indicate that mercury exposure of general populations does not adversely affect bone mineral status.

Other studies found positive associations between HHg and the risk of periodontitis in men, but not women (Han et al. 2009), and between BHg and the risk of sarcopenia in men and women (Yoo et al. 2016). These findings have not been corroborated.

Mechanisms of Action. Mechanisms for possible positive effects of mercury on bone mineral status have not been well-investigated. It has been proposed that mercury may alter activity of osteoclasts and osteoblasts (Cho et al. 2012; Kim et al. 2016a).

2.10 HEPATIC

Overview. Hepatic effects of mercury have not been extensively studied in humans or animals. Few epidemiological studies have evaluated hepatic effects associated with mercury exposures, most likely because the liver does not appear to be a sensitive target organ for mercury, relative to other systems (e.g., nervous system). No epidemiological studies of hepatic effects that reported mercury biomarkers were identified for exposure to elemental mercury or in populations with high fish diets. A few studies on liver effects in general populations were identified; these studies evaluated associations between mercury biomarkers and dyslipidemias. Data are not adequate to determine if general exposure to mercury adversely affects the liver.

Studies evaluating hepatic effects are available for inhalation exposure to mercury vapor and oral exposure to mercuric chloride, mercuric sulfide, or methylmercury. There is limited evidence of moderate-to-severe liver damage following inhalation exposure to mercury vapor at high acute-duration concentrations or repeated exposure to lower concentrations. Available data do not indicate that the liver is a sensitive target of toxicity following oral exposure to inorganic mercury salts or organic mercury. There is no evidence of histopathological damage following oral exposure, and very limited evidence of mild hepatic effects (altered clinical chemistry and serum lipids; decreased liver weight).

The following summarizes results of epidemiological and animal studies on hepatic outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - No studies evaluating effects from exposure to elemental mercury in workers or amalgam-exposed populations were identified.
  - *Animal studies*
    - Limited data indicate that acute-duration exposure to high concentrations or continuous exposure to low concentrations may cause moderate-to-severe liver damage.
- ***Inorganic mercury salts***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to inorganic mercury salts and hepatic effects were identified.
  - *Animal studies*
    - Hepatic lesions have not been reported in rodents following exposure to mercuric chloride.
    - Evidence of mild hepatic effects in rodents following exposure to mercuric chloride (altered serum chemistry, decreased liver weight) is limited and inconsistent, especially at low oral doses.
    - One study found no adverse hepatic effects in mice exposed to extremely high levels of mercuric sulfide.
- ***Organic mercury***
  - *Epidemiology studies*
    - No studies reporting mercury biomarkers and hepatic endpoints in populations with high fish diets were identified.
    - No adverse hepatic effects were observed in a long-term follow-up study of the Minamata population; biomarkers were not reported.
  - *Animal studies*
    - Hepatic lesions have not been reported in cats or rodents following exposure to methylmercury.
    - Evidence of mild hepatic effects in rodents is very limited following exposure to methylmercury; one study reported decreased liver weight and one study reported a duration-related increase in serum cholesterol following exposure to moderate-to-high doses of methylmercury.

- ***Predominant mercury form unknown (general populations)***
    - A few studies evaluated associations between mercury biomarkers and serum liver enzyme activities, with inconsistent results. For studies showing positive associations between biomarkers and liver enzymes, the magnitude of changes was small and did not represent toxicologically significant increases.
    - One study reported positive associations between toenail mercury and total and LDL-cholesterol in blood. The magnitude of changes was small and results have not been corroborated.

Confounding Factors. Numerous factors that can affect measures of hepatic function may also be associated with mercury exposure status. These include: age; obesity; family history of liver disease; alcohol use; smoking; exposure to other chemicals; concurrent disease; and drug use, including prescription drugs and over-the-counter medications.

Elemental Mercury—Epidemiological Studies. Studies evaluating associations between elemental mercury exposure and hepatic function in occupationally exposed populations or populations exposed to dental amalgam were not identified.

Elemental Mercury—Animal Studies. Serious liver effects have been noted in a two animal studies. Extensive hepatocyte degeneration was reported in female rats continuously exposed to 1 mg Hg/m^3 for 45 days (Yahyazedeh et al. 2017). Additional histopathological findings included enlarged blood vessels, dilated sinusoids, and increased perivascular connective tissue. Stereology showed increased liver volume in the sinusoids and decreased volume of the parenchyma. The numerical density and total number of hepatocytes were significantly decreased, but the mean numerical density and total number of binucleated hepatocytes were significantly elevated. The nuclear diameter of hepatocytes was significantly decreased. A series of studies in rabbits reported hepatic effects ranging from moderate pathological changes to severe liver necrosis of the colon following exposure to 28.8 mg Hg/m^3 for 6–30 hours or 6 mg Hg/m^3 for 6–11 weeks (7 hours/day, 5 days/week) (Ashe et al. 1953). Mild pathological changes were observed at shorter exposure durations and following intermittent exposure to 3 mg Hg/m^3 for up to 12 weeks (Ashe et al. 1953). The usefulness of these results is limited because of small animal numbers per timepoint, lack of controls (in acute studies), lack of incidence data, lack of details regarding observed pathological changes, and unclear distinction between primary and secondary effects (i.e., pathological changes secondary to induced shock). Due to lack of controls, acute studies are not presented in the LSE table.

In other studies, no changes in liver histology were reported in rats following exposure to 8 mg Hg/m^3 for 2 hours/day for up to 10 days (Morgan et al. 2002) or 3 mg Hg/m^3 for 12–42 weeks (5 days/week; 3 hours/day) (Kishi et al. 1978).

Inorganic Mercury Salts—Animal Studies. Available data do not indicate that the liver is a sensitive target of toxicity in rodents orally exposed to mercuric chloride or sulfide.

No changes in liver weight or histology were observed in rats exposed to mercuric chloride at acute-duration doses up to 9.24 mg Hg/kg/day (Lecavalier et al. 1994) or intermediate- or chronic-duration doses up to 4 mg Hg/kg/day (NTP 1993), or in mice at intermediate- or chronic-duration doses up to 15 or 7.4 mg Hg/kg/day, respectively (NTP 1993). However, decreased liver weight has been reported following oral exposure to mercuric chloride in one rat and one mouse study. In a 2-generation study in rats, relative liver weights were decreased >20% in F0 females exposed to gavage doses ≥0.55 mg Hg/kg/day; no changes in liver weight were observed in F1 females at doses up to 1.98 mg Hg/kg/day or F0 or F1 males at doses up to 1.31 mg Hg/kg/day (Atkinson et al. 2001). In mice, absolute liver weight was decreased by 14 and 16% following exposure to 2 or 11 mg Hg/kg/day, respectively, as mercuric chloride in drinking water for 7 weeks (Dieter et al. 1983). Relative organ weights were not reported, but body weight effects were only noted at 11 mg Hg/kg/day. In 16-day gavage studies that only evaluated liver weight, no changes were observed in rats or mice at intermediate doses up to 15 mg Hg/kg/day and 30 mg Hg/kg/day, respectively (NTP 1993); findings were not included as NOAELs in the LSE table (inadequate hepatic endpoint evaluation).

Altered hepatic clinical chemistry values (alkaline phosphatase [ALP], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], cholinesterase) have been reported in rodents in some oral exposure studies, generally at high doses (see Table 2-17). No changes in serum alanine aminotransferase (ALT), acid phosphatase, sorbitol dehydrogenase, and/or bilirubin were observed in studies included in Table 2-17. Acute exposure to gavage doses up to 9.24 mg Hg/kg/day was not associated with adverse changes in serum chemistry; however, a significant decrease in serum LDH (non-adverse direction) was observed at ≥7.4 mg Hg/kg/day (Lecavalier et al. 1994). Dietary exposure to doses ≥11.9 mg Hg/kg/day resulted in increased serum ALP and AST levels in rats; no changes were observed at ≤11.4 mg Hg/kg/day (Jonker et al. 1993). One study reported increased ALP, AST, and LDH in Wistar rats exposed to 0.4 mg Hg/kg/day via an unspecified oral route for 6 months (Agrawal et al. 2014). However, no alterations in hepatic serum chemistry were observed at intermediate- or chronic-duration gavage

doses up to 4 mg Hg/kg/day (NTP 1993). In mice, alterations in clinical chemistry are limited to increased serum cholinesterase levels in males exposed to drinking water doses ≥2 mg Hg/kg/day (Dieter et al. 1983). In other studies, no changes in hepatic clinical chemistry were observed at intermediate- or chronic-duration doses up to 15 or 7.4 mg Hg/kg/day, respectively (Khan et al. 2004; Kim et al. 2003; NTP 1993).

Table 2-17. Hepatic Clinical Chemistry in Rodents Orally Exposed to Mercuric Chloride

Species; duration	Dose (mg Hg/kg/day)	ALP[a]	AST[a]	LDH[a]	Cholinesterase[a]	Reference
Rat; 1 day	7.4–9.24	0	0	↓ (38–54)	–	Lecavalier et al. 1994
Rat; 28 days	5.8	0	0	–	–	Jonker et al. 1993
Rat; 28 days	6.1	0	0	–	–	Jonker et al. 1993
Rat; 28 days	11.4	0	0	–	–	Jonker et al. 1993
Rat; 28 days	11.9	↑ (21)	0	–	–	Jonker et al. 1993
Rat; 28 days	20.9	↑ (28)	↑ (16)	–	–	Jonker et al. 1993
Rat; 28 days	23.6	↑ (22)	↑ (18)	–	–	Jonker et al. 1993
Rat; 182 days	0.230	0	0	0	0	NTP 1993
Rat; 182 days	0.4	↑ (40)	↑ (56)	↑ (21)	–	Agrawal et al. 2014
Rat: 182 days	0.462–4	0	0	0	0	NTP 1993
Rat: 450 days	1.8–4	0	–	–	0	NTP 1993
Mouse; 14 days	0.06–4.81	–	0	–	–	Kim et al. 2003
Mouse; 49 days	0.4	–	0	0	0	Dieter et al. 1983
Mouse: 49 days	2	–	0	0	↑ (59)	Dieter et al. 1983
Mouse: 49 days	11	–	0	0	↑ (55)	Dieter et al. 1983
Mouse: 61–79 days	0.18–0.74	0	0	0	–	Khan et al. 2004

Table 2-17. Hepatic Clinical Chemistry in Rodents Orally Exposed to Mercuric Chloride

Species; duration	Dose (mg Hg/kg/day)	ALP[a]	AST[a]	LDH[a]	Cholinesterase[a]	Reference
Mouse; 182 days	0.923–15	0	0	–	–	NTP 1993
Mouse: 450 days	4–7.4	0	–	–	0	NTP 1993

[a]Numbers in ( ) are percent change compared to control, calculated from quantitative data.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; ALP = alkaline phosphatase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase

Two intermediate-duration dietary studies evaluated serum lipids in wild-type and spontaneously hypertensive Wistar rats exposed to mercuric chloride (Takahashi et al. 2000a, 2000b). In spontaneously hypertensive rats, serum high-density lipoprotein (HDL) and triglycerides were decreased in a dose-related manner at all tested doses (≥0.07 mg Hg/kg/day); however, HDL was not decreased in wild-type rats until doses of 1.7 mg Hg/kg/day and triglycerides were unaffected. No exposure-related changes in total cholesterol or LDL were observed in spontaneously hypertensive or wild-type rats at doses up to 2.2 or 1.7 mg Hg/kg/day (Takahashi et al. 2000a, 2000b). In other studies, no changes in total cholesterol were observed in rats at acute gavage doses up to 9.24 mg Hg/kg/day (Lecavalier et al. 1994), or in mice at intermediate-duration water or gavage doses up to 11 or 0.74 mg Hg/kg/day, respectively (Dieter et al. 1983; Khan et al. 2004).

No changes in hepatic clinical chemistry, weight, or histology were observed in mice exposed to mercuric sulfide at gavage doses up to 1,700 mg Hg/kg/day for 4 weeks (Son et al. 2010).

Organic Mercury—Epidemiological Studies. No studies evaluating hepatic effects in populations with high fish diets and reporting exposures based on mercury biomarkers were identified. A cross-sectional screening survey of the Minamata population (n=1,406) did not find an increase in the prevalence of liver disease or abnormal findings on ultrasonographic examinations; no mercury biomarkers were reported (Futatsuka et al. 1992).

Organic Mercury—Animal Studies. Available data do not indicate that the liver is a sensitive target of toxicity in rodents orally exposed to methylmercury. No changes in liver histology were observed in mice or cats at intermediate-duration doses up to 9.5 or 0.176 mg Hg/kg/day, respectively (Charbonneau et al. 1976; MacDonald and Harbison 1997), or in rats, mice, or cats at chronic-duration doses up to 0.18, 0.724, or 0.074 mg Hg/kg/day, respectively (Charbonneau et al. 1976; Hirano et al. 1986; Mitsumori et al.

1990; Verschuuren et al. 1976). One study in rats reports a 20% decrease in relative liver weight following exposure to 0.879 mg Hg/kg/day for 28 days (Wildemann et al. 2015a). No changes in liver weight were observed in rats or mice at acute doses up to 2.8 and 9.99 mg Hg/kg/day, respectively or intermediate-duration doses up to 0.216 or 0.77 mg Hg/kg/day, respectively (Belles et al. 2002; Fossato da Silva et al. 2011; Ilback 1991; Wildemann et al. 2015a, 2015b). Studies evaluating liver weight in the absence of histology or clinical chemistry were not included in the LSE table due to inadequate endpoint evaluation.

One study evaluated serum lipids in mice following acute- or intermediate-duration exposure; no other hepatic endpoints were evaluated (Moreira et al. 2012). In C57BL/6 mice, total cholesterol was increased approximately 40 and 80% after exposure to 5.6 mg Hg/kg/day for 14 or 21 days; no changes in total cholesterol were observed after a 7-day exposure, and no changes in HDL, non-HDL, or triglycerides were observed at any time point. In Swiss mice, total cholesterol, HDL, non-HDL, and triglyceride levels were all increased by approximately 110, 135, 110, and 90%, respectively.

Predominant Mercury Form Unknown (General Populations). Few studies have evaluated associations between mercury exposure and hepatic effects in general populations. Four studies examined associations between mercury exposure and the liver enzymes ALT, AST, and gamma-glutamyltransferase (GGT); and one study evaluated associations between NHg and dyslipidemia, including interactions with selenium, in a Korean population (Park and Seo 2017).

Studies examining potential associations between mercury exposure and liver enzymes are summarized in Table 2-18. Of these, three assessed populations from Korea (Choi et al. 2017; Lee et al. 2014, 2017a) and one evaluated data from NHANES (Lin et al. 2014a). Total BHg concentrations ranged from 0.94 µg/L (median) in the NHANES population (Lin et al. 2014a) to 4.33 µg/L (geometric mean at baseline) in a Korean study population (Choi et al. 2017). Results of associations between BHg and liver enzymes were inconsistent. Positive associations were observed between BHg and ALT (Lee et al. 2014, 2017a), AST (Lee et al. 2014), and GGT (Choi et al. 2017); no associations were observed between BHg and ALT (Choi et al. 2017; Lin et al. 2014a), AST (Choi et al. 2017; Lee et al. 2017a; Lin et al. 2014a), and GGT (Lee et al. 2017a; Lin et al. 2014a). The magnitude of changes in serum liver enzymes was very small. For example, GGT was increased by 10.3% compared to baseline at the 5-year follow-up period (Choi et al. 2017). Lee et al. (2014) reported that ALT increased by 1.067 U/L and AST increased 0.676 U/L per doubling of BHg; mean ALT 22.23 U/L and mean AST 22.21 U/L. These changes represent a small increase per doubling of BHg and do not represent toxicologically significant increases;

the study authors classified changes in ALT and AST as subclinical. Given the inconsistent results and the small magnitude of changes, the liver does not appear to be a sensitive organ for mercury in the general population.

Table 2-18. Results of Epidemiological Studies Evaluating Exposure to Mercury (Predominant Mercury Form Unknown) and Hepatic Effects in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated		
		ALT	AST	GGT
Choi et al. 2017 Longitudinal; 508 adults; biomarker and liver enzymes were assessed at baseline and at a 4-year follow-up (Korea)	BHg Gmean Baseline: 4.33 µg/L Follow-up: 4.08 µg/L	0 (BHg)	0 (BHg)	↑ (BHg)
Lee et al. 2014 Cross-sectional; 6,689 adults (KNHANES)	BHg Gmean: 3.987 µg/L	↑ (BHg)	↑ (BHg)	NR
Lee et al. 2017a Longitudinal (panel); 550 elderly adults ≥60 years of age (Korea)	BHg Gmean: 2.78 µg/L Q4 men: ≥5.41 µg/L Q4 women: ≥3.53 µg/L	↑ (BHg, Q4) OR for abnormal ALT	0 (BHg, Q4)	0 (BHg, Q4)
Lin et al. 2014a Cross-sectional; 3,769 adults (NHANES)	Median BHg (total): 0.94 µg/L BMeHg: 0.60 µg/L	0 (BHg)	0 (BHg)	0 (BHg)

↑ = positive association; ↓ = inverse association; 0 = no association; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BHg = blood mercury; BMeHg = blood methyl mercury; GGT = gamma-glutamyltransferase; Gmean = geometric mean; KNHANES = Korean National Health and Nutrition Examination Survey; NHANES = National Health and Nutrition Examination Survey; NR = not reported; Q = quartile

In addition to studies evaluating liver enzymes, two studies evaluated associations between mercury biomarkers and dyslipidemias (Fan et al. 2017; Park and Seo 2017). Fan et al. (2017) investigated associations between BHg and blood levels of triglycerides, LDL cholesterol, HDL cholesterol, and total cholesterol in 5,404 children and adolescent (ages 6–19 years) NHANES participants. The mean SHg was 0.65 µg/L. Positive associations were observed between SHg and total cholesterol in females ages 6–12 years and in males and females ages 13–19 years, but not in males ages 6–12 years. No associations were observed for triglycerides, LDL cholesterol, or HDL cholesterol. Park and Seo (2017) evaluated associations between NHg and dyslipidemias (hypercholesterolemia, LDL-hypercholesterolemia, HDL-hypocholesterolemia, and hypertriglyceridemia) and the potential modifying effect of selenium (measured in toenails) in a population of adults from Korea. Mean NHg concentrations in men and women were

0.47 and 0.43 µg/g, respectively. Although the study authors stated that the study population had a high fish intake, no measurements were provided for BHg or HHg to compare exposures to biomarkers levels reported in other populations with high fish diets reviewed in this profile (e.g., Faroe Islands or Seychelle Islands). LDL-hypercholesterolemia was positively associated with NHg, and hair selenium did not affect the association. Hypercholesterolemia and dyslipidemia were positively associated with NHg in participants with low, but not high, selenium. No associations were observed between NHg and HDL-hypocholesterolemia and hypertriglyceridemia in low- and high-selenium groups. The magnitude of changes in blood lipid profiles was small (LDL-cholesterol, 2.4% increase; triglyceride, 12% increase). Data are not adequate to determine if mercury exposure of the general population is associated with altered lipid profiles.

Mechanisms of Action. General mechanisms of toxicity of mercury (reviewed in Section 2.21) are likely involved in the development of hepatic effects. These general mechanisms include: increased ROS production and oxidative stress; degeneration of fatty acids; mitochondrial depolarization and ATP depletion; damage to hepatic cell membranes; and cell necrosis and death.

2.11 RENAL

Overview. The renal toxicity of mercury is well established and is not in dispute. All forms of mercury are nephrotoxic, but inorganic forms appear to be more nephrotoxic than organic forms (Zalups 2000). Nephrotoxicity of mercury is characterized primarily by damage to the *pars recta* segment of the proximal tubule, with involvement of proximal convoluted tubules and distal tubule in severe toxicity (Berlin et al. 2015; Zalups and Diamond 2005). Damage to the *pars recta* segment of the proximal tubule is consistent with localized uptake of mercury in the renal cortex and outer stripe of the outer medulla (see Section 3.1.2). In the proximal tubule, early changes include loss of the brush boarder membrane, resulting in urinary excretion of brush boarder enzymes, such as ALP and GGT. As damage to the proximal tubule becomes more severe and progresses to necrosis, intracellular enzymes, such as alanine aminopeptidase (AAP) and N-acetyl-β-D-glucosaminidase (NAG), are excreted in the urine. The glomerular basement membrane has also been shown to be a target of inorganic mercuric mercury in rabbits and some strains of rats (Druet et al. 1978; Roman-Franco et al. 1978; Sapin et al. 1977). The mechanism for mercury-induced glomerulonephritis in these animal models involves auto-immunity and deposition of immune complexes in the glomerular basement membrane. Although mercury has not been definitively shown to be a cause of glomerulonephritis in humans, were it to occur, the primary outcomes could include proteinuria and declines in glomerular filtration rate (GFR).

While it is established that mercury is nephrotoxic, results of epidemiological studies evaluating renal effects of mercury at occupational and environmental exposure levels are inconsistent with regard to markers of glomerular and tubular damage. There is some evidence that supports associations between elemental mercury exposure and adverse renal effects and between mercury exposure and renal effects in the general population; however, the kidney does not appear to be a sensitive target organ for mercury under these occupational and environmental exposure conditions. Epidemiological data are from studies evaluating associations between mercury and renal effects in workers exposed to elemental mercury, populations exposed to elemental mercury through dental amalgam fillings, and general populations exposed to unknown forms of mercury. Few studies have been conducted in populations exposed to mercury from high fish diets, presumably because the kidney is not a sensitive target organ for methylmercury at these environmental exposures. Although there are no epidemiological studies on populations exposed to inorganic mercury salts, case reports of accidental or intentional ingestion show severe renal damage from high-dose exposure. In this discussion, the following markers were interpreted to be indicative of changes in glomerular function: GFR; blood urea nitrogen (BUN), or serum urea nitrogen (SUN); serum creatinine and serum 2-microglobuin (β_2M); and urine protein and albumin. In most studies in which GFR was assessed, GFR was estimated using equations relating GFR to serum creatinine and other factors that contribute to variance in GFR (e.g., body size, age, sex, race) (Levey et al. 2009). GFR estimated from these equations is referred to as eGFR to distinguish it from estimates based on measurements of clearance of GFR markers (e.g., creatinine, iothalamate). Decreases in GFR typically result in increases in BUN, SUN, serum creatinine, and serum β_2M. Increases in urinary excretion of protein or albumin is typically observed in association with impaired glomerular function (i.e., increased glomerular filtration of protein); however, impaired renal tubule processing of filtered protein can also contribute to proteinuria. Renal tubular damage was assessed from measurements of renal tubule cell proteins in urine, which are not typically released from renal tubule cells unless the cells are damaged. These proteins include AAP, ALP, glycosaminoglycans (GAG), NAG, and GGT. Renal tubular damage was assessed in some studies from measurements of urinary excretion of proteins that are typically removed from the glomerular filtrate unless tubular reabsorption of protein is disrupted. These include α_1-microglobulin (α_1M), β_2M, and retinol binding protein (RBP).

Nephrotoxicity of inorganic and organic mercury has been extensively studied in animal models (Berlin et al. 2015; Zalups and Diamond 2005). Inorganic mercuric mercury produces a lesion in the proximal tubule that is initially focused in the *pars recta*, with toxicity developing within 24 hours after a single dose of mercuric chloride. The rapid onset of this focal lesion has prompted use of mercuric chloride as a

tool for studying structural and functional correlates to damage to the proximal tubule. As noted above, auto-immune glomerulonephritis has been observed in rabbits and some strains of rats following dosing with mercury chloride (Druet et al. 1978; Roman-Franco et al. 1978; Sapin et al. 1977).

The following summarizes results of epidemiological and animal studies on renal outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - Several studies in workers exposed to elemental mercury vapor provide some evidence of decrements in glomerular function and tubular injury, although conflicting results are reported.
    - Results of studies on populations with amalgam fillings (at lower exposures than mercury workers) also report some evidence of decrements in glomerular function and tubular injury; however, results are not consistent.
    - Elemental mercury appears to be associated with glomerular and tubular damage, but the kidney is not a sensitive target for elemental mercury at exposure levels in these studies.
  - *Animal studies*
    - Available studies indicate dose- and duration-dependent increases in the occurrence and severity of renal effects in animals, although some studies are limited based on lack of quantitative data and/or inadequate description of pathological lesions.
    - One study in maternal rats suggests impaired renal function following inhalation exposure based on urinalysis parameters.
- ***Inorganic mercuric salts***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to inorganic mercury salts and renal effects were identified.
    - Severe renal damage has been reported in case studies of accidental or intentional ingestion of high doses of inorganic mercury salts.
  - *Animal studies*
    - There is consistent evidence of dose- and duration-dependent increases in the occurrence and severity of renal effects in animals.
- ***Organic mercury***
  - *Epidemiology studies*
    - Little information is available on effects of methylmercury exposure in populations with high fish diets.

- Minamata disease is associated with renal dysfunction.
- Limited information suggests that the kidney is not a highly sensitive target for methylmercury, even in populations with very high methylmercury exposures from fish.

- *Animal studies*
  - Available studies indicate dose-dependent increases in the occurrence and severity of renal effects in animals, although some studies are limited based on lack of quantitative data.
  - Impaired renal function was reported in one study in mice at lethal/near-lethal acute oral doses.

- ***Predominant mercury form unknown (general populations)***
  - Studies indicate that mercury exposure of the general population may be associated with glomerular and tubular damage, but few studies have been conducted and results are inconsistent.

Confounding Factors. Inconsistencies in the reported outcomes for renal effects across studies may derive from several causes, including failure to account for confounding factors. Various factors that can affect kidney function may also be associated with mercury exposure status, including age, underlying diseases (e.g., hypertension), and concomitant exposure to other nephrotoxicants (e.g., lead, cadmium). Kidney function is also important for elimination of mercury since mercuric mercury is excreted in urine (see Section 3.1.4). Decreased GFR or impaired renal tubular transport could decrease clearance of mercury and contribute to correlations between renal GFR or indicators of tubular damage and blood mercury levels. This is an example of reverse causation, in which impaired renal function results in higher blood mercury levels due to decreased clearance.

In epidemiological studies in which GFR appears to have been severely depressed, reverse causation (lower mercury clearance contributing to higher mercury body burden) could be a substantial complication in interpreting causal relationships from statistical associations between blood mercury and GFR. Studies that evaluate associations between UHg and urinary renal outcome markers typically adjust the urinary concentrations relative to creatinine (e.g., µg Hg/g creatinine; mg albumin/g creatinine). This adjustment reduces autocorrelation resulting from interindividual variation in urine flow rate (L/day) similarly affecting the concentrations of mercury and the renal outcome marker (Diamond 1988). Autocorrelation would tend to strengthen the observed association between UHg and the urinary renal outcome marker.

Elemental Mercury—Epidemiological Studies. Studies evaluating effects of elemental mercury on renal function include cross-sectional and retrospective studies in workers, and cross-sectional studies, survey studies, and clinical trials in participants with amalgam fillings; studies are summarized in Table 2-19. Most studies evaluated effects by comparison of exposed versus control groups. Based on UHg (the main biomarker in most studies), exposure of workers was greater than nonoccupational exposure from amalgam fillings. For example, the highest UHg in workers (23.7 µg/g creatinine) (Boogaard et al. 1996) is approximately 10-fold greater than the highest UHg in nonoccupational amalgam studies (2.94 µg/g creatinine) (Al-Saleh et al. 2013). In general, population sizes in worker studies (range 40–291) were smaller than in nonoccupational amalgam studies (range 46–801).

Table 2-19. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Renal Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Workers			
Afrifa et al. 2017 Cross-sectional; 61 male gold miners and 49 controls (Ghana)	BHg mean Workers: 18.37 µg/L Controls: 2.90 µg/L	eGFR	↓ (BHg)
		Urine protein	↑ (BHg)
		Microalbuminuria	↑ (BHg)
		Serum creatinine	↑ (BHg)
Boogaard et al. 1996 Cross-sectional; male natural gas workers, 18 high exposure, 22 low exposure, and 19 controls (The Netherlands)	UHg mean High: 23.7 µg/g Cr Low: 4.1 µg/g Cr Controls: 2.4 µg/g Cr	Urine albumin	0 (UHg, high versus low and controls)
		Urine total protein	0 (UHg, high versus low and controls)
		Urine NAG	↑ (UHg, high versus low and controls)
		Urine β_2M	↑ (UHg, high versus low)
Cardenas et al. 1993 Cross-sectional; male chloralkali workers, 44 workers and 49 controls (Belgium)	UHg Gmean Workers: 21.9 µg/g Cr Controls: 1.6 µg/g Cr	Serum creatinine	↓ (UHg, workers versus controls)
		Urine albumin	0 (UHg, workers versus Ellingsen controls)
		Urine protein	0 (UHg, workers versus controls)
		Urine β_2M	↓ (UHg, workers versus controls)
		Urine NAG	0 (UHg, workers versus controls)
		Urine GAG	↓ (UHg, workers versus controls)
		Urine BBA[a]	↑ (UHg, workers versus controls)
		Urine BB50[a]	↑ (UHg, workers versus controls)

Table 2-19. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Renal Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Urine HF5[a]	↑ (UHg, workers versus controls)
Ellingsen et al. 2000a Cross-sectional; 47 chloralkali workers and 47 controls (Norway)	UHg mean Workers: 10.5 µg/g Cr Controls: 2.3 µg/g Cr	Urine albumin	0 (UHg, workers versus controls)
		Urine β_2M	0 (UHg, workers versus controls)
		Urine NAG	↑ (UHg, workers versus controls)
		Urine AAP	0 (UHg, workers versus controls)
		Urine ALP	0 (UHg, workers versus controls)
		Urine GAG	0 (UHg, workers versus controls)
Franko et al. 2005 Cross-sectional; male mercury miners, 33 active miners, 20 retired miners, and 53 controls (Slovenia)	UHg mean All miners: 2.12 µg/g Cr Active: 2.50 µg/g Cr Retired: 1.42 µg/g Cr Controls: 1.36 µg/g Cr	Urine albumin	↑ (UHg, all miners versus controls)
		Urine NAG	0 (UHg, all miners versus controls)
		Urine α_1M	↑ (UHg, all miners versus controls)
Frumkin et al. 2001 Retrospective cohort; males and females, 147 chloralkali workers, 132 controls (Georgia)	UHg mean Workers: 2.76 µg/g Cr Controls: 2.31 µg/g Cr	Serum creatinine	0 (UHg, workers versus controls)
		Urine albumin	0 (UHg, workers versus controls)
		Urine NAG	0 (UHg, workers versus controls)
		Urine AAP	0 (UHg, workers versus controls)
		Urine RBP	0 (UHg, workers versus controls)
Jarosinska et al. 2008 Cross-sectional; 179 chloralkali workers (Italy, Poland, Sweden)	UHg median in workers Italy: 4.6 Poland (1): 6.0 Poland (2): 45.9 Sweden: 3.8	Urine NAG	↑ (UHg)
		Urine α_1M	↑ (UHg)
Kobal et al. 2004 Cross-sectional; 54 mercury miners and 58 controls (Slovenia)	UHg mean Miners: 2.1 µg/L Controls: 1.4 µg/L	Urine albumin	↑ (UHg, miners versus controls)
		Urine NAG	0 (UHg, miners versus controls)
		Urine α_1M	↑ (UHg, miners versus controls)

Table 2-19. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Renal Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Piikivi and Ruokonen 1989 Cross-sectional; 60 male chloralkali workers and 60 matched controls (Finland)	UHg mean: Workers: 17.9 µg/g Cr Controls: 2.1 µg/g Cr	Urine albumin	0 (UHg, workers versus controls)
		Urine NAG	0 (UHg, workers versus controls)
Rodriguez et al. 2017 Cross-sectional; 164 gold miners and 127 controls (Columbia)	UHg median Miners: 3.9 µg/g Cr Controls: 1.5 µg/g Cr BHg median Miners: 7.0 µg/L Controls: 2.5 µg/L	Blood Cr	0 (UHg, miners versus controls)
		Cr clearance	0 (UHg, miners versus controls)
		GFR	↑ (UHg, miners versus controls) 0 (UHg, BHg, multivariable regression)
		Urine albumin	0 (UHg, miners versus controls)
		Urine β_2M	0 (UHg, miners versus controls)
Amalgam fillings			
Al-Saleh et al. 2012 Survey; 106 children with amalgam fillings and 76 children without amalgam fillings (Saudi Arabia)	UHg median Amalgam: 2.94 µg/g Cr No amalgam: 2.42 µg/g Cr	Urine NAG	↑ (UHg)
Barregard et al. 2008 Randomized clinical trial; 534 children, 267 receiving amalgam fillings and 267 receiving resin fillings over 5 years (Boston, Massachusetts)	HHg mean Amalgam: 0.4 µg/g No amalgam: 0.4 µg/g	Urine albumin	0 (HHg, amalgam versus no amalgam)
		Microalbuminuria	↑ (HHg, amalgam versus no amalgam)
		Urine NAG	0 (HHg, amalgam versus no amalgam)
		Urine α_1M	0 (HHg, amalgam versus no amalgam)
		Urine GGT	0 (HHg, amalgam versus no amalgam)
Eti et al. 1995 Cross-sectional; 100 adults, 66 with amalgam fillings and 34 without amalgam fillings (New York, New York)	UHg median Amalgam: 1 µg/L No amalgam: 0 µg/L	Urine NAG	↑ (UHg, amalgam versus no amalgam)

Table 2-19. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Renal Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Herrstrom et al. 1995 Cross-sectional; 23 men with amalgam fillings and 23 men without amalgam fillings	UHg median Amalgam: 0.32 µg/g Cr No amalgam: 0.17 µg/g Cr	Urine albumin	0 (UHg, amalgam versus no amalgam)
		Urine Cr	0 (UHg, amalgam versus no amalgam)
		Urine NAG	0 (UHg, amalgam versus no amalgam)
		Urine α_1M	0 (UHg, amalgam versus no amalgam)
Mortada et al. 2002 Cross-sectional; 101 adults with amalgam fillings and 52 adults without amalgam fillings (Egypt)	UHg mean Amalgam: 1.79 µg/g Cr No amalgam: 0.48 µg/g Cr	Serum Cr	0 (UHg, amalgam versus no amalgam)
		Serum β_2M	0 (UHg, amalgam versus no amalgam)
		BUN	0 (UHg, amalgam versus no amalgam)
		Urine albumin	↑ (UHg, amalgam versus no amalgam)
		Urine NAG	↑ (UHg, amalgam versus no amalgam)
		Urine β_2M	0 (UHg, amalgam versus no amalgam)
		Urine ALP	0 (UHg, amalgam versus no amalgam)
		Urine GGT	↑ (UHg, amalgam versus no amalgam)
Woods et al. 2008 Randomized clinical trial 507 children, age 8–12 years (Portugal)	UHg mean Amalgam: 1.8 µg/g Cr No amalgam: 1.9 µg/g Cr	Urine albumin	0 (amalgam versus no amalgam)
		Urine GGT-α	0 (amalgam versus no amalgam)
		Urine GGT-π	0 (amalgam versus no amalgam)
Ye et al. 2009 Cross-sectional; 403 children (ages 7–11 years), 198 with amalgam fillings and 205 without amalgam fillings (China)	UHg Gmean: Amalgam: 1.6 µg/g Cr No amalgam: 1.4 µg/g Cr	Urine albumin	0 (UHg, amalgam versus no amalgam)
		Urine NAG	0 (UHg, amalgam versus no amalgam)

[a]Brush border tubular antigens.

↑ = positive association; ↓ = inverse association; 0 = no association; α_1M = α_1-microglobulin; β_2M = β_2-microglobulin; AAP = alanine aminopeptidase; ALP = alkaline phosphatase; BHg = blood mercury; BUN = blood urea nitrogen; Cr = creatinine; eGFR = estimated glomerular filtration rate; GAG = glycosaminoglycans; GFR = glomerular filtration rate; GGT = gamma-glutamyltransferase; Gmean = geometric mean; HHg = hair mercury; NAG = N-acetyl-β-D-glucosaminidase; RBP = retinol binding protein; UHg = urine mercury

Several studies in mercury workers provide some evidence of impaired glomerular function or renal tubular damage, although conflicting results are reported. For assessments of glomerular function, results are inconsistent. Some studies reported signs of impaired glomerular function, including decreased GFR, increased urine protein and albumin, microalbuminuria, decreased urine β_2M, and increased serum creatinine (Afrifa et al. 2017; Cardenas et al. 1993; Franko et al. 2005; Kobal et al. 2004), whereas other studies did not observe alterations in markers of glomerular function (Boogaard et al. 1996; Ellingsen et al. 2000a; Frumkin et al. 2001; Piikivi and Ruokonen 1989; Rodriguez et al. 2017). For studies showing altered glomerular function, the magnitude of changes is toxicologically significant. Afrifa et al. (2017) reported marked alterations in GFR markers in gold miners compared to controls; mean estimated GFR in exposed miners (blood mercury ≥5 μg/L) was 52.6% lower than the control group (blood mercury <5 μg/L), and mean urine protein and serum creatinine were higher by 68- and 2.3-fold, respectively. Given the very large differences in GFR between exposed and non-exposed subjects, reverse causation is a potential contributor to the relatively high age-adjusted ORs for low GFR reported in this study (263; 95% CL 48, 1,420). Urine albumin was higher by 1.33–1.6-fold in mercury miners than in controls (Franko et al. 2005; Kobal et al. 2004). Results of evaluations of occupational exposure and tubular damage are also inconsistent. Some studies showed altered urinary excretion of at least one marker of tubular damage, including increased urine NAG and α_1M, and decreased β_2M (Boogaard et al. 1996; Ellingsen et al. 2000a; Franko et al. 2005; Jarosinska et al. 2008; Kobal et al. 2004). In other studies, no changes indicative of tubular damage were observed (Franko et al. 2005; Frumkin et al. 2001; Piikivi and Ruokonen 1989; Woods et al. 2008). Although Cardenas et al. (1993) did not find elevated urinary markers of tubular damage, brush border tubular antigens in urine were increased, indicative of an immune response against the proximal tubule. Taken together, results suggest that studies of occupational exposures are inconsistent. Some studies have found associations between exposure to mercury and decreased GFR or tubular damage; however, these outcomes were not consistently observed across studies at similar exposures (based on exposure biomarkers). These inconsistencies may reflect differences in exposure levels as well as differences in study designs or the exposure markers utilized.

Several studies have examined associations between indicators of impaired glomerular function or tubular damage and exposures to elemental mercury from mercury amalgam restorations. Exposures to elemental mercury in these populations (UHg mean or median <3 μg/g creatinine) were lower than exposures observed in workers (UHg mean or median: 2–24 μg/g creatinine). A clinical trial reported microalbuminuria (urinary albumin >30 mg/g creatinine) in children in the amalgam group (Barregard et al. 2008) and a cross-sectional study reported increased urine albumin in adults with amalgam fillings

compared to those with no amalgam fillings (Mortada et al. 2002). Other studies did not observe differences in glomerular function markers in children (Herrstrom et al. 1995) or adults (Ye et al. 2009) with amalgam fillings compared to no amalgam fillings. Urine NAG and/or GGT were increased in amalgam groups compared to no amalgam groups in children and adults (Al-Saleh et al. 2012; Eti et al. 1995; Mortada et al. 2002); however, other urinary markers of tubular damage (β_2M, ALP) were not increased (Mortada et al. 2002). In addition, other studies did not observe increased urinary excretion of any markers of tubular damage, including NAG, α_1M, GGT, and ALP (Barregard et al. 2006, 2008; Herrstrom et al. 1995; Ye et al. 2009). Together, these results do not provide consistent evidence of associations between low-level exposure to elemental mercury from amalgam fillings and renal effects.

Elemental Mercury—Animal Studies. Data following acute exposure of rats to elemental mercury suggest that that occurrence and severity of renal effects are increased in a dose- and duration-dependent manner. A series of experiments evaluated maternal kidney effects in rats following exposure to elemental mercury vapor at concentrations up to 8 mg Hg/m^3 for 1, 5, or 10 days during pregnancy (Morgan et al. 2002). After exposure to 1, 2, and 4 mg Hg/m^3 for 10 days (GDs 6–15), total urinary protein was increased 1.7-, 1.9-, and 1.8-fold, respectively, and urinary ALP activity was increased 7-, 2-, and 10-fold, respectively (urinalysis was not conducted at 8 mg Hg/m^3). Maternal relative kidney weights were significantly increased by >30% at ≥4 mg Hg/m^3; findings may be attributable in part to body weight effects (maternal weight gain decreases of 7–17% at ≥4 mg Hg/m^3). Absolute kidney weights were not reported. No histopathological lesions were observed in maternal kidneys at concentrations up to 8 mg Hg/m^3. No exposure-related renal effects were noted in dams similarly exposed for 1 day (GD 6) or 5 days (GDs 6–10). In nonpregnant rats, no exposure-related changes in kidney weight were observed in Sprague-Dawley rats following acute exposure to concentrations up to 4 mg Hg/m^3 for 2 hours/day (Davis et al. 2001); however, renal function and histology were not evaluated in this study and a NOAEL for renal effects was therefore not included in the LSE table (inadequate endpoint evaluation).

Intermediate-duration studies in rats also provide evidence for dose- and duration-dependent increases in occurrence and severity of renal lesions, although no measures of renal function were conducted in intermediate-duration studies. In rats, slight degenerative changes (i.e., dense deposits in tubule cells and lysosomal inclusions) in the renal tubular epithelium were evident following exposure to 3 mg Hg/m^3 for 3 hours/day, 5 day/week for 12–42 weeks (Kishi et al. 1978). Akgul et al. (2016) also reported histopathological and stereological changes in renal glomeruli in male and female rats following exposure to 0.0487 mg Hg/m^3 for 45 days for an unspecified daily duration. Due to lack of exposure details, this study was not included in the LSE table, but findings are discussed below. Mercury-exposed rats showed

reductions in the mean numerical density of glomeruli (-5%), total number of glomeruli (-7%), and mean volumes of glomeruli (-19%), cortex (-21%), and proximal tubule (-38%), compared to controls. Additionally, increased mean volume of medulla (29%) and distal tubule (250%) were seen in exposed rats, compared to controls. Histopathological findings, reported qualitatively only, included changes in vacuoles, pyknotic nuclei of glomerular and tubular cells, tubular necrosis, glomerular sclerosis, glomerular degeneration, and dilation of Bowman's space. In addition, kidneys of treated rats had cells with darkly stained cytoplasm, collecting tubules that were indistinguishable from cytoplasm borders, tubules with dead cells, and structures that were possible residue of dead cells. No pathological kidney changes were noted in control animals. Electron microscopy evaluations revealed pathological changes in the vacuole, nucleus, and mitochondria of distal tubule cells of exposed animals as well as cytoplasmic disorganization and damage to the podocytes, mesangial cells, glomerular cells, and basement membrane.

Inorganic Mercury Salts—Exposure of Humans. No epidemiological studies assessing associations between inorganic mercury salts and renal function were identified. As discussed in Section 2.1 (Introduction), exposure of humans to inorganic mercury salts in the environment is minimal relative to exposures to other forms of mercury and, as a result, it would be difficult to discern outcomes associated with exposure to inorganic mercury salts from outcomes contributed by exposures to other forms of mercury. However, the kidney, specifically the proximal tubule, is the primary target organ for inorganic mercury salts (Bhan and Sarkar 2005; Clarkson and Magos 2006; Clarkson et al. 2003). Case reports of acute accidental or intentional ingestion of high doses of inorganic mercury salts show that renal damage can be very severe, including necrosis of the tubular epithelium and anuria, with complete collapse of renal function (Clarkson and Magos 2006; Magos and Clarkson 2006; Syversen and Kaur 2012).

Inorganic Mercury Salts—Animal Studies. The kidney is a clear target of toxicity for inorganic mercury. There is clear and consistent evidence of dose- and duration-dependent increases in occurrence and severity of renal effects in rats and mice following oral exposure to mercuric chloride.

Histopathological lesions have been reported in rats and mice following acute-, intermediate-, and chronic-duration oral exposure to mercuric chloride. In general, occurrence and severity of lesions appear to increase in a dose- and duration-related manner for specific exposure routes (e.g., gavage, diet, drinking water), beginning with mild histopathological damage after lower, shorter exposures (e.g., mild protein casts, cellular casts, interstitial sclerosis, tubular regeneration) and progressing to greater incidence and severity of renal nephropathy and necrosis with higher and/or longer durations (see lesion types, incidence, and severity in Tables 2-20 and 2-21). In both rats and mice, males appear more

susceptible than females. In rats, renal lesions have been consistently observed following gavage exposure to ≥7.4 mg Hg/kg/day for 1–16 days (Dieter et al. 1992; Lecavalier et al. 1994; NTP 1993) or ≥0.923 mg Hg/kg/day for >180 days (Dieter et al. 1992; NTP 1993). One study qualitatively reported histopathological changes in the kidney in rats after gavage exposure to 0.015 mg Hg/kg/day for 28 days (Apaydin et al. 2016), but other repeat-dose studies did not confirm findings at doses <0.923 mg Hg/kg/day. Gavage studies in mice are less consistent, with renal lesions observed after single exposures ≥10 mg Hg/kg/day (Nielsen et al. 1991) but not until doses ≥30 mg Hg/kg/day following up to 12 doses over 16 days (NTP 1993). In longer-duration gavage studies, renal lesions were observed in mice at ≥4 mg Hg/kg/day (NTP 1993). In both rats and mice, renal lesions have been consistently observed following intermediate-duration dietary or drinking water exposure to >5 mg Hg/kg/day; no changes were observed at ≤2 mg Hg/kg/day (Boscolo et al. 1989; Carmignani et al. 1989; Dieter et al. 1983; Jonker et al. 1993; Khan et al. 2004).

Table 2-20. Kidney Lesions in Rats[a] Orally Exposed to Mercuric Chloride

Duration; dose (mg Hg/kg/day)	Histology	Lesion details	Reference
Gavage studies			
1 day; Dose: 7.4	↑ (F)	Mild protein casts, cellular casts, interstitial sclerosis[a]	Lecavalier et al. 1994
1 day; Dose: 9.24	↑ (F)	Mild protein casts, cellular casts, interstitial sclerosis[a]	Lecavalier et al. 1994
16 days; Dose: 0.923–4	0 (M, F)		Dieter et al. 1992; NTP 1993
16 days; Dose: 7.4	M: ↑ F: 0	Acute renal necrosis M: 3/5 minimal, 2/5 mild (control 0/5)	Dieter et al. 1992; NTP 1993
16 days; Dose: 15	↑ (M, F)	Acute renal necrosis M: 2/5 mild; 3/5 moderate F: 1/5 minimal; 4/5 mild (M, F control: 0/5)	Dieter et al. 1992; NTP 1993
28 days; Dose: 0.015	↑ (NS)	Renal tubular dilation and glomerular lobulation[a]	Apaydin et al. 2016
182 days; Dose: 0.23–0.462	0 (M, F)		Dieter et al. 1992; NTP 1993
182 days; Dose: 0.923	M: ↑ F: 0	Renal nephropathy M: 6/10 minimal; 4/10 mild (control 8/10 minimal)	Dieter et al. 1992; NTP 1993
182 days; Dose: 1.8	M: ↑ F: 0	Renal nephropathy M: 7/10 minimal; 3/10 mild (control 8/10 minimal)	Dieter et al. 1992; NTP 1993

Table 2-20. Kidney Lesions in Rats[a] Orally Exposed to Mercuric Chloride

Duration; dose (mg Hg/kg/day)	Histology	Lesion details	Reference
182 days; Dose: 4	↑ (M, F)	Renal nephropathy M: 6/10 minimal; 4/10 mild (control 8/10 minimal) F: 4/10 minimal (control 0/10)	Dieter et al. 1992; NTP 1993
450–730 days; Dose: 1.8	M: ↑ F: 0	M: Increased severity of nephropathy (32% increase in severity score at 15 months and 15% at 2 years)	Dieter et al. 1992; NTP 1993
450–730 days; Dose: 4	M: ↑ F: 0	M: Increased severity of nephropathy (mild to marked; 68% increase in severity score at 15 months; 22% at 2 years)	Dieter et al. 1992; NTP 1993
Dietary studies			
28 days; Dose: 0.61–0.76	0 (M, F)		Jonker et al. 1993
28 days; Dose: 5.1–5.5	M: ↑ F: 0	Basophilic tubules in outer cortex M: 5/10 single-to-few; 5/10 several (Control: 3/10 single-to-few)	Jonker et al. 1993
28 days; Dose: 5.8–23.6	↑ (M, F)	Nephrosis and proteinaceous casts[a]	Jonker et al. 1993
Drinking water studies			
180 days; Dose: 24	↑ (M)	Focal tubule degeneration, mesangial proliferative glomerulonephritis in 80% of glomeruli[a]	Carmignani et al. 1992
350 days; Dose: 6	↑ (M)	Tubular degeneration and desquamation[a]	Boscolo et al. 1989; Carmignani et al. 1989
350 days; Dose: 6	↑ (M)	Membranous glomerulonephritis in 30% of glomeruli and tubular degeneration[a]	Boscolo et al. 1989
350 days; Dose: 24	↑ (M)	Membranous glomerulonephritis in 100% of glomeruli and tubular degeneration[a]	Boscolo et al. 1989

[a]Reported qualitatively only (incidence data not provided).

↑ = increase in histopathological lesions; 0 = no change; – = not assessed; F = female; M = male; NS = not specified

Table 2-21. Kidney Lesions in Mice[a] Orally Exposed to Mercuric Chloride

Duration; dose (mg Hg/kg/day)	Histology	Lesion details	Reference
Gavage studies			
1 day; Dose: 5	0 (F)		Nielsen et al. 1991
1 day; Dose: 10	↑ (F)	Proximal tubule regeneration F: 10/10; severity grade 2/3 (control 0/10)	Nielsen et al. 1991
1 day; Dose: 20	↑ (F)	Proximal tubule degeneration F; 10/10; severity grade 2.5/3 Proximal tubule regeneration F: 10/10; severity grade 2.5/3 (control 0/10)	Nielsen et al. 1991
1 day; Dose: 40	↑ (F)	Proximal tubule degeneration F; 10/10; severity grade 3/3 Proximal tubule regeneration F: 10/10; severity grade 0.25/3 (control 0/10)	Nielsen et al. 1991
2–4 days; Dose: 59	↑ (M, F)	Acute renal necrosis M: 5/5 (control 0/5) F: 5/5 (control 0/5)	NTP 1993
14 days; Dose: 4–15	0 (M, F)		NTP 1993
14 days; Dose: 30	M: ↑ F: 0	Acute renal necrosis M: 2/5 (control 0/5)	NTP 1993
61–79 days; Dose: 0.18–0.74	0 (M, F)		Khan et al. 2004
182 days; Dose: 0.923–1.8	0 (M, F)		NTP 1993
182 days; Dose: 4–15	M: ↑ F: 0	Dose-related increase in incidence and severity of cytoplasmic vacuolation in the renal tubule epithelium[b]	NTP 1993
450–730 days; Dose: 4	↑ (M, F)	Renal nephropathy M: Severity grade increased 61% F: Severity grade increased by 117%; incidence increased, 43/50 versus 21/49	NTP 1993
450–730 days; Dose: 7.4	↑ (M)	Renal nephropathy M: Severity grade increased 132% F: Severity grade increased by 164%; incidence increased, 42/50 versus 21/49	NTP 1993
Drinking water studies			
49 days; Dose: 0.4–2	0 (M)		Dieter et al. 1983
49 days; Dose: 11	↑ (M)	Minimal renal nephropathy[b]	Dieter et al. 1983

[a]Sexes evaluated are indicated in the results columns.
[b]Reported qualitatively only (incidence data not provided).

↑ = increase in histopathological lesions; 0 = no change; – = not assessed; F = female; M = male

Renal lesions associated with autoimmunity (e.g., IgG deposits in renal vessels) have been observed in mouse strains genetically susceptible to autoimmune disease following oral exposure to mercuric chloride. Due to the autoimmune nature of these lesions, these studies are discussed in Section 2.15. (Immunological) and are included in the LSE table as evidence of immune-complex disease.

Increased kidney weights have been consistently reported in rats following intermediate- and chronic-duration oral exposure to mercuric chloride. In general, findings are dose-dependent; however, duration of exposure does not seem to greatly impact magnitude of effect (see Table 2-22). In male rats, significant dose-related increases in kidney weights were observed following repeated exposure to gavage doses ≥1.8 mg Hg/kg/day for 12 days (over 16 days), at all tested intermediate- and chronic-duration gavage doses (≥0.23 and 1.8 mg Hg/kg/day, respectively), at ≥5.1 mg Hg/kg/day in the diet for 28 days, at all tested dietary doses following exposure for 35–147 days (≥0.06 mg Hg/kg/day), and at drinking water doses ≥0.244 mg Hg/kg/day (Atkinson et al. 2001; Dieter et al. 1992; Jonker et al. 1993; NTP 1993; Takahashi et al. 2000a, 2000b; Wildemann et al. 2015a, 2016). In female rats, no change in kidney weight was observed following single gavage doses up to 0.24 mg Hg/kg/day (Lecavalier et al. 1994). In repeat-dose studies, significant dose-related increases in kidney weights were observed in female rats following gavage doses ≥4 mg Hg/kg/day for 12 days (over 16 days), at all tested intermediate- and chronic-duration gavage doses in non-breeding animals (≥0.23 and 1.8 mg Hg/kg/day, respectively), and at all tested intermediate-duration dietary doses (≥0.76 mg Hg/kg/day) (Dieter et al. 1992; Jonker et al. 1993; NTP 1993). In breeding females from a 2-generation study, no changes in kidney weight were observed in the F0 generation, but F1 females showed a significant increase in kidney weight at a gavage dose of 1.98 mg Hg/kg/day (Atkinson et al. 2001). No changes in kidney weight were observed in male rats at dietary doses of 0.61 mg Hg/kg/day for 28 days or in male or female rats at drinking water doses ≤0.037 mg Hg/kg/day (Jonker et al. 1993; Oliveira et al. 2012; Wildemann et al. 2015a).

Table 2-22. Kidney Weight and Clinical Chemistry in Rats[a] Orally Exposed to Mercuric Chloride

Duration dose (mg Hg/kg/day)	Kidney weight[b]	BUN/ SUN	Serum creatinine	Serum uric acid	Reference
Gavage studies					
1 day Dose: 7.4–9.24	0 (F)	–	–	0 (F)	Lecavalier et al. 1994
16 days Dose: 0.923	0 (F)	–	–	–	Dieter et al. 1992; NTP 1993

Table 2-22. Kidney Weight and Clinical Chemistry in Rats[a] Orally Exposed to Mercuric Chloride

Duration dose (mg Hg/kg/day)	Kidney weight[b]	BUN/ SUN	Serum creatinine	Serum uric acid	Reference
16 days Dose: 4	↑ (M) (19[c]) ↑ (F) (38[c])	–	–	–	Dieter et al. 1992; NTP 1993
16 days Dose: 7.4	↑ (M) (35[c]) ↑ (F) (34[c])	–	–	–	Dieter et al. 1992; NTP 1993
16 days Dose: 15	↑ (M, F) (43[c])	–	–	–	Dieter et al. 1992; NTP 1993
28 days Dose: 0.015	–	↑ (NS) (28[c])	↑ (NS) (17[c])	↑ (NS) (54[c])	Apaydin et al. 2016
79 days Dose: 0.55–1.11	0 (F)	–	–	–	Atkinson et al. 2001
79 days Dose: 1.98	F_0: 0 (F) F_1:↑ (F) (14[c])	–	–	–	Atkinson et al. 2001
81 days Dose: 0.37	F_0: ↑ (M)(14[c]) F_1: 0 (M)	–	–	–	Atkinson et al. 2001
81 days Dose: 0.74	F0: ↑ (M) (14[c]) F1: 0 (M)	–	–	–	Atkinson et al. 2001
81 days Dose: 1.31	F0: ↑ (M) (29[c]) F1: 0 (M)	–	–	–	Atkinson et al. 2001
182 days Dose: 0.23	↑ (M) (10[c]) ↑ (F) (8[c])	0 (M,F)	0 (M) ↓ (F) (11[c])	–	Dieter et al. 1992; NTP 1993
182 days Dose: 0.462	↑ (M) (18[c]) ↑ (F) (13[c])	–	–	–	Dieter et al. 1992; NTP 1993
182 days Dose: 0.923	↑ (M) (18[c]) ↑ (F) (17[c])	0 (M, F)	0 (M) ↓ (F) (5[c])	–	Dieter et al. 1992; NTP 1993
182 days Dose: 1.8	↑ (M) (19[c]) ↑ (F) (20[c])	–	–	–	Dieter et al. 1992; NTP 1993
182 days Dose: 4	↑ (M) (14[c]) ↑ (F) (22[c])	0 (M) ↓ (F) (11[c,d])	M: 0 ↓ (F) (11[c])	–	Dieter et al. 1992; NTP 1993
450 days Dose: 1.8	↑ (M) (20[c]) ↑ (F) (18[c])	0 (M, F)	–	–	Dieter et al. 1992; NTP 1993
450 days Dose: 4	↑ M: (15[c]) ↑ F: (18[c])	0 (M, F)	–	–	Dieter et al. 1992; NTP 1993

Table 2-22. Kidney Weight and Clinical Chemistry in Rats[a] Orally Exposed to Mercuric Chloride

Duration dose (mg Hg/kg/day)	Kidney weight[b]	BUN/ SUN	Serum creatinine	Serum uric acid	Reference
Dietary studies					
28 days Dose: 0.61	0 (M)	0 (M)	0 (M)	–	Jonker et al. 1993
28 days Dose: 0.76	↑ (F) (13[c])	0 (F)	0 (F)	–	Jonker et al. 1993
28 days Dose: 5.1–5.5	↑ (M) (17[c]) ↑ (F) (20[c])	0 (M, F)	0 (M, F)	–	Jonker et al. 1993
28 days Dose: 5.8–6.1	M: ↑ (13[c]) F: ↑ (16[c])	0 (M, F)	0 M, F)	–	Jonker et al. 1993
28 days Dose: 11.4–11.9	M: ↑ (17[c]) F: ↑ (21[c])	0 (M, F)	0 M, F)	–	Jonker et al. 1993
28 days Dose: 20.9–23.6	↑ (M) (25[c]) ↑ (F) (22[c])	0 (M, F)	0 M, F)	–	Jonker et al. 1993
35 days Dose: 0.07	↑ (M) (10[e])	–	–	–	Takahashi et al. 2000b
35 days Dose: 0.21	↑ (M) (14[e])	–	–	–	Takahashi et al. 2000b
35 days Dose: 0.72	↑ (M) (16[e])	–	–	–	Takahashi et al. 2000b
35 days Dose: 2.2	↑ (M) (24[e])	–	–	–	Takahashi et al. 2000b
147 days Dose: 0.06	↑ (M) (11[e])	0 (M)	0 (M)	–	Takahashi et al. 2000a
147 days Dose: 0.17	↑ (M) (18[e])	0 (M)	0 (M)	–	Takahashi et al. 2000a
147 days Dose: 0.51	↑ (M) (15[e])	0 (M)	0 (M)	–	Takahashi et al. 2000a
147 days Dose: 1.7	↑ (M) (12[e])	↓ (M) (NS[cd])	0	–	Takahashi et al. 2000a
Drinking water studies					
21 days Dose: 0.0002–0.0301	0	0	–	–	Oliveira et al. 2012
28 days Dose: 0.005–0.01	0 (M)	–	–	–	Wildemann et al. 2015a
28 days Dose: 0.021–0.037	0 (M)	–	–	–	Wildemann et al. 2015a
28 days Dose: 0.244–0.264	↑ (M) (15[c])	–	0 (M)	–	Wildemann et al. 2015a, 2016
28 days Dose: 1.18	↑ (M) (26[c])	–	–	–	Wildemann et al. 2015a
28 days Dose: 2.07	↑ (M) (32[c])	–	–	–	Wildemann et al. 2015a

Table 2-22. Kidney Weight and Clinical Chemistry in Rats[a] Orally Exposed to Mercuric Chloride

Duration dose (mg Hg/kg/day)	Kidney weight[b]	BUN/ SUN	Serum creatinine	Serum uric acid	Reference
28 days Dose: 2.955	–	–	0 (M)	–	Wildemann et al. 2016
28 days Dose: 5.91	↑ (M) (77[c,f])	–	–	–	Wildemann et al. 2015a

[a]Sexes evaluated are indicated in the results columns.
[b]Relative-to-body organ weight.
[c]Percent change compared to control, calculated from quantitative data.
[d]Biological relevance of decreased BUN is unclear.
[e]Percent change compared to control, estimated from graphically reported data.
[f]Organ weight effects may be due in part to observed body weight loss; 100% mortality at this dose.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; BUN = blood urea nitrogen; F = female; F0 = F0 generation; F1 = F1 generation; M = male; NS = not specified; SUN = serum urea nitrogen

Increased kidney weights have also been consistently reported in mice following acute-, intermediate-, and chronic-duration oral exposure to mercuric chloride. In general, findings are dose- and duration-dependent in male mice; however, findings in female mice are less consistent than effects in males (see Table 2-23). In male BALB/c and B6C3F1 mice, significant dose-related increases in kidney weights were consistently observed following exposure to acute oral doses ≥1.39 mg Hg/kg/day, intermediate-duration oral doses ≥2 mg Hg/kg/day, and at all tested chronic-duration oral doses ≥4 mg Hg/kg/day (Dieter et al. 1983; Kim et al. 2003; NTP 1993). One study reported an unspecified increase in kidney weight in C57Bl/6 male mice at intermediate-duration gavage doses ≥0.18 mg Hg/kg/day (Khan et al. 2004)); however, no exposure-related changes were observed at intermediate-duration oral doses ≤1.8 mg Hg/kg/day in male B6C3F1 mice (Dieter et al. 1993; NTP 1993). In female B6C3F1 mice, elevated kidney weights were reported following 12 gavage exposures (over 16 days) or 15 months at doses ≥4 mg Hg/kg/day; however, kidney weights were not altered at doses up to 15 mg Hg/kg/day for 6 months (NTP 1993). In C57Bl/6 mice, elevated kidney weights were observed in females after exposure to doses ≥0.37 mg Hg/kg/day for 79 days (Khan et al. 2004).

Table 2-23. Kidney Weight and Clinical Chemistry in Mice[a] Orally Exposed to Mercuric Chloride

Duration dose (mg Hg/kg/day)	Kidney weight[b,c]	BUN[b]	Reference
Gavage studies			
14 days Dose: 0.06–0.31	0 (M)	–	Kim et al. 2003
14 days Dose: 1.39	↑ (M) (11)	–	Kim et al. 2003
14 days Dose: 4.81	↑ (M) (12)	–	Kim et al. 2003
16 days Dose: 4	↑ (M) (21) ↑ (F) (20)	–	NTP 1993
16 days Dose: 7.4	↑ (M) (25) ↑ (F) (27)	–	NTP 1993
16 days Dose: 15	↑ (M) (38) ↑ (F) (19)	–	NTP 1993
16 days Dose: 15	↑ (M) (31) ↑ (F) (29)	–	NTP 1993
61 days Dose: 0.18–0.74	↑ (NS)	–	Khan et al. 2004
79 days Dose: 0.18	0 (F)	–	Khan et al. 2004
79 days Dose: 0.37–0.74	↑ (NS)	–	Khan et al. 2004
182 days Dose: 1.8	0 (M, F)	0 (M, F)	NTP 1993
182 days Dose: 4	↑ (M) (19[d]) 0 (F)	0	NTP 1993
182 days Dose: 7.4	↑ (M) (32) 0 (F)	0	NTP 1993
182 days Dose: 15	↑ (M) (46) 0 (F)	0	NTP 1993
450 days Dose: 4	↑ (M) (21[d]) ↑ (F) (24)	0	NTP 1993
450 days Dose: 7.4	↑ (M) (39) ↑ (F) (28)	↓ (M) (20[e]) ↓ (F) (22[e])	NTP 1993
Drinking water studies			
49 days Dose: 0.4	0 (M)	0 (M)	Dieter et al. 1983
49 days Dose: 2	↑ (M) (19[f])	↓ (M) (13[e])	Dieter et al. 1983

Table 2-23. Kidney Weight and Clinical Chemistry in Mice[a] Orally Exposed to Mercuric Chloride

Duration dose (mg Hg/kg/day)	Kidney weight[b,c]	BUN[b]	Reference
49 days Dose: 11	↑ (M) (23[f])	↓ (M) (13[e])	Dieter et al. 1983

[a]Sexes evaluated are indicated in the results columns.
[b]Numbers in ( ) are percent change compared to control, calculated from quantitative data.
[c]Relative-to-body organ weight, unless otherwise noted.
[d]Absolute kidney weight; change in relative kidney weight not significant at this dose.
[e]Biological relevance of decreased BUN is unclear.
[f]Absolute kidney weights; relative organ weights were not reported, body weights decreased at 11 mg Hg/kg/day.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; BUN = blood urea nitrogen; F = female; M = male; NS = not specified

No consistent alterations in renal clinical chemistry parameters were observed in rats or mice (see Tables 2-22 and 2-23, respectively). One gavage study reported increased SUN, creatinine, and uric acid levels in rats (sex not specified) following exposure to 0.015 mg Hg/kg/day for 28 days (Apaydin et al. 2016). However, these findings have not been confirmed in other oral studies in rats or mice. No changes in serum uric acid were observed in rats following a single gavage exposure to doses up to 9.24 mg Hg/kg/day (Lecavalier et al. 1994). Increased levels of BUN were not observed in rats following intermediate or chronic oral doses up to 23.6 and 4 mg Hg/kg/day, respectively (Dieter et al. 1992; Jonker et al. 1993; NTP 1993; Oliveira et al. 2012; Takahashi et al. 2000a), or in mice following intermediate or chronic oral doses up to 15 and 7.4 mg Hg/kg/day, respectively (Dieter et al. 1983; NTP 1993). Occasional observations of significantly decreased BUN are of unclear biological significance. Additionally, increases in serum creatinine were not observed in rats at intermediate-duration doses up to 23.6 mg Hg/kg/day (Dieter et al. 1992; Jonker et al. 1993; NTP 1993; Takahashi et al. 2000a; Wildemann et al. 2016).

In general, most urinalysis findings in rats following oral exposure to mercuric chloride were inconsistent between studies and sexes (see Table 2-24). Elevated urinary ALT was observed in male (but not female) rats after 12 gavage exposures (over 16 days) to 4 mg Hg/kg/day (Dieter et al. 1992; NTP 1993), male rats exposed to drinking water doses of 2.2 mg Hg/kg/day for 84 days or ≥0.06 mg Hg/kg/day for 14 days (Takahashi et al. 2000a, 2000b), and female (but not male rats) at a gavage dose of 0.462 mg Hg/kg/day for 6 months or ≥1.8 mg Hg/kg/day for 15 months (Dieter et al. 1992; NTP 1993). Similarly, elevated urinary AST was observed in male (but not female) rats after12 gavage exposures (over 16 days) to 4 mg Hg/kg/day, in male (but not female) rats after exposure to 1.8 mg Hg/kg/day for 6 months, and in male

and female rats after exposure to 4 mg Hg/kg/day for 15 months; no changes were observed in males or females exposed to 0.462 mg Hg/kg/day for 6 months (Dieter et al. 1992; NTP 1993). Occasional reports of elevated urinary creatinine, protein, amino acids, GGT, and LDH were reported; however, no exposure-related trends were observed within or across studies (see Table 2-24). In a 28-day dietary study, urinary ketones were present in male rats exposed to ≥5.1 mg Hg/kg/day; ketones were not present in females at doses up to 23.6 mg Hg/kg/day (Jonker et al. 1993). One study showed no exposure-related changes in creatinine clearance in male rats following exposure to mercuric chloride at doses up to 1.955 mg Hg/kg/day for 28 days via drinking water (Wildemann et al. 2016).

Table 2-24. Urinalysis in Rats[a] Orally Exposed to Mercuric Chloride

Duration; dose (mg Hg/kg/day)	Cr	TP	AA	ALP	AST	LDH	GGT	Reference
Gavage studies								
16 days; Dose: 4	–	–	–	↑ (M) (80[b,c]) 0 (F)	↑ (M) (83[c]) 0 (F)	0 (M,F)	0 (M, F)	Dieter et al. 1992; NTP 1993
182 days; Dose: 0.462	–	–	–	0 (M) ↑ (F) (570[c])	0 (M, F)	0 (M) ↑ (F) (70[c])	0 (M) ↑ (F) (145[c])	Dieter et al. 1992; NTP 1993
450 days; Dose: 1.8	0 (M,F)	–	–	0 (M) ↑ (F) (172[d])	↑ (M) (7[d]) F: 0	0	0	Dieter et al. 1992; NTP 1993
450 days; Dose: 4	0 (M.F)	–	–	0 (M) ↑ (F) (61[d])	↑ (M) (29[c]) ↑ (F) (50[c])	0	↓ (M) (52[c]) ↑ (F) (28[c])	Dieter et al. 1992; NTP 1993
Dietary studies								
28 days; Dose: 0.61–23.6	–	0 (M)	–	–	–	–	–	Jonker et al. 1993
35 days; Dose: 0.07–2.2	–	0 (M)	0 (M)	–	–	–	–	Takahashi et al. 2000b
84 days; Dose: 0.07	–	0 (M)	0 (M)	0 (M)	–	–	0 (M)	Takahashi et al. 2000b
84 days; Dose: 0.21	–	0 (M)	0 (M)	0 (M)	–	–	↑ (M) (75[c])	Takahashi et al. 2000b
84 days; Dose: 0.72	–	0 (M)	↑ (M) (45[c])	0 (M)	–	–	0 (M)	Takahashi et al. 2000b
84 days; Dose: 2.2	–	0 (M)	↑ (70)	↑ (M) (100[c])	–	–	0 (M)	Takahashi et al. 2000b
147 days; Dose: 0.06	–	0 (M)	–	↑ (M) (100)	–	–	–	Takahashi et al. 2000a
147 days; Dose: 0.17	–	0 (M)	–	↑ (M) (110[c])	–	–	–	Takahashi et al. 2000a

Table 2-24. Urinalysis in Rats[a] Orally Exposed to Mercuric Chloride

Duration; dose (mg Hg/kg/day)	Cr	TP	AA	ALP	AST	LDH	GGT	Reference
147 days; Dose: 0.51	–	0 (M)	–	↑ (M) (105[c])	–	–	–	Takahashi et al. 2000a
147 days; Dose: 1.7	–	↑ (M) (90c)	–	0(M)	–	–	–	Takahashi et al. 2000a
Drinking water studies								
28 days; Dose: 0.264	↑ (M) (100[c])	–	–	–	–	–	–	Wildemann et al. 2016
28 days; Dose: 2.955	0 (M)	–	–	–	–	–	–	Wildemann et al. 2016

[a]Sexes evaluated are indicated in the results columns.
[b]Numbers in ( ) are percent change compared to control, calculated from quantitative data.
[c]Percent change compared to control, estimated from graphically reported data.
[d]Percent change compared to control, calculated from quantitative data.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; AA = amino acids; ALP = alkaline phosphatase; AST = aspartate aminotransferase; Cr = creatinine; F = female; GGT = gamma-glutamyl transferase; LDH = lactate dehydrogenase; M = male; TP = total protein

Urinalysis was only conducted in mice exposed to mercuric chloride following gavage exposure for 15 months (NTP 1993); no consistent findings indicative of renal damage or impaired renal function were observed. Urinary ALP was significantly elevated by 63% in male mice at 4 mg Hg/kg/day; however, urinary ALP was not elevated in male mice at 7.4 mg Hg/kg/day or female mice at either dose. No exposure-related changes in urinary urea nitrogen, AST, LDH, or GGT were observed in males or females at either dose (NTP 1993).

Organic Mercury—Epidemiological Studies. Little information on renal effects of organic mercury in populations with high fish diets is available, presumably because most studies of high fish consumers have focused on evaluating outcomes in other more sensitive organ systems (e.g., neurological system and developing fetus). Anuria was reported following acute ingestion of high doses of organic mercury (Magos and Clarkson 2006).

Studies of patients with Minamata disease provide some information regarding renal effects of chronic methylmercury exposure, although studies did not provide data on associations with mercury exposure biomarkers. Reviews indicate that there is little clinical evidence of renal damage in the Minamata population, except some evidence of proteinuria and high urinary β_2M in severely affected patients (George 2011; Igata et al. 1993). Increased urine levels of renal tubular epithelial antigen and β_2M were

observed in 19 Minamata disease patients, compared to 35 healthy controls, indicating that renal tubular function is associated with Minamata disease (Iesato et al. 1977). Follow-up studies of Minamata disease patients have examined long-term renal effects. In two studies following >1,000 patients with Minamata disease patients for at least 40 years, no effects were observed on creatinine clearance or the prevalence of renal disease (Futatsuka et al. 2000, 2005). In contrast, a study of 1,483 Minamata disease patients followed through 1981 reported increased mortality due to combined nephritis, nephrosis, and nephrotic syndrome, with SMRs (95% CI) of 3.23 (1.05, 7.54) in men and 4.74 (1.54, 11.07) in women (Tamashiro et al. 1985). Although limited data are available to evaluate associations between organic mercury and renal effects, the kidney appears to be less sensitive than other targets such as the nervous system and developing fetus.

Organic Mercury—Animal Studies. Nephrotoxicity has been observed in rats, mice, and rabbits following intermediate- and chronic-duration exposure. Impaired renal function was reported in one study in mice at lethal/near-lethal acute doses.

Renal function was assessed in one acute oral study in mice following gavage exposure to methylmercury. Impaired renal function (96–100% inhibition of phenolsulfonphthalein excretion) was observed in males 24 hours after a single exposure to ≥16 mg Hg/kg (Yasutake et al. 1991). In females, phenolsulfonphthalein excretion was decreased by approximately 60 and 90% at 32 and 40 mg Hg/kg, respectively. Renal impairment mostly occurred at doses associated with 67% mortality (≥16 mg Hg/kg in males and 40 mg Hg/kg in females); therefore, observed effects may be secondary to widespread toxicity rather than renal-specific damage. The study authors noted slight pathological changes in the kidney in rats exposed the methylmercury, but dose- and sex-specific data were not reported.

Damage to the renal proximal tubules and increased incidence and/or severity of chronic nephropathy have been observed in rats, mice, and rabbits following intermediate and/or chronic oral exposure to organic mercury (see Table 2-25). In rats, chronic drinking water exposure to phenylmercuric acetate resulted in increased severity of chronic renal nephrosis at ≥0.37 mg Hg/kg/day (Solecki et al. 1991). No exposure-related kidney lesions were observed in rats following dietary exposure to methylmercury at intermediate-duration doses up to 0.25 mg Hg/kg/day (Khera and Tabacova 1973) or chronic-duration doses up to 0.18 mg Hg/kg/day (Verschuuren et al. 1976). In mice, dietary exposure to methylmercury resulted in damage to the renal proximal tubules at intermediate doses ≥0.627 mg Hg/kg/day and dose-related proximal tubule damage, urinary casts, pelvic dilatation, cystic kidney, and chronic nephropathy at chronic doses ≥0.139 mg Hg/kg/day (Hirano et al. 1986; Mitsumori et al. 1990). Intermediate-duration

drinking water exposure to methylmercury also resulted in damage to the proximal tubule at ≥5.6 mg Hg/kg/day (MacDonald and Harbison 1977; Moreira et al. 2012). Damage to the proximal renal tubule was also observed in rabbits following intermediate-duration exposure to methylmercury at dietary doses ≥1 mg Hg/kg/day (Koller et al. 1977). No exposure-related renal lesions were observed in cats following intermediate or chronic dietary exposure to methylmercury at doses up to 0.176 mg or 0.074 Hg/kg/day, respectively (Charbonneau et al. 1976).

Table 2-25. Kidney Lesions in Animals[a] Orally Exposed to Organic Mercury

Species; duration	Dose (mg Hg/kg/day)	Histology	Lesion details	Reference (compound)
Rat; 122 days	0.002–0.25	0 (F)		Khera and Tabacova 1973 (MMC)
Rat; 721 days	0.37	↑ (M)	Chronic renal nephrosis >grade 2: 19/20 (control: 7/20)	Solecki et al. 1991 (PMA)
Rat; 721 days	3.7	↑ (M)	Chronic renal nephrosis >grade 2: 14/20 (control: 7/20)	Solecki et al. 1991 (PMA)
Rat; 730 days	0.006–0.18	0 (M, F)		Verschuuren et al. 1976 (MMC)
Mouse; 21 days	5.6	↑ (M)	Glomerular shrinkage and tubular vacuolization[b]	Moreira et al. 2012 (MM)
Mouse; 182 days	0.0254–0.15	0 (M, F)		Hirano et al. 1986 (MMC)
Mouse; 182 days	0.627	↑ (F)	Epithelial degeneration and regeneration of the renal proximal tubules[b]	Hirano et al. 1986 (MMC)
Mouse; 182 days	0.724	↑ (M)	Epithelial degeneration and regeneration of the renal proximal tubules; more severe than females[b]	Hirano et al. 1986 (MMC)
Mouse; 196 days	0.89	0 (M)		MacDonald and Harbison 1977 (MMC)
Mouse; 196 days	9.5	↑ (M)	Slight degenerative changes in proximal tubular epithelial cells[b]	MacDonald and Harbison 1977 (MMC)
Mouse; 728 days	0.0254–0.115	0 (M, F)		Hirano et al. 1986 (MMC)
Mouse; 728 days	0.0265–0.133	0 (M, F)		Mitsumori et al. 1990 (MMC)
Mouse; 728 days	0.139	↑ (M)	Chronic nephropathy: 27/60 (control: 8/60)	Mitsumori et al. 1990 (MMC)

Table 2-25. Kidney Lesions in Animals[a] Orally Exposed to Organic Mercury

Species; duration	Dose (mg Hg/kg/day)	Histology	Lesion details	Reference (compound)
Mouse; 728 days	0.150	↑ (M)	Mild epithelial degeneration of the renal proximal tubules: 12/28 Increased incidence of urinary cast and pelvic dilatation[b]	Hirano et al. 1986 (MMC)
Mouse; 728 days	0.601	↑ (F)	Chronic nephropathy: 56/60 (control: 5/60)	Mitsumori et al. 1990 (MMC)
Mouse; 728 days	0.627	↑ (F)	Epithelial degeneration and regeneration of the renal proximal tubules: 19/60	Hirano et al. 1986 (MMC)
Mouse; 728 days	0.686	↑ (M)	Chronic nephropathy: 59/60 (control: 8/60)	Mitsumori et al. 1990 (MMC)
Mouse; 728 days	0.724	↑ (M)	Epithelial degeneration and regeneration of the renal proximal tubules: 40/59 Focal hyperplasia of tubular epithelium: 13/59 Cystic kidney: 8/59	Hirano et al. 1986 (MMC)
Rabbit; 98 days	0.05–0.52	0 (M, F)		Koller et al. 1977 (MMC)
Rabbit; 98 days	1–1.1	↑ (M, F)	Mild-to-moderate proximal tubule necrosis: 20/20[c]	Koller et al. 1977 (MMC)
Cat; ~112 days	0.176	0 (M, F)		Charbonneau et al. 1976 (MMC)
Cat; 730 days	0.0084–0.074	0 (M, F)		Charbonneau et al. 1976 (MMC)

[a]Sexes evaluated are indicated in the results columns.
[b]Reported qualitatively only (incidence data not provided).
[c]Eight rabbits per sex died by 4 weeks; the remaining rabbits died by 12 weeks.

↑ = increase in histopathological lesions; 0 = no change; – = not assessed; F = female; M = male; MM = methylmercury; MMC = methylmercury chloride; PMA = phenylmercuric acetate

Data regarding alterations in kidney weights following oral exposure to organic mercury are limited. Relative kidney weights were significantly elevated by 18% in male rats following gavage exposure to methylmercury at 2.8 mg Hg/kg/day for 14 days; no changes were observed at ≤0.93 mg Hg/kg/day (Fossato da Silva et al. 2011). Following chronic dietary exposure to methylmercury, relative kidney weights were significantly increased by 30% in males exposed to 0.16 mg Hg/kg/day and 36% in females exposed to 0.18 mg Hg/kg/day; no changes were observed at ≤0.04 mg Hg/kg/day (Verschuuren et al. 1976).

Adverse changes in renal clinical chemistry values following oral exposure to methylmercury were only observed in one acute study in mice at doses associated with increased mortality. Serum creatinine was elevated in a dose-related manner in male mice following a single oral gavage exposure to methylmercury at doses ≥16 mg Hg/kg, doses that also resulted in ≥67% mortality (Yasutake et al. 1991). No changes in serum creatinine were observed in similarly exposed females at single doses up to 40 mg Hg/kg. In other studies, no adverse, exposure-related changes in renal clinical chemistry (e.g., creatinine, uric acid, urea, BUN) were observed in rats at chronic dietary doses up to 0.18 mg Hg/kg/day (Verschuuren et al. 1976), mice at intermediate-duration drinking water doses up to 5.6 mg Hg/kg/day (Moreira et al. 2012), rabbits at intermediate-duration dietary doses up to 0.53 mg Hg/kg/day for 98 days (Koller et al. 1977), or cats at an intermediate-duration dose of 0.176 mg Hg/kg/day or chronic-duration dietary doses up to 0.074 mg Hg/kg/day (Charbonneau et al. 1976). No changes in urinalysis parameters were observed in rats at chronic-duration dietary doses up to 0.18 mg Hg/kg/day (Verschuuren et al. 1976) or cats at an intermediate-duration dose of 0.176 mg Hg/kg/day or chronic-duration dietary doses up to 0.074 mg Hg/kg/day (Charbonneau et al. 1976).

Rats given methylmercuric chloride in the diet for 2 years at a dose of 0.1 mg Hg/kg/day had decreased enzymes (ALP, ATPase, NADH- and NADPH-oxidoreductase, and AMPase) in the proximal convoluted tubules (Verschuuren et al. 1976).

Predominant Mercury Form Unknown (General Populations). Renal effects of mercury in general populations have not been extensively studied. Studies (summarized in Table 2-26) include prospective, cross-sectional, and retrospective cohort designs, and examined markers of glomerular function and tubular damage. Several studies were of large populations (n=804–5,924). Mercury exposure was assessed using BHg and UHg.

Table 2-26. Results of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Renal Effects in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Al-Saleh et al. 2017 Cross-sectional; 944 lactating mother-infant pairs[a] (Saudi Arabia)	UHg Gmean Mothers: 0.955 µg/g Cr Infants: 0.635 µg/L	Urine albumin	↑ (UHg, mothers) 0 (UHg, infants)
		Urine NAG	↑ (UHg, mothers) 0 (UHg, infants)
		Urine α_1M	↑ (UHg, mothers) 0 (UHg, infants)

Table 2-26. Results of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Renal Effects in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
De Burbure et al. 2006 Cross-sectional; 804 children (age: 8.5–12.3 years) (France, Poland, Czech Republic)	UHg mean Exposed females: France: 1.19 µg/g Cr Poland: 0.06 µg/g Cr Czech Republic: 0.18 µg/g Cr Exposed males: France: 0.92 µg/g Cr Poland: 0.06µg/g Cr Czech Republic: 0.13 µg/g Cr Control males: France: 0.99 µg/g Cr Poland: 0.06 µg/g Cr Czech Republic: 0.26 µg/g Cr	Urine NAG	↑ (UHg)
Kim and Lee 2012 Cross-sectional; 5,924 adults (KNHANES 2008–2010)	BHg Gmean: 4.3 µg/L	GFR	0 (BHg)
Kim et al. 2015b Cross-sectional; 1,797 adults (KNHANES 2011)	BHg mean: 4.35 µg/L	CKD	0 (BHg)
Li et al. 2013 Cross-sectional; 54 participants living near a mercury mine and 47 controls (China)	BHg mean Near mine: 6.09 µg/L Control: 3.67 µg/L	SCr	↑ (BHg, exposed versus controls)
		SUN	↑ (BHg, exposed versus controls)
Li et al. 2015 Cross-sectional; 4,250 participants living near a mercury mine (China)	UHg Gmean: 8.32 µg/g Cr	SCr	↑ (UHg)
		BUN	0 (UHg)
Lin et al. 2014b Cross-sectional; 1,046 adults (NHANES 2003–2004)	BHg: <0.66–>1.64	GFR	↓ (BHg)
		Albuminuria	0 (BHg)
Ohno et al. 2007 Cross-sectional; 59 women (Japan)	UHg mean: 0.86 µg/g Cr HHg mean: 1.51 µg/g NHg mean: 0.59 µg/g	Urine NAG	↑ (UHg, HHg, NHg)
		Urine α_1M	↑ (UHg, HHg, NHg)
		Urine β_2M	0 (UHg, HHg, NHg)

Table 2-26. Results of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Renal Effects in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Pollack et al. 2015 Prospective cohort; 259 women followed for two menstrual cycles (Buffalo, New York)	BHg median: 1.1 µg/L BHg mean: 1.50 µg/L	GFR	0 (BHg)
		BUN	0 (BHg)
		SCr	0 (BHg)
Sommar et al. 2013 Population-based, prospective nested case-referent; 118 cases and 378 referents (Sweden)	ErHg Gmean: Cases: 2.44 µg/L Referents: 3.06 µg/L	ESRD	0 (ErHg)

[a]415 infants and 41 mothers were excluded from the analysis because samples were not obtained, or sample volume was inadequate.

↑ = positive association; ↓ = inverse association; 0 = no association; α_1M = α_1-microglobulin; β_2M = β_2-microglobulin; BHg = blood mercury; BUN = blood urea nitrogen; CKD = chronic kidney disease; Cr = creatinine; ErHg = erythrocyte mercury; ESRD = end-stage renal disease; GFR = glomerular filtration rate; Gmean = geometric mean; HHg = hair mercury; KNHANES = Korea National Health and Nutrition Examination Survey; NAG = N-acetyl-β-D-glucosaminidase; NHANES = National Health and Nutrition Examination Survey; NHg = toenail mercury; SCr = serum creatinine; SUN = serum urea nitrogen; UHg = urine mercury

Similar to studies on elemental mercury, results of studies evaluating mercury exposure in general populations are inconsistent. Some evidence of altered glomerular function (increased urine albumin, serum creatinine, and SUN) was observed in two cross-sectional studies (Al-Saleh et al. 2017; Li et al. 2013). However, no change in GFR was observed in a large (n=5,924) cross-sectional study using KNHANES data (Kim and Lee 2012), or in other cross-sectional or prospective studies evaluating markers of glomerular function (Lin et al. 2014b; Pollack et al. 2015). The few cross-sectional studies evaluating markers of tubular damage found positive associations between UHg and urine NAG, and α_1M (Al-Saleh et al. 2017; De Burbure et al. 2006; Ohno et al. 2007). No associations were observed between BHg and chronic kidney disease or ErHg and end-stage renal disease (Kim et al. 2015b; Sommar et al. 2013). Few epidemiological studies in general populations have been conducted of renal outcomes associated with exposure to mercury. The results of these studies indicate that mercury exposure of the general population may be associated with glomerular and tubular damage.

Mechanisms of Action. Numerous mechanisms for renal toxicity have been proposed (Barnett and Cummings 2018; Jan et al. 2011; Zalups 2000); these include decreased function of renal transporters; blockage of aquaporins (water channels); decreased renal content of glutathione; formation of ROS,

leading to lipid peroxidation and oxidative stress leading to cellular injury; decreases in the activity of SOD, catalase, GPX, and glutathione disulfide reductase, leading to enhanced susceptibility of renal epithelial cells to oxidative injury; interference with mitochondrial respiratory function; altered intracellular distribution of calcium; inactivation of the plasma membrane (Na^+K^+)-stimulated ATPase; increased expression of stress proteins; and interactions between mercury and cellular microtubular networks.

An important contributing factor to the nephrotoxicity of mercury is that absorbed mercuric mercury accumulated in the renal proximal tubule with the highest concentrations occurring in the region of the kidney (inner cortex and outer stripe of the outer medulla) where mercury-induced tubule damage is initiated (Berlin et al. 2015; Zalups and Diamond 2005). This region of the kidney receives a relatively high dose of mercury regardless of the form of mercury absorbed. This includes inorganic mercuric mercury following absorption and oxidation of elemental mercury, as well as absorbed methylmercuric mercury, and inorganic mercuric mercury produced from demethylation of absorbed methylmercury (see Section 3.1.2). Accumulation of mercuric mercury in the kidneys is facilitated by several membrane transport systems in the proximal tubule that recognize S-conjugates of mercuric mercury as transport substrates. These transport systems, coupled with oxidative metabolism of mercury compounds to mercuric mercury species, and the high affinity of mercuric mercury for the thiolate anion explain why mercury in most of its forms can be nephrotoxic at a sufficiently high absorbed dose (Berlin et al. 2015). The exact mechanisms by which mercury impairs renal cellular function and damages the proximal tubule have not been fully characterized and are likely to involve many different molecular targets, as discussed above. Central to these mechanisms are ligand exchange reactions that enable mercuric mercury to distribute to membrane and intracellular sulfhydryl groups that are important in the structure or catalytic activity of structural proteins and enzymes critical to cell metabolism and function (Carty and Malone 1979).

2.12 DERMAL

Studies of dermal effects associated with an immunological mechanism of action (e.g., dermal hypersensitivity reactions and acrodynia) are discussed in Section 2.15 (Immunological).

Overview. One epidemiological study that investigated associations between biomarkers and non-immunological dermal effects was identified; this study evaluated effects in a population of dentists. No

epidemiological studies were identified for populations with high fish diets or general populations. Data are insufficient to determine if non-immunological dermal effects are associated with mercury exposure.

A few animal studies evaluating dermal effects are available for oral exposure to mercuric chloride or methylmercury. Available data do not indicate that the skin is a sensitive target of mercury toxicity following oral exposure.

The following summarizes results of epidemiological and animal studies on dermal outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - One epidemiological study found an increased risk of self-reported dermal hyperpigmentation in dentists exposed to elemental mercury, compared to controls.
  - *Animal studies*
    - No studies evaluating dermal effects following exposure to elemental mercury were identified.
- ***Inorganic mercury salts***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to inorganic mercury salts and dermal effects were identified.
  - *Animal studies*
    - Available data are inadequate to assess potential dermal effects following exposure to inorganic mercury salts.
- ***Organic mercury***
  - *Epidemiology studies*
    - No epidemiological studies on non-immunological dermal effects of exposure to organic mercury compounds were identified.
    - Case reports have noted rashes in individuals exposed to phenylmercury.
  - *Animal studies*
    - No evidence of dermal effects was found in rodents following intermediate- or chronic-duration oral exposure to methylmercury.
- ***Predominant mercury form unknown (general populations)***
    - No epidemiological studies of general populations evaluating non-immunological dermatological changes in general populations exposed to mercury were identified.

Confounding Factors. One epidemiological study evaluating non-immunological dermal effects from exposure to elemental mercury in dentists was identified (Neghab et al. 2011). Covariates considered in this study as potential cofounders were age, marital status, number of personal amalgam fillings, and dental clinic type.

Elemental Mercury—Epidemiological Studies. One epidemiological study evaluating dermatological effects of elemental mercury was identified (Neghab et al. 2011). This cross-sectional study compared self-reported dermal symptoms (dermatitis, eczema, and hyperpigmentation) in exposed dentists (n=106; median UHg: 3.16 µg/g creatinine) to a control group of physician general practitioners (n=94; median UHg: 2.18 µg/g creatinine) from Iran. The OR for hyperpigmentation in exposed dentists compared to controls was 4.62 (95% CI 1.2, 17.68), although no increased risk was observed for dermatitis or eczema. Results of this study have not been corroborated.

Elemental Mercury—Animal Studies. No studies were located regarding dermal effects in animals after exposure to elemental mercury.

Inorganic Mercury Salts—Animal Studies. No exposure-related changes in skin histology were observed in rats exposed once to mercuric chloride at gavage doses up to 9.24 mg Hg/kg/day (Lecavalier et al. 1994). No additional studies evaluating dermal effects in animals after exposure to inorganic mercury compounds were identified.

Organic Mercury—Epidemiological Studies. Epidemiological studies evaluating dermatological effects of exposures to methylmercury from high fish diets were not identified. A case report of three individuals exposed to phenylmercury through weed killers and pharmaceutical ointments reported pruritic papular rashes (Morris 1960). No biomarkers were evaluated and the underlying mechanism of action for the rashes was not identified.

Organic Mercury—Animal Studies. No exposure-related changes in skin histology were observed in rats following chronic-duration exposure to doses up to 0.18 mg Hg/kg/day (Verschuuren et al. 1976) or mice following intermediate- or chronic-duration exposure up to 0.724 mg Hg/kg/day (Hirano et al. 1986; Mitsumori et al. 1990).

Predominant Mercury Form Unknown (General Populations). No epidemiological studies of general populations evaluating non-immunological dermatological changes in general populations exposed to mercury were identified.

Mechanisms of Action. Mechanisms of potential non-immunological dermatological changes associated with mercury exposure have not been established.

2.13 OCULAR

Studies evaluating neurological ocular effects are reviewed in Section 2.16 (Neurological).

Overview. One epidemiological study that investigated associations between biomarkers and non-neurological ocular effects was identified; this study evaluated effects in a general population. No epidemiological studies were identified for populations exposed to elemental mercury or in populations with high fish diets. Data are insufficient to determine if adverse non-neurological ocular effects are associated with mercury exposure. The clinically distinct brownish discoloration of the lens known as mercurialentis (Byrns and Penning 2017; El-Sherbeeny et al. 2006) is not discussed below as it is not associated with adverse ocular effects; see Section 3.3.1 (Biomarkers of Exposure) for additional details.

A few animal studies evaluating ocular effects are available for oral exposure to mercuric chloride or methylmercury. Available data do not indicate that the eye is a sensitive target of mercury toxicity following oral exposure. Observed visual impairment in primates following oral exposure to methylmercury are considered neurological in nature and are discussed in Section 2.16 (Neurological).

The following summarizes results of epidemiological and animal studies on non-neurological ocular outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - No epidemiological studies on non-neurological ocular effects of exposure to elemental mercury were identified.
  - *Animal studies*
    - No studies evaluating ocular effects following exposure to elemental mercury were identified.

- ***Inorganic mercury salts***
  - *Epidemiology studies*
    - No epidemiological studies on non-neurological ocular effects of exposure to inorganic mercury salts were identified.
  - *Animal studies*
    - Available data are inadequate to assess potential ocular effects following oral exposure to inorganic mercury salts.
- ***Organic mercury***
  - *Epidemiology studies*
    - No epidemiological studies on non-neurological ocular effects of exposure to organic mercury compounds were identified.
  - *Animal studies*
    - No evidence of ocular damage was found in rodents following intermediate- or chronic-duration oral exposure to methylmercury.
- ***Predominant mercury form unknown (general populations)***
    - One epidemiological study of the general population found an increased risk of dry eye symptoms in higher versus lower BHg groups. These results have not been corroborated.
    - Data are inadequate to determine if non-neurological ocular effects are associated with mercury exposure in general populations.

Confounding Factors. One epidemiological study regarding non-neurological ocular effects of mercury was identified (Chung and Myong 2016). Covariates considered in this study as potential confounders were age, gender, education, household income, smoking status, alcohol consumption, sleeping time, perceived stress status, and history of atopy.

Elemental Mercury—Epidemiological Studies. Epidemiological studies evaluating non-neurological ocular effects in populations exposed to elemental mercury were not identified.

Elemental Mercury—Animal Studies. No studies were located regarding ocular effects in animals after exposure to elemental mercury.

Inorganic Mercury Salts—Animal Studies. No histopathological changes in the eye were observed in rats exposed once to mercuric chloride at gavage doses up to 9.24 mg Hg/kg/day (Lecavalier et al. 1994). No additional studies evaluating ocular effects in animals after exposure to inorganic mercury were identified.

Organic Mercury—Epidemiological Studies. Epidemiological studies evaluating non-neurological ocular effects of exposures to methylmercury from high fish diets were not identified.

Organic Mercury—Animal Studies. No histopathological changes in the eye were observed in rats following chronic-duration exposure to doses up to 0.18 mg Hg/kg/day (Verschuuren et al. 1976) or mice following intermediate- or chronic-duration exposure up to 0.724 mg Hg/kg/day (Hirano et al. 1986; Mitsumori et al. 1990).

Predominant Mercury Form Unknown (General Populations). One study that evaluated associations between mercury biomarkers and non-neurological ocular effects was located (Chung and Myong 2016). In a cross-sectional study of a KNHANES population (n=4,761 adults) with a median BHg of 3.7 µg/L, the odds of self-reported dry eye symptoms (persistent dryness or eye irritation) were increased in the high (BHg ≥3.7 µg/L) relative to the low (BHg <3.7 µg/L) exposure groups (OR 1.324; 95% CI 1.059, 1.655).

Mechanisms of Action. Chung and Myong (2016) speculated that the following mechanisms could be involved in the development of dry eye: (1) altered conjunctival mucus; (2) induction of conjunctival inflammation; (3) recruitment and activation of inflammatory and immune cells on the ocular surface; and (4) depletion of antioxidant proteins (e.g., metallothionein) in the lacrimal glands and conjunctiva.

2.14 ENDOCRINE

Overview. Data on endocrine effects of mercury are available from studies in humans and animals. Compared to other systems, effects of mercury on endocrine functions have not been well investigated in humans. Studies are available in workers exposed to elemental mercury, a population with a high fish diet, and in general populations with exposure to unspecified forms of mercury. Epidemiological studies have focused on associations between mercury biomarkers and thyroid function and glucose homeostasis. Studies of effects on thyroid function and glucose homeostasis report inconsistent findings and do not provide evidence that the endocrine system is a sensitive target for mercury.

A few animal studies have evaluated endocrine function following oral exposure to inorganic salts or organic mercury compounds. Based on the limited number of studies and endpoints assessed, limited information on dose- or duration-response (e.g., single exposure level study design), and/or inconsistent findings between studies, available data are insufficient to determine if the endocrine system is a sensitive target for mercury.

The following summarizes results of epidemiological and animal studies on endocrine outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - A few studies evaluating effects of elemental mercury exposure on thyroid function provide conflicting results, with most studies showing no differences in thyroxine (T4), triiodothyronine (T3), and thyroid-stimulated hormone (TSH) levels between workers and controls.
  - *Animal studies*
    - No studies evaluating endocrine effects following exposure to elemental mercury were identified.
- ***Inorganic mercury salts***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to inorganic mercury salts and endocrine effects were identified.
  - *Animal studies*
    - Data are insufficient to determine if exposure to inorganic mercury salts is associated with adverse endocrine effects. A limited number of studies suggest that inorganic mercury salts may alter thyroid, pancreatic, or adrenocortical function; however, findings are inconsistent across studies, doses, and/or durations.
- ***Organic mercury***
  - *Epidemiology studies*
    - Data are insufficient to determine if exposure to organic mercury is associated with adverse endocrine effects. The only identified study showed a very small increase in the risk of increased fasting glucose levels and type 2 diabetes in a population with a high fish diet.

- *Animal studies*
  - Data are insufficient to determine if exposure to organic mercury is associated with adverse endocrine effects. One study suggested that organic mercury may impair pancreatic function, while another provided limited evidence of adrenocortical dysfunction.

- ***Predominant mercury form unknown (general populations)***
  - Few studies have evaluated the effects of mercury exposure on thyroid function in general populations. Evidence for associations between exposure to mercury and thyroid function, based on circulating levels of thyroid hormones, is conflicting.
  - Effects of mercury exposure on glucose homeostasis has not been well-studied. In the few available studies, most results showed no associations between mercury and type 2 diabetes. However, two studies showed positive associations between mercury biomarkers and insulin resistance.

Confounding Factors. Several factors that may be associated with mercury exposure status can complicate interpretation of studies on thyroid function. These include selenium status (selenium-containing enzymes are involved in thyroid hormone homeostasis), negative iodine balance (iodine deficiency is rare in the United States), underlying thyroid disease, genetic predisposition for thyroid disease, and some pharmaceutical agents. The epidemiological studies reviewed in this section have not considered most of these potential confounders. For glucose homeostasis, there are numerous potential confounding factors. These include body weight/BMI (obesity), age, diet, family history of diabetes, age, exercise, high blood pressure, and low HDL cholesterol. Most epidemiological studies reviewed below include some of these adjustments when appropriate. No specific confounder or covariate was mandatory for the inclusion of the study into the profile; however, studies of thyroid and glucose homeostasis outcomes that did not consider the aforementioned potential confounders are potentially more confounded than studies that did consider these variables.

Elemental Mercury—Epidemiological Studies. Studies evaluating effects of elemental mercury on endocrine function are summarized in Table 2-27. The database consists of a few cross-sectional studies examining associations between exposure to elemental mercury and markers of thyroid function in miners, chloralkali workers, and dentists. Worker populations in these studies were small ($n \leq 80$), limiting the power to detect associations between exposure to elemental mercury and thyroid effects. Primary outcomes measures to evaluate thyroid function included measurements of plasma or serum levels of T4, T3, and TSH, with comparisons between exposed workers and controls.

Table 2-27. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Effects on Thyroid Hormones

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Afrifa et al. 2018 Cross-sectional; 80 gold miners and 57 controls (Ghana)	BHg median Miners: 8.0 µg/L Controls: 1.0 µg/L	T4[a]	↓ (BHg, miners versus controls)
		T3[a]	↓ (BHg, miners versus controls)
		TSH	0 (BHg, miners versus controls)
Barregard et al. 1994a Cross-sectional; 41 male chloralkali workers and 41 matched controls (Sweden)	UHg mean Workers: 27 µg/g Cr Controls: 3.4 µg/g Cr	Free T4	0 (BHg, workers versus controls)
		Free T3	0 (BHg, workers versus controls)
		TSH	0 (BHg, workers versus controls)
Ellingsen et al. 2000b Cross-sectional; 47 chloralkali workers and 47 controls (Norway)	UHg median Workers: 10.5 µg/g Cr Controls: 2.3 µg/g Cr	Free T4	0 (UHg, workers versus controls)
		Free T3	0 (UHg, workers versus controls)
		Reverse T3	↑ (UHg, workers versus controls)
		Anti-TPO	↓ (UHg, workers versus controls)
Erfurth et al. 1990 Cross-sectional; 9 male dentists and 11 controls and 11 chloralkali workers and 10 controls (Sweden)	UHg mean Dentists: 2.3 µg/g Cr Controls: 0.71 µg/g Cr UHg mean, Workers Workers: 46 µg/g Cr Controls: 1.1 µg/g Cr	Free T4	0 (UHg, workers or dentists versus respective controls)
		Free T3	0 (UHg, workers or dentists versus respective controls)
		TSH	0 (UHg, workers or dentists versus respective controls)

[a]Not specified if total or free T4 and T3.

↑ = increased levels; ↓ = decreased levels; 0 = no difference; Anti-TPO = thyroid peroxidase antibodies; BHg = blood mercury; Cr = creatinine; T4 = thyroxine; T3 = triiodothyroxine; TSH = thyroid stimulating hormone; UHg = urine mercury

Evidence for effects on the thyroid gland in workers exposed to elemental mercury is inconclusive. Three studies did not find differences in T4, T3, or TSH levels in workers compared to controls (Barregard et al. 1994a; Ellingsen et al. 2000b; Erfurth et al. 1990). Ellingsen et al. (2000b) observed a 15% increase in reverse T3 (a thyroid hormone metabolite) in chloralkali workers compared to controls (Ellingsen et al. 2000b); however, in the absence of effects on T4 and T3, the clinical significance of this finding is uncertain. In contrast to the studies showing no effects on T4 and T3 levels in exposed chloralkali workers, a study in gold miners (median BHg 8 µg/L) reported decreases in T4 and T3 of 39 and 43%,

respectively, compared to controls (median BHg 1 µg/L), although TSH levels were similar between miners and controls (Afrifa et al. 2018).

Elemental Mercury—Animal Studies. No studies were located regarding endocrine effects in animals after exposure to elemental mercury.

Inorganic Mercury Salts—Animal Studies. A limited number of studies in laboratory animals have evaluated effects of inorganic mercury salts on thyroid, pancreas, and adrenocortical function following acute- or intermediate-duration oral exposure. Additional data regarding endocrine gland weight and/or histology are available from acute-, intermediate-, and chronic-duration oral studies. Overall, available data are insufficient to determine if exposure to inorganic mercury salts is associated with adverse endocrine effects due to the limited number of studies, limitations of study design (e.g., single exposure level), and/or inconsistent findings.

Thyroid function has been evaluated in a limited number of studies in rats and mice following acute- and intermediate-duration oral exposure to mercuric chloride or mercuric sulfide (see Table 2-28). In a series of experiments, Goldman and Blackburn (1979) evaluated thyroid function in female rats following acute- or intermediate-duration exposure to mercuric chloride. Increased thyroid function, as evidence by increased iodine uptake, release, and/or turnover, was observed following gavage exposure to 7.4 or 9.4 mg Hg/kg/day for 6 or 40 days, respectively. However, decreased iodine uptake, release, and turnover were observed following dietary exposure to 2.2 mg Hg/kg/day for 90 days. It is unclear if the opposing effects were attributable to exposure route (gavage versus dietary) and/or evidence of non-monotonic dose or duration effects (since only one dose was tested at each duration, biphasic responses cannot be evaluated). Evidence for decreased T3 synthesis in the thyroid was also observed following exposure to 9.4 mg Hg/kg/day for 40 days (not evaluated at other durations). In mice, significant decreases in plasma T3 were observed following acute gavage exposure to 6 mg Hg/kg/day as mercuric chloride or mercuric sulfide; plasma T4 was also decreased with mercuric chloride exposure (Sin et al. 1990). However, in an intermediate-duration study with mercuric sulfide, significant decreases were observed in plasma T4, but not T3, 1–4 weeks post-exposure to 6 mg Hg/kg/day (Sin and Teh 1992). Study designs in mice are inadequate to assess dose- or duration-dependence of observed effects.

Table 2-28. Thyroid Function and Hormone Levels in Female Rats and Mice Orally Exposed to Inorganic Mercury Salts

Species; Duration	Dose (mg Hg/kg/day)	T3[a]	T4[a]	Iodine uptake[a]	Iodine release ½ life[a]	Iodine turnover rate[a]	Reference (compound)
Rat; 6 days	7.4	–	–	–	↓ (69)	↑ (200)	Goldman and Blackburn 1979 (MC)
Rat; 40 days	9.4	↓ Thyroid (19)	0 Thyroid	↑ (108)	–	–	Goldman and Blackburn 1979 (MC)
Rat; 90 days	2.2	–	–	↓ (27)	↑ (56)	↓ (37)	Goldman and Blackburn 1979 (MC)
Mouse; 10 days	6	↓ Plasma (70)	↓ Plasma (42)	–	–	–	Sin et al. 1990 (MC)
Mouse; 10 days	6	↓ Plasma (59)	0 Plasma	–	–	–	Sin et al. 1990 (MS)
Mouse; 28 days	6	0	↓ Plasma (28–41[b])	–	–	–	Sin and Teh 1992 (MS)

[a]Numbers in ( ) are percent change compared to control, calculated from quantitative data.
[b]Measured 1–4 weeks post-exposure.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; MC = mercuric chloride; MS = mercuric sulfide; T3 = triiodothyronine; T4 = thyroxine

One study showed a 28% increase in absolute thyroid weight in female rats following gavage exposure to mercuric chloride at 9.4 mg Hg/kg/day for 40 days; relative organ weights were not reported but no body weight effects were noted (Goldman and Blackburn 1979). Based on evidence of increased thyroid function in this study, elevated thyroid weights are considered treatment related. Thyroid weights were not assessed in other identified studies.

In a series of experiments, Argawal and Chansouria (1989) evaluated adrenocortical function in male rats exposed to mercuric chloride via drinking water for 60, 120, or 180 days (see Table 2-29). Corticosterone levels in the adrenal gland were significantly elevated in a dose- and duration-dependent manner after exposure to ≥2.9 mg Hg/kg/day for 60–120 days. Plasma corticosterone levels also showed a significant, dose-related increase following exposure for 120 days, but findings were biphasic at 60 days (levels increased at 2.9 mg Hg/kg/day but decreased at ≥5.8 mg Hg/kg/day). After 180 days of exposure, adrenal and plasma corticosterone levels were comparable to controls. The study authors considered recovery at 180 days an indication of acquired resistance to mercury. Argawal and Chansouria (1989) also reported significantly elevated relative adrenal weights after exposure to 2.9 mg Hg/kg/day for 60, 120, or

180 days, but findings do not show a clear dose- or duration-dependence (see Table 2-29). Altered relative adrenal gland weight findings should be interpreted with caution because neither absolute adrenal gland weights nor body weights were reported. Other studies do not show exposure-related changes in adrenal gland weights in male or female rats following exposure to mercuric chloride at intermediate dietary doses up to 20.9 or 23.6 mg Hg/kg/day, respectively (Jonker et al. 1993), or gavage doses up to 1.65 mg Hg/kg/day (Atkinson et al. 2001). In mice, no exposure-related changes in adrenal gland weight were observed following intermediate-duration exposure to mercuric chloride at gavage doses up to 0.74 mg Hg/kg/day (Khan et al. 2004).

Table 2-29. Corticosterone levels and Adrenal Gland Weight in Rodents[a] Orally Exposed to Mercuric Chloride

Species Duration	Dose (mg Hg/kg/day)	Plasma corticosterone[b]	Adrenal corticosterone[b]	Adrenal weight[b]	Reference
Rat (B) 28 days	0.61–23.6	–	–	0 (M, F)	Jonker et al. 1993
Rat (M) 60 days	2.9	↑ (M) (33)	↑ (M) (146)	↑ (M) (31)	Agrawal and Chansouria 1989
Rat (M) 60 days	5.8	↓ (M) (31)	↑ (M) (157)	↑ (M) (34)	Agrawal and Chansouria 1989
Rat (M) 60 days	11.8	↓ (M) (60)	↑ (M) (203)	↑ (M) (27)	Agrawal and Chansouria 1989
Rat (B) 79–81 days	0.37–1.98	–	–	0 (M, F)	Atkinson et al. 2001
Rat (M) 120 days	2.9	↑ (M) (87)	↑ (M) (218)	↑ (M) (19)	Agrawal and Chansouria 1989
Rat (M) 120 days	5.8	↑ (M) (42)	↑ (M) (313)	↑ (M) (10)	Agrawal and Chansouria 1989
Rat (M) 120 days	11.8	↑ (M) (20)	↑ (M) (372)	↑ (M) (51)	Agrawal and Chansouria 1989
Rat (M) 180 days	2.9	0 (M)	0 (M)	↑ (M) (14)	Agrawal and Chansouria 1989
Rat (M) 180 days	5.8	0 (M)	0 (M)	↑ (M) (30)	Agrawal and Chansouria 1989
Rat (M) 180 days	11.8	0 (M)	0 (M)	↑ (M) (31)	Agrawal and Chansouria 1989
Mouse (B) 61–79 days	0.18–0.74	–	–	0 (M, F)	Khan et al. 2004

[a]Sexes evaluated are indicated in the results columns.
[b]Numbers in ( ) are percent change compared to control, calculated from quantitative data.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; B = both; F = female; M = male

Pancreatic function was evaluated in one study in mice following exposure to mercuric chloride at a gavage dose of 3.7 mg Hg/kg/day for 14 days (Chen et al. 2012). Fasting insulin levels were significantly decreased by 60%. In a glucose tolerance test (after fasting), blood glucose levels were significantly elevated by 45–70% when measured 30–150 minutes after glucose administration. For reference, baseline insulin levels were increased by 17% and baseline glucose levels were decreased 15% in treated mice, compared to controls. However, exposure to the same dose for 28 or 42 days resulted in duration-dependent increases of 70–95% in baseline insulin levels and a 35% increase in baseline glucose levels; glucose tolerance was not tested in longer-duration studies (Chen et al. 2012). After the 14-day exposure, apoptosis in pancreatic islet cells was significantly increased. In other studies, blood glucose levels were unaltered by exposure to mercuric chloride in rats at acute-duration doses up to 9.24 mg Hg/kg/day (Lecavalier et al. 1994) and in mice at intermediate-duration doses up to 0.74 mg Hg/kg/day (Khan et al. 2004).

Parathyroid hyperplasia was observed in male rats following chronic exposure to mercuric chloride at dietary doses ≥1.8 mg Hg/kg/day; however, this lesion was considered secondary to impaired renal function observed in male rats at ≥1.8 mg Hg/kg/day (Dieter et al. 1992; NTP 1993). Parathyroid hyperplasia was not observed in similarly exposed female rats (with normal renal function) at doses up to 4 mg Hg/kg/day (Dieter et al. 1992; NTP 1993). No exposure-related parathyroid lesions were observed following intermediate-duration gavage doses up to 4 or 15 mg Hg/kg/day in rats or mice, respectively (Dieter et al. 1992; Khan et al. 2004; NTP 1993), or chronic-duration gavage doses up to 7.4 mg Hg/kg/day in mice (NTP 1993).

No exposure-related histopathological changes were observed in the pancreas or the thyroid, adrenal, or pituitary glands following exposure to mercuric chloride at acute-duration dietary doses up to 9.24 mg Hg/kg/day (Lecavalier et al. 1994); intermediate-duration gavage doses up to 4 or 15 mg Hg/kg/day in rats or mice, respectively (Dieter et al. 1992; Khan et al. 2004; NTP 1993); or chronic-duration gavage doses up to 4 or 7.4 mg Hg/kg/day in rats or mice, respectively (Dieter et al. 1992; NTP 1993).

Organic Mercury—Epidemiological Studies. Data are not sufficient to determine if exposure to mercury in populations with high fish diets produces adverse effects to the endocrine system, with only one study meeting inclusion criteria for this toxicological profile (see inclusion criteria, Section 2.1). Jeppesen et al. (2015) examined measures of glucose tolerance in 2,640 Inuit adults from Greenland with a median blood mercury of 16.5 µg/L. Results showed that, for each 5 µg/L in total BHg, the odds of impaired fasting glycemia (fasting plasma glucose ≥6.1 and <6.9 mmol/L and 2-hour challenge plasma glucose

<7.8 mmol/L) and type 2 diabetes (fasting plasma glucose ≥7.0 mmol/L or 2-hour challenge plasma glucose ≥11.1 mmol/L) were increased by 3% (adjusted OR 1.03; 95% CI 1.02, 1.05) and 2% (adjusted OR 1.02; 95% CI 1.01, 1.04), respectively. No increased risk was observed for impaired glucose tolerance (fasting plasma glucose <7.0 and <6.9 mmol/L and 2-hour challenge plasma glucose ≥7.8 and <11.1 mmol/L; adjusted OR 0.97; 95% CI 0.94, 1.0).

Organic Mercury—Animal Studies. A very limited number of studies in laboratory animals have evaluated effects of organic mercury on pancreatic and adrenocortical function following acute- or intermediate-duration oral exposure. Additional data regarding endocrine gland weight and/or histology are available from intermediate and chronic-duration oral studies. Available data are insufficient to determine if organic mercury adversely affects the endocrine system in laboratory animals.

Pancreatic function was evaluated in mice following exposure to methylmercury at a gavage dose of 1.6 mg Hg/kg/day for 14 days (Chen et al. 2012). Baseline and fasting insulin levels were significantly decreased by 60–70%. In a glucose tolerance test (after fasting), blood glucose levels were significantly elevated by 30–65% when measured 30–150 minutes after glucose administration (no changes in baseline blood glucose levels). Exposure to the same dose for 28 or 42 days resulted in duration-dependent increases of 80–95 and 25–40% in baseline insulin and glucose levels, respectively; glucose tolerance was not tested in longer-duration studies (Chen et al. 2012). After the 14-day exposure, apoptosis in pancreatic islet cells was significantly increased.

One study evaluated adrenocortical function in male rats following exposure to methylmercuric chloride or bis(methylmercury)sulfide at drinking water doses of 0.0004 or 0.04 mg Hg/kg/day for 8 or 16 weeks (Ortega et al. 1997b). Following exposure to methylmercuric chloride, serum levels of adrenocorticotropic hormone (ACTH) were significantly increased by >100% at ≥0.0004 mg Hg/kg/day after 8 or 16 weeks; however, findings were not dose- or duration-dependent. For bis(methylmercury)sulfide, a dose-dependent 105–220% increase in ACTH was observed at ≥0.0004 mg Hg/kg/day after 8 weeks only. No consistent dose-response relationship was found for serum corticosterone for either compound after 8 or 16 weeks of exposure.

No exposure-related changes in endocrine organ weight and/or histology were observed following dietary exposure to methylmercury at intermediate-duration doses up to 0.627 or 0.176 mg Hg/kg/day in mice or cats, respectively (Charbonneau et al. 1976; Hirano et al. 1986), or chronic-duration doses up to 0.18, 0.686, or 0.074 mg Hg/kg/day in rats, mice, or cats, respectively (Charbonneau et al. 1976; Hirano et al.

1986; Mitsumori et al. 1990; Verschuuren et al. 1976). Additionally, no exposure-related changes in adrenal gland weight or histology were observed in rats following chronic-duration exposure to phenylmercuric acetate at drinking water doses up to 3.7 mg Hg/kg/day (Solecki et al. 1991).

Predominant Mercury Form Unknown (General Populations). Endocrine effects of mercury on endocrine effects in general populations have not been well-studied. Available studies have examined associations between mercury exposure and thyroid function and glucose homeostasis. Studies on thyroid function used cross-sectional or cohort designs and measured plasma or serum levels of T4, T3, TSH, and thyroid autoantibodies. Glucose homeostasis was assessed by examining type 2 diabetes and insulin resistance in prospective and cross-sectional studies and in a meta-analysis. Nearly all studies evaluated large populations (n ≥1,100) and the most common biomarkers were BHg and NHg.

Thyroid function. Few studies have examined associations between mercury exposure in general populations and thyroid function; results are summarized in Table 2-30. Due to the small number of studies and conflicting results, evidence for effects of mercury exposure on thyroid function are inconclusive. A study using NHANES 2007–2008 data examined the relationship between BHg and blood methylmercury in adults and adolescents (Chen et al. 2013). In adolescents, inverse associations were observed between total BHg and total T4 and free T3 and between blood methylmercury and free T3, although there were no associations between BHg or blood methylmercury and TSH. In adults, total BHg and blood methylmercury were inversely associated with total T4, total T3, and free T3 in adults. However, no associations were observed between TSH and total BHg or blood methylmercury in adolescents or adults; therefore, the clinical significance the inverse associations between mercury and T4 and T3 is unclear. In contrast, no effects on T4, T3, or TSH were observed in a population of pregnant Spanish women (Llop et al. 2015). Two studies of the NHANES 2007–2008 population evaluated associations between mercury exposure and thyroid auto-antibodies, with conflicting results (Chen et al. 2013; Gallagher and Meliker 2012). Chen et al. (2013) did not find associations between BHg or blood methylmercury levels and anti-thyroglobulin (anti-Tg) or anti-thyroid peroxidase (anti-TPO) in adults or adolescents. However, the Gallagher and Meliker (2012) study of women reported an increase in anti-Tg, but not anti-TPO.

Table 2-30. Overview of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Thyroid Hormones in General Populations

Reference, study type and population	Biomarker	Outcome evaluated	Result
Chen et al. 2013 Cross-sectional: 1,109 adolescents (NHANES 2007–2008)	BHg Gmean: 0.47 µg/L	T4	↓ (BHg) 0 (BMeHg)
		Free T4	0 (BHg, BMeHg)
		T3	0 (BHg, BMeHg)
		Free T3	↓ (BHg) ↓ (BMeHg)
		TSH	0 (BHg, BMeHg)
		Tg	0 (BHg, BMeHg)
		Anti-Tg	0 (BHg, BMeHg)
		Anti-PO	0 (BHg, BMeHg)
Chen et al. 2013 Cross-sectional: 4,409 adults (NHANES 2007–2008)	BHg Gmean: 0.96 µg/L	T4	↓ (BHg, BMeHg)
		Free T4	0 (BHg, BMeHg)
		T3	↓ (BHg, BMeHg)
		Free T3	↓ (BHg, BMeHg)
		TSH	0 (BHg, BMeHg)
		Tg	0 (BHg, BMeHg)
		Anti-Tg	0 (BHg, BMeHg)
		Anti-TPO	0 (BHg, BMeHg)
Gallagher and Meliker 2012 Cross-sectional; 2,047 women (NHANES 2007–2008)	BHg quintiles: Q1: ≤40 µg/L Q2: >0.40–≤0.68 µg/L Q3: >0.68–≤1.06 µg/L Q4: >1.06–≤1.18 µg/L Q5: >1.18–≤15.10 µg/L	Anti-Tg	↑ (BHg, Q5)
		Anti-TPO	0 (BHg)
		Thyrotropin	0 (BHg)
Llop et al. 2015 Cohort; 1,407 pregnant women (Spain)	Cord BHg Gmean: 7.7 µg/L	Free T4 (M)	0 (cord BHg)
		Free T3 (M)	0 (BHg)
		TSH (M)	0 (BHg)

↑ = positive association; ↓ = inverse association; 0 = no association; – = not reported; Anti-Tg = thyroglobulin antibodies; Anti-TPO = thyroid peroxidase antibodies; BHg = blood mercury; BMeHg = blood methylmercury; M = maternal; NHANES = National Health and Nutrition Examination Survey; Q = quintile; T3 = triiodothyroxine; T4 = thyroxine; TSH = thyroid stimulating hormone

Glucose homeostasis. Studies evaluating effects of mercury exposure of general populations on glucose homeostasis (type 2 diabetes, insulin resistance, and β-cell function) report conflicting results, with most studies showing no associations; studies are summarized in Table 2-31. Type 2 diabetes is the most studied outcome for effects of mercury exposure on glucose homeostasis. Two prospective studies of U.S. populations, with 18–20-year follow-up periods, provide conflicting results (He et al. 2013;

Mozaffarian et al. 2013). He et al. (2013) reported a positive association between NHg and type 2 diabetes, whereas Mozzafarian et al. (2013), in a larger study population, did not find an association. Mozzafarian et al. (2013) conducted a meta-analysis of combined data from both studies, with results showing no association. A cross-sectional study of Taiwanese adults reported a positive association between erythrocyte mercury and type 2 diabetes (Tsai et al. 2019), although a cross-sectional study of Korean adults did not find an association between BHg and type 2 diabetes (Moon 2013). Kim et al. (2015c) reported a positive association between NHg and insulin resistance in men, but not in women, whereas Moon (2013) did not find associations between BHg and insulin resistance or β-cell function in adults.

Table 2-31. Overview of Epidemiological Studies Evaluating Associations between Mercury Exposure (Predominant Mercury Form Unknown) Glucose Homeostasis in General Populations

		Outcome evaluated		
Reference, study type and population	Biomarker	Insulin resistance	β-cell function	Type 2 diabetes
Chang et al. 2011 Cross-sectional; 1,449 adults (Taiwan)	BHg mean: 10.8 µg/L	↑ (BHg)	−	−
He et al. 2013 Prospective; 3,875 adults, followed for 18 years; free of diabetes in 1987 with follow-up until 2005); CARDIA cohort, (United States)	NHg quintile median: Q1: 0.073 µg/g Q2: 0.139 µg/g Q3: 0.213 µg/g Q4: 0.331 µg/g Q5: 0.607 µg/g	−	−	↑ (NHg, Q5)
Kim et al. 2015c Cross-sectional; 2,643 men and 2,745 women (KNHANES 2008–2010)	Men BHg quartile median Q1: 2.6 µg/L Q2: 4.3 µg/L Q3: 6.1 µg/L Q4: 11.5 µg/L Women BHg Quartile median Q1: 2.0 µg/L Q2: 3.0 µg/L Q3: 4.2 µg/L Q4: 7.5 µg/L	↑ (BHg, men, Q4) 0 (BHg, women)	−	−
Moon 2013 Cross-sectional; 2,851 adults without diabetes and 333 adults with diabetes (KNHANES 2009–2010)	BHg mean with diabetes: 4.42 µg/L BHg mean, without diabetes: 4.37 µg/L	0 (BHg)	0 (BHg)	0 (BHg)

Table 2-31. Overview of Epidemiological Studies Evaluating Associations between Mercury Exposure (Predominant Mercury Form Unknown) Glucose Homeostasis in General Populations

Reference, study type and population	Biomarker	Outcome evaluated		
		Insulin resistance	β-cell function	Type 2 diabetes
Mozaffarian et al. 2013 Prospective cohort; 9,267 adults without diabetes at study enrollment (2,541 men and 6,726 women) from the HPFS (men) and NHS (women) cohorts, with follow-up of approximately 20 years (US)	NHg median Men: 0.30 µg/g Women: 0.21 µg/g	−	−	0 (NHg)
Mozaffarian et al. 2013 Meta-analysis; combined data from He et al. (2013) and Mozaffarian et al. (2013); 13,142 adults (United States)	Combined NHg not reported; see individual study biomarker data	−	−	0 (NHg)
Tsai et al. 2019 Cross-sectional; 646 adults (Taiwan NAHSIT 2005-2008)	ErHg Gmean with diabetes: 18.95 ErHg Gmean without diabetes: 13.21	−	−	↑ (ErHg)

↑ = positive association; 0 = no association; – = not reported; BHg = blood mercury; CARDIA = Coronary Artery Risk Development in Young Adults; ErHg = erythrocyte mercury; HPFS = Health Professionals Follow-up Study; KNHANES = Korea National Health and Nutrition Examination Survey; NAHSIT = National Nutrition and Health survey in Taiwan; NHANES = National Health and Nutrition Examination Survey; NHg = toenail mercury; NHS = Nurses' Health Study; Q = quartile or quintile

Mechanisms of Action. Numerous mechanisms have been proposed that may be involved in mercury-induced effects on thyroid function (Afrifa et al. 2018; Chen et al. 2013; Gallagher and Meliker 2012; Llop et al. 2015; Soldin et al. 2008; Tan et al. 2009; Zhu et al. 2000). These include: (1) inhibition of the biosynthesis of thioredoxin reductase; (2) binding of mercury to sulfhydryl (SH)-containing ligands in the thyroid; (3) reduced TSH production; (4) inhibition of deiodinases; (5) inhibition of TPO and lysosomal enzymes; and (6) decreased iodine uptake. In addition, mercury has been shown to significantly accumulate in the pituitary and thyroid glands, providing a toxicokinetic mechanism for mercury-induced effects (Kosta et al. 1975).

Potential mechanisms for effects of mercury on pancreatic β-cell function were recently reviewed by Schumacher and Abbott (2017). Proposed mechanisms for β-cell dysfunction include: (1) disruption of cell protein structure and function due to binding of mercury to sulfhydryl groups; (2) inhibition of

mitochondrial enzymes; (3) depolarization of mitochondrial membranes; (4) decreased mitochondrial ATP synthesis; and (5) decreased insulin gene expression. These mechanisms can contribute to increased formation of ROS, causing metabolic and oxidative stress to pancreatic β-cells. Mercury biomarkers have also been associated with changes in microbiome profiles observed in gestational diabetes (Zhang et al. 2021).

2.15 IMMUNOLOGICAL

Overview. Epidemiological and animal studies have investigated effects of mercury on the immune system. Epidemiological studies are available in workers exposed to elemental mercury and in dental workers or children exposed to amalgams, populations with a high fish diet, and in general populations in which the chemical form of mercury exposures are unknown. Immunological endpoints examined were primarily serum antibodies, immunoglobulins, cytokines, and immune cell counts; and findings are often conflicting. The toxicological and clinical significance of associations between mercury biomarkers and these endpoints has not been established. Studies in general populations also examined associations between mercury exposure biomarkers and immunological diseases. Dermal sensitization has been shown in skin patch tests in general populations. Epidemiological studies evaluating associations between mercury biomarkers and thyroid antibodies are discussed in Section 2.14 (Endocrine).

Studies evaluating immune function in animals are available for inhalation exposure to mercury vapor and oral exposure to mercuric chloride, mercuric sulfide, or methylmercury. Oral exposure to mercuric chloride or methylmercury results in the induction of autoimmunity in mouse strains prone to autoimmune disease. Mercury-induced autoimmunity is characterized by the presence of serum antinucleolar antibodies (ANoAs), antinuclear antibodies (ANAs), and/or antichromatin antibodies (ACAs); polyclonal B-cell activation; elevated serum immunoglobulins; and (with mercuric chloride only) immune complex deposits in the kidney and spleen. Very limited evidence from inhalation studies suggests that elemental mercury can also stimulate the immune system and result in formation of immune complexes. In non-susceptible animals, the majority of data indicate that oral exposure to methylmercury results in immune suppression following exposure during development or adulthood (e.g., decreased antibody production, lymphoproliferative responses; natural killer cell activity); however, there is limited evidence that very low exposure levels may stimulate T-cell immune responses. Available data in non-susceptible animals following oral exposure to inorganic mercury salts are insufficient to determine potential exposure-related effects on the immune system. No inhalation data were available in non-susceptible animals.

The following summarizes results of epidemiological and animal studies on immunological outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - No associations were observed between occupational exposure to elemental mercury or exposure to amalgam and immune system effects. Available studies did not examine the same immunological endpoints; therefore, data are insufficient to draw conclusions on the immunological effects of elemental mercury.
  - *Animal studies*
    - A single study in a mouse strain genetically susceptible to autoimmune disease reported general stimulation of the immune system and formation of immune complexes following intermediate-duration inhalation exposure. No other studies evaluating potential immune effects from exposure to mercury vapor were available.
- ***Inorganic mercury salts***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to inorganic mercury salts and immunological effects were identified.
  - *Animal studies*
    - Immune stimulation and immune complex disease can occur in mouse strains genetically susceptible to autoimmune disease following oral exposure to mercuric chloride.
    - Data in wild-type mice are limited, but report alterations in T- and B-cell subpopulations in immune organs and altered immune responses (some stimulated, some suppressed) following oral exposure to mercuric chloride.
    - One study reported alterations in splenic and thymic histology and cell populations in wild-type mice following oral exposure to mercuric sulfide at high doses. No other studies evaluating potential immune effects from exposure to mercuric sulfide were available.
- ***Organic mercury***
  - *Epidemiology studies*
    - Associations between BHg and some immunological markers (serum cytokine levels, immunoglobulins, and immune cell counts) were observed; however, it is not known if immune system function was altered in these study populations.
    - Data are insufficient to determine if exposure to organic mercury is associated with adverse immunological effects.

- *Animal studies*
  - Immune stimulation in the absence of immune complexes can occur in mouse strains genetically susceptible to autoimmune disease following developmental or post-pubertal (adult) exposure.
  - One developmental study in wild-type mice reports immune stimulation in offspring following exposure during gestation plus lactation.
  - Developmental exposure in rats and adult exposure in wild-type animals are generally associated with immune suppression (decreased antibody production, lymphoproliferative responses; natural killer cell activity); however, limited data suggest that very low doses may be associated with immune stimulation (increased immune responses to T-cell antigens).

- ***Predominant mercury form unknown (general populations)***
  - Studies examining immune diseases found associations between mercury biomarkers and atopic dermatitis (but not eczema), systemic lupus erythematosus (SLE), and celiac disease seropositivity.
  - A few studies found associations between mercury biomarkers and other immunological endpoints (serum cytokines, antibodies, and immune cell counts). The clinical significance of these findings has not been established.
  - Several studies in general populations indicate that mercury exposure induces dermal sensitization based on positive skin patch tests to elemental and/or inorganic mercuric salts.

Confounding Factors. The immune system is responsive to a multitude of environmental and physiological factors, which can be confounding factors in studies of associations between mercury exposure and immunological outcomes. Potential confounders that have been considered in some studies, but not consistently across studies, include age, sex, smoking, physical activity, allergen exposures, history of inflammatory and immune diseases, socioeconomic status (SES) factors, recreational activities, and co-exposures to other chemicals. No specific confounder or covariate was mandatory for the inclusion of the study into the profile; however, studies of immunological outcomes that did not consider the aforementioned potential confounders are potentially more confounded than studies that did consider these variables.

Elemental Mercury—Epidemiological Studies. Immune effects of elemental mercury have not been well studied and few epidemiological studies meeting inclusion criteria were identified (see inclusion

criteria, Section 2.1). Studies were conducted in chloralkali workers (Barregard et al. 1997; Langworth et al. 1992b; Vimercati et al. 2001), miners (Sanchez Rodriguez et al. 2015), dental workers (Farahat et al. 2009), and children with amalgam fillings (Shenker et al. 2008); results are summarized in Table 2-32. Studies evaluated several different endpoints, including immune cell counts and function; and serum antibodies, immunoglobulins, immune complexes, and cytokines. No studies found associations between mercury biomarkers and immunological endpoints. However, studies did not evaluate the same immunological endpoints; therefore, data are not sufficient to determine if occupational exposure to elemental mercury or exposure to amalgam is associated with adverse effects to the immune system.

Table 2-32. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Immunological Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Barregard et al. 1997 Cross-sectional; 41 male chloralkali workers and 41 male controls (Sweden)	BHg mean Workers: 9.2 µg/L Controls: 3.4 µg/L UHg mean Workers: 27 µg/g Controls: 3.4 µg/g	Serum ANA	0 (workers versus controls)
		Serum CIC	0 (workers versus controls)
Langworth et al. 1992b Cross-sectional; 89 chloralkali workers and 75 controls (Sweden)	BHg median Workers: 11 µg/L Controls: 3 µg/L UHg median Workers: 25.4 µg/g Cr Controls: 1.9 µg/g Cr	Serum IgA	0 (workers versus controls)
		Serum IgG	0 (workers versus controls)
		Serum IgM	0 (workers versus controls)
Sanchez Rodriguez et al. 2015 Cross-sectional; 164 gold miners and 127 controls (Columbia)	BHg median Miners: 7.03 µg/L Controls: 2.46 µg/L UHg median Miners: 3.96 µg/g Cr Controls: 1.48 µg/g Cr HHg median Miners; 0.79 µg/g Controls: 0.39 µg/g	Elevated serum ANA	0 (miners versus controls)
		Elevated serum RF	0 (miners versus controls)
Shenker et al. 2008 Randomized clinical trial; 59 children (6–10 years of age at baseline); 29 children randomized to amalgam fillings and 30 randomized to control composite fillings (New England)	BHg, baseline mean Amalgam: 0.4 µg/L Composite: 0.4 µg/L UHg, 5-year mean Amalgam: 0.85 µg/g Cr Composite: 0.68 µg/g Cr	Lymphocyte function	0 (amalgam versus composite)
		Monocyte function	0 (amalgam versus composite)
		Neutrophil function	0 (amalgam versus composite)

Table 2-32. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Immunological Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Vimercati et al. 2001 Cross-sectional; 19 mercury workers and 25 controls	UHg mean Workers: 9.7 µg/L Controls: 2.4 µg/L	Monocyte-macrophage cell count[a]	0 (workers versus controls)
		Cytokines	
		IL-8	0 (workers versus controls)
		GM-CSF	0 (workers versus controls)
		TNF-α	0 (workers versus controls)
		NK cell count	0 (workers versus controls)

[a]Includes the following cell types: leukocytes, lymphocytes, monocytes, CD13, CD14, CD15, CD33D, and CD45.

↓ = inverse association; 0 = no association; ANA = antinuclear antibodies; BHg = blood mercury; CIC = circulating immune complexes; Cr = creatinine; GM-CSF = Granulocyte-macrophage colony-stimulating factor; HHg = hair mercury; IL = interleukin; RF = rheumatoid factor; NK cell = natural killer cell; TNF-α = tumor necrosis factor-alpha; UHg = urine mercury

Elemental Mercury—Animal Studies. A single study evaluating immunological endpoints following inhalation exposure to elemental mercury reported a general stimulation of the immune system in a mouse strain genetically susceptible to autoimmune disease (Warfvinge et al. 1995). In this study, susceptible SJL/N mice were exposed to 0.3, 0.05, or 1 mg Hg/m^3 for 0.5–19 hours/day, 5 days/week, for 10 weeks (time-weighted average [TWA] concentrations of 0.01–0.4 mg Hg/kg/day). All mice exposed to TWA concentrations ≥0.03 mg Hg/kg/day (absorbed dose of 0.170 mg Hg/kg/week) showed positive ANoA; this was not observed at the TWA concentration of 0.01 mg Hg/kg/day (absorbed dose of 0.075 mg/kg/day). Mice exposed to TWA concentrations ≥0.06 mg Hg/kg/day also showed B-cell stimulation (increased serum immunoglobins) and glomerular disease accompanied by vascular immune complex deposits.

Inorganic Mercury Salts—Animal Studies. Data from oral studies indicate that exposure to mercuric chloride can result in immune stimulation and immune complex disease in mouse strains genetically susceptible to autoimmune disease. In one series of experiments, positive ANoA and/or ANA were observed in susceptible SJL/N, A.SW, and B10.S mice at ≥0.14, ≥0.199, and ≥0.444 mg Hg/kg/day, respectively, for up to 10 weeks (Hultman and Enestrom 1992; Hultman and Nielsen 2001 ; Nielsen and Hultman 2002). Evidence of immune complex disease (e.g., renal, splenic, and cardiac vessel immune

deposits, renal mesangium deposits) was observed in SJL/N, A.SW, and B10.S mice at ≥0.14, ≥0.401, and ≥1.774 mg Hg/kg/day, respectively. Additional effects included polyclonal B-cell activation in male A.SW mice at 0.942 mg Hg/kg/day and male and female B10.S mice at ≥0.118 mg Hg/kg/day, and elevated serum IgE in male A.SW mice at 0.942 mg Hg/kg/day and male and female B10.S mice at ≥1.774 mg Hg/kg/day. Another series of studies reported induction of serum IgG antibodies to brain antigens and/or elevated serum IgG in susceptible A.SW, FvSF1, and SFvF1 dams and offspring following gestational and lactation exposure to 2.7 mg Hg/kg/day (Zhang et al. 2011, 2013). Additional findings in offspring only included IgG deposits in the brain and brain inflammation. Immune stimulation was not observed in similarly exposed wild-type A/WySnJ dams or offspring (Zhang et al. 2011). However, immune stimulation (increased splenocyte proliferation and interferon gamma (IFNγ) and interleukin-4 (IL-4) production in mitogen assay) was observed in wild-type DBF1 adult offspring (progeny of DBA/1 males × BALB/c females) following exposure to 1.5 mg Hg/kg/day throughout gestation (Pilones et al. 2009).

Data on immunotoxicity in wild-type adult mice following exposure to mercuric chloride is limited. In an acute study, changes in immune cell populations of the spleen and thymus were observed in BALB/c mice following exposure to mercuric chloride for 14 days, including dose-related changes in T-lymphocytes (CD3+), T-helper (CD4+), and T-suppressor (CD8+) cells in the spleen at ≥0.31 mg Hg/kg/day and CD4-/CD8+ suppressor cells in the thymus at ≥1.39 mg Hg/kg/day (Kim et al. 2003). In an intermediate-duration study, dose-related increases in splenocyte proliferation in response to the B-cell antigen *Escherichia coli* lipopolysaccharide (LPS) were observed in B6C3F1 mice exposed to ≥2 mg Hg/kg/day, respectively, for 7 weeks (Dieter et al. 1983). Non-dose-dependent decreases in mitogenic response to T-cell antigens (concanavalin A, phytohemagglutinin) and mixed lymphocyte responses were also observed at ≥2 mg Hg/kg/day. In the plaque-forming assay, exposed mice showed a 60% decrease in the antibody response to a T-dependent antigen (sheep red blood cells) at 11 mg Hg/kg/day; no changes in the antibody response to the B-cell antigen LPS were observed. No exposure-related changes in serum IgG, IgM, or IgA were observed (Dieter et al. 1983).

No histopathological changes in the bone marrow, thymus, or spleen were observed in rats after acute-, intermediate-, or chronic-duration oral exposure to mercuric chloride doses up to 9.23, 4, or 4 mg Hg/kg/day, respectively, or wild-type mice after intermediate- or chronic-duration oral exposure to doses up to 30 or 7.4 mg Hg/kg/day, respectively (Dieter et al. 1983, 1992; Lecavalier et al. 1994; NTP 1993).

One study evaluated immune endpoints in ICR mice following oral exposure to mercuric sulfide for 4 weeks (Son et al. 2010). Treatment-related changes in T-lymphocyte populations in the spleen were observed at ≥17 mg Hg/kg/day, including increased CD4+CD8+ and CD8 single-positive lymphocytes. There were no treatment related changes in T-lymphocytes of the thymus. Pathological findings observed at 1,700 mg Hg/kg/day included enlargement of the spleen and marked hyperplasia of the white pulp, increased cellular density in the splenic lymphoid follicles, and increased density of lymphoid cells in the thymus. There was no exposure-related effect on splenocyte or thymocyte proliferation.

Organic Mercury—Epidemiological Studies. Few studies have evaluated immunological effects in populations with high fish diets; studies meeting inclusion criteria are summarized in Table 2-33 (see inclusion criteria, Section 2.1). Studies consist of two prospective studies in children (Hui et al. 2016; Oulhote et al. 2017a), one cross-sectional study in mother-infant pairs (Nyland et al. 2011), one cohort study in pregnant women (McSorley et al. 2018), and a cohort of children (Wyatt et al. 2019). Endpoints examined include serum levels of cytokines (Hui et al. 2016; McSorley et al. 2018; Nyland et al. 2011) and immunoglobulins (Hui et al. 2016; Nyland et al. 2011), immune cell counts (Oulhote et al. 2017a), and antibody response to vaccinations (Wyatt et al. 2019).

Table 2-33. Results of Epidemiological Studies Evaluating Immunological Effects in Populations with High Fish Diets

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Hui et al. 2016 Prospective; 407 children from a high fish-eating population; cytokines measured at ages 6–9 years (China)	BHg median Cord: 9.2 µg/L Current: 2.6 µg/L	Cytokines	
		IL-4	0 (BHg, cord and current)
		IL-5	0 (BHg, cord and current)
		IL-6	0 (BHg, cord and current)
		IL-8	0 (BHg, cord and current)
		IL-10	0 (BHg, cord), ↓ (BHg, current)
		IL-13	0 (BHg, cord and current)
		TNF-α	0 (BHg, cord and current)
McSorley et al. 2018 Cohort; 1,158 pregnant women assessed at 28 weeks of gestation (Seychelles)	BHg mean: 18.14 µg/L	Th1 cell cytokines	
		IL-1β	↓ (BHg)
		IL-2	↓ (BHg)
		IFN-γ	0 (BHg)
		TNF-α	↓ (BHg)
		Total	↓ (BHg)
		Th2 cell cytokines	
		IL-4	↓ (BHg)
		IL-5	0 (BHg)
		IL-10	↓ (BHg)
		Total	0 (BHg)
		Th1:Th2 cytokine ratio	↓ (BHg)

Table 2-33. Results of Epidemiological Studies Evaluating Immunological Effects in Populations with High Fish Diets

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Other cell cytokines	
		CRP	↓ (BHg)
		IL-6	0 (BHg)
		MCP-1	0 (BHg)
		TARC	↑ (BHg)
		sFlt-1	0 (BHg)
		VEGF-D	↑ (BHg)
Nyland et al. 2011 Cross-sectional; 61 mother-infant pairs (Brazilian Amazon); fetal and immune responses were assessed	BHg Gmean Maternal: 6.90 µg/L Cord: 9.63 µg/L	IgG	↓ (BHg, maternal and cord)
		IgA, IgE, IgM	0 (BHg, maternal and cord)
		ANA	↓ (BHg, maternal and cord)
		Cytokines	
		IL-1β	↑ (BHg, maternal and cord)
		IL-6	↑ (BHg, maternal and cord)
		IL-1ra	0 (BHg, maternal and cord)
		TNF-α	↑ (BHg, maternal and cord)
		IFN-γ	0 (BHg, maternal and cord)
Oulhote et al. 2017a Prospective 53 mother-child pairs; endpoints assessed at 5 years of age (Faroe Islands)	BHg Gmean Maternal: 3.066 µg/L Cord: 4.649 µg/L Child age 5-years: 2.328 µg/L HHg Gmean Maternal: 0.748 µg/L Child age 5-years: 0.611 µg/L Maternal exposure based on a composite factor of cord and maternal BHg and maternal HHg; child exposures based on a composite of child BHg and HHg at 5 years of age	WBC counts	
		Neutrophils	0 (BHg, maternal and cord)
		Basophils	0 (BHg, maternal and cord)
		Eosinophils	0 (BHg, maternal and cord)
		Lymphocytes	↓ (BHg, maternal) 0 (BHg, cord)
		Monocytes	0 (BHg, maternal and cord)
		Total WBC	↓ (BHg, maternal) 0 (BHg, cord)
		Lymphocyte counts	
		CD3	↓ (BHg, maternal) 0 (BHg, cord)
		CD4	↓ (BHg, maternal) 0 (BHg, cord)
		CD8	0 (BHg, maternal and cord)
		CD4-RTE	↓ (BHg, maternal) 0 (BHg, cord)
		NK cells	0 (BHg, maternal and cord)
		B-lymphocytes	↓ (BHg, maternal) 0 (BHg, cord)
Wyatt et al. 2019 Longitudinal study of children, age 4–8 years (n=98), Peru	HHg Mean Child: 1.5 µg/g	Post-vaccination diphtheria-specific antibodies response	↓ (BHg, child with malnutrition)
		Post-vaccination measles-specific antibody response	↓ (BHg, child with malnutrition)

Table 2-33. Results of Epidemiological Studies Evaluating Immunological Effects in Populations with High Fish Diets

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Post-vaccination pertussis-specific antibody response	↓ (BHg, child with malnutrition)

↑ = positive association; ↓ = inverse association; 0 = no association; BHg = blood mercury; CD3 = T-cell; CD4 = t-helper cells; CD8 = t-cytotoxic cells; CD4-RTE = CD4+ recent thymic emigrant cells; CRP = C-reactive protein; Gmean = geometric mean; IFN-γ = interferon-gamma; Ig = immunoglobulin; IL = interleukin; MCP-1 = monocyte chemotactic protein-1; NK cells = natural killer cells; sFlt-1 = soluble fms-like tyrosine kinase-1; TARC = thymus- and activation-regulated chemokine; Th1 = T-helper cell 1 (cell-mediated immunity); Th2 = T-helper cell 2 (humoral immunity); TNF-α = tumor necrosis factor-alpha; VRFG-D = vascular endothelial growth factor-D; WBC = white blood cell

Plasma cytokine levels are the only immunological endpoint evaluated in more than one study; however, results are conflicting. Inverse associations were observed between BHg and several cytokines in a cohort of pregnant women (McSorley et al. 2018); however, the study authors noted that changes were small and of unknown clinical significance. In contrast, a prospective study in children did not find any associations between cord or child BHg and several interleukins and tumor necrosis factor-alpha (Hui et al. 2016), and positive associations were observed between maternal and cord BHg and some cytokines in mothers and infants in a cross-sectional study (Nyland et al. 2011). In addition to plasma cytokine levels, Nyland et al. (2011) also reported an inverse association between mother and cord BHg and plasma IgG levels, but not IgA, IgE, or IgM; the toxicological significance of this association was not established. For cell counts, inverse associations were observed between maternal and child BHg and total leukocyte and total lymphocyte counts, and some lymphocyte subpopulation counts (CD3, CD4, and B cells) (Oulhote et al. 2017a). Cell counts for CD4-RTE also were inversely associated with BHg in mothers, but not in children. Although associations between BHg and some immunological endpoints were observed, it is not known if alterations in immune markers or cell counts are associated with compromised immune system function in these study populations. A study of children who resided in the Amazonian River Basin, where exposure to dietary methylmercury occurs as a result of wastes from gold mining operations, found decreased antibody response to diphtheria, measles, and pertussis vaccinations in association with a combination of malnutrition and increasing hair mercury levels (Wyatt et al. 2019).

Organic Mercury—Animal Studies. Most available data are from oral intermediate-duration studies. Data indicate that exposure to methylmercury can result in immune stimulation in the absence of an immune complex formation in mouse strains genetically susceptible to autoimmune disease. There is limited evidence of immune stimulation in wild-type mice following developmental exposure.

Developmental exposure in rats and exposure during adulthood in rats, mice, and rabbits is generally associated with immune suppression; however, there are limited data for immune stimulation at very low doses.

Polyclonal B-cell activation and serum ANoA and ACA were observed in autoimmune susceptible A.SW mice at 0.420 mg Hg/kg/day immediately after a 30-day exposure to methylmercury; ANoA was still detected 8 weeks post-exposure. Serum IgG was elevated immediately and 2 weeks after the 30-day exposure; serum IgE was not significantly elevated. No significant increases in tissue immune complex deposits were observed in the kidneys or spleen at any timepoint (Havarinasab et al. 2007). Another study evaluated immune stimulation in A.SW dams and offspring following gestational and lactation exposure to methylmercury at 0.06 mg Hg/kg/day (Zhang et al. 2011). No evidence of serum IgG antibodies to brain antigens or IgG deposition in the brain was observed in dams or offspring; however, cerebellar inflammation was observed in exposed female offspring and IL-12 was decreased in male offspring at PND 21. Exposure-related changes were not observed in similarly exposed wild-type A/WySnJ dams or offspring (Zhang et al. 2011).

Functional immune assays in rats and wild-type mice following developmental exposure to methylmercury indicate a complicated pattern of immunomodulatory effects, including nonmonotonic findings and differential findings between rats and mice (see Table 2-34). In rats, low exposure levels during gestation and lactation periods are associated with increased lymphoproliferative responses to T-cell mitogens, with smaller or no effect at higher exposure levels (Ilback et al. 1991; Tonk et al. 2010; Wild et al. 1997). No clear pattern was observed for cytokine release in response to T-cell mitogens (Tonk et al. 2010). Exposure during the postnatal period only was associated with a decreased response in rat offspring (Ilback et al. 1991). Other findings in rat offspring following gestational plus lactational exposure generally indicate immune suppression, including decreased lymphoproliferation in response to B-cell mitogens, decreased antibody production and cytokine release in response to the Keyhole Limpet hemocyanin antigen, and decreased natural killer cell activity (Ilback et al. 1991; Tonk et al. 2010; Wild et al. 1997). Data in wild-type mice following developmental exposure are limited to a single study, which reports decreased lymphoproliferative responses to T-mitogens at low doses, with increased responses at higher doses, increased lymphoproliferative responses to B-mitogens, increased antibody production following influenza inoculation, and increased natural killer cell activity (Thuvander et al. 1996).

Table 2-34. Functional Immune Assays in Rodents Orally Exposed to Methylmercury During Development[a]

Species; duration	Dose (mg Hg/kg/day)	T-cell mitogen	B-cell mitogen	CK production	AB production	NKC activity	Reference (compound)
Rat; 15 days [PNDs 1–15]	0.37	Con A Th: 0 Sp: ↓ (32)[b] [PND 15]	LPS: 0	–	–	S: 0	Ilback et al. 1991 (MM)
Rat 26 days [GD 6–PND 10]	0.08	Con A: 0	LPS: 0	Con A: ↑ (20)[c] [PND 70] KHL: 0 [PND 63]	KHL: ↓ (30)[c] [PND 35]	S: 0 [PND 70]	Tonk et al. 2010 (MMC)
Rat 26 days [GD 6–PND 10]	0.3	Con A: 0	LPS: ↓ (8)[c] [PND 42]	Con A: ↓ (6)[c] [PND 70] KHL: ↓ (28)[c] [PND 63]	KHL: ↓ (55)[c] [PND 35]	S: ↓ (>5)[d] [PND 70]	Tonk et al. 2010 (MMC)
Rat 26 days [GD 6–PND 10]	0.6	Con A: 0	LPS: ↓ (21)[c] [PND 42]	Con A: ↑ (24)[c] [PND 70] KHL: ↓ (34)[c] [PND 63]	KHL: ↓ (70)[c] [PND 35]	S: ↓ (>5)[d] [PND 70]	Tonk et al. 2010 (MMC)
Rat 26 days [GD 6–PND 10]	0.8	Con A: 0	LPS: ↓ (32)[c] [PND 42]	Con A: ↑ (26)[c] [PND 70] KHL: ↓ (36)[c] [PND 63]	KHL: ↓ (75)[c] [PND 35]	S: ↓ (>5)[d] [PND 70]	Tonk et al. 2010 (MMC)
Rat 26 days [GD 6–PND 10]	1.2	Con A: 0	LPS: ↓ (22)[c] [PND 42]	Con A: ↑ (28)[c] [PND 70] KHL: ↓ (3)[c] [PND 63]	KHL: ↓ (55)[c] [PND 35]	S: ↓ (>5)[d] [PND 70]	Tonk et al. 2010 (MMC)
Rat 26 days [GD 6–PND 10]	1.6	Con A: 0	LPS: ↓ (>5)[d] [PND 70]	Con A: ↑ (96)[c] [PND 70] KHL: ↓ (54)[c] [PND 63]	KHL: ↓ (95)[c] [PND 35]	S: ↓ (>5)[d] [PND 70]	Tonk et al. 2010 (MMC)
Rat 105 days [8 weeks PM–PND 21]	0.0006	Con A: 0 PWM ↑ (250)[b] [PND 42] ↑ (110)[b] [PND 84]	–	–	–	S: ↓ (56)[b] [PND 84]	Wild et al. 1997 (MMC)

Table 2-34. Functional Immune Assays in Rodents Orally Exposed to Methylmercury During Development[a]

Species; duration	Dose (mg Hg/kg/day)	T-cell mitogen	B-cell mitogen	CK production	AB production	NKC activity	Reference (compound)
Rat 105 days [8 weeks PM–PND 21]	0.003	Con A: ↑ (9)[b] PWM ↑ (120)[b] [PND 84]	–	–	–	S: 0	Wild et al. 1997 (MM2S)
Rat 105 days [8 weeks PM–PND 21]	0.06	Con A: ↑ (290)[b] [PND 42] PWM ↑ (160)[b] [PND 42] ↑ (88)[b] [PND 84]	–	–	–	S: ↓ (56)[b] [PND 84]	Wild et al. 1997 (MMC)
Rat 105 days [11 weeks PM–GD 21]	0.37	Con A: 0	LPS: 0	–	–	S: 0	Ilback et al. 1991 (MM)
Rat 119 days [11 weeks PM–PND 15]	0.37	Con A Th: ↑ (47)[b] Sp: 0 [PND 15]	LPS: 0	–	–	S: ↓ (42)[b] [PND 15]	Ilback et al. 1991 (MM)
Mouse 112 days [10 weeks PM–PND 15]	0.098	Con A Th: 0 Sp:↓ (45)[b] [PND 50]	LPS: 0	–	Influenza: ↑ (11)[b] [14 dpi] 0 [35 dpi]	S: 0	Thuvander et al. 1996 (MMC)
Mouse 112 days [10 weeks PM–PND 15]	0.98	Con A Th: 0 Sp: ↑ (50)[b] [PND 50]	LPS: S: ↑ (35)[b] [PND 22] S: ↑ (25)[b] [PND 50]	–	Influenza: 0 [14 or 35 dpi]	S: ↑ (255)[b] [PND 22] S: 0 [PND 50]	Thuvander et al. 1996 (MMC)

[a]Studies with exposure prior to puberty only, including studies that evaluate adult animals after developmental exposure. These findings are listed under "Develop" in the LSE table.
[b]Percent change compared to control, calculated from quantitative data.
[c]Percent change compared to control, estimated from graphically presented data.
[d]Dose-specific data not reported; data based on reported BMD_5 values.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; AB = antibody; BMD = benchmark dose; Con A = concanavalin A (T-cell mitogen); dpi = days post-infection; GD = gestation day; KHL = Keyhole Limpet hemocyanin; LPS = *Escherichia coli* lipopolysaccharide (B-cell mitogen); LSE = Level of Significant Exposure; MM = methylmercury; MM2S = bis(methylmercury)sulfide; MMC = methylmercuric chloride; NKC = natural killer cell; PM = premating; PND = postnatal day; PWM = pokeweed mitogen (T-cell mitogen); Sp = spleen/splenocytes; Th = thymus/thymocytes

Studies evaluating functional immune assays in animals following exposure during adulthood are reviewed in Table 2-35. Intermediate-duration functional immune assays in laboratory animals orally exposed to methylmercury during adulthood generally show dose-related suppression of immune function, including suppressed antibody production in response to antigen exposure, decreased IgM- and IgG producing cells in the spleen during the plaque forming assay, and decreased natural killer cell activity in the blood and the spleen (Blakely et al. 1980; Ilback 1991; Koller et al. 1977). However, a series of studies in rats indicate that there may be an initial increase in the lymphoproliferative response to T-cell mitogens at very low doses prior to suppression of proliferation at higher doses (Ortega et al. 1997a, 1997b). Different response patterns were observed with different forms of methylmercury (methylmercury chloride, methylmercury sulfide, bis(methylmercury)sulfide, tris(methylmercuric) sulphonium ion). One study reported increased lymphoproliferation in mice in response to a B-cell mitogen; no change was observed for T-cell mitogen responses (Ilback 1991).

Table 2-35. Functional Immune Assays in Laboratory Animals Orally Exposed to Methylmercury During Adulthood

Species; duration	Dose (mg Hg/kg/day)	Mitogen	HG titers	AB production	PFA	NKC activity	Reference (compound)
Rat; 56 days	0.0004	PHA: ↑ (533)[a] Con A: ↑ (350)[a]	–	–	–	–	Ortega et al. 1997a, 1997b (MMC)
Rat; 56 days	0.0004	PHA: ↑ (267)[a]	–	–	–	–	Ortega et al. 1997a (MMS)
Rat; 56 days	0.0004	PHA: ↑ (300)[a] Con A: ↑ (150)[a]	–	–	–	–	Ortega et al. 1997a, 1997b (MM2S)
Rat; 56 days	0.0004	PHA: ↓ (56)[a]	–	–	–	–	Ortega et al. 1997a (MM3S)
Rat; 56 days	0.04	PHA: ↓ (67)[a] Con A: ↓ (64)[a]	–	–	–	–	Ortega et al. 1997a, 1997b (MMC)
Rat; 56 days	0.04	PHA: 0	–	–	–	–	Ortega et al. 1997a (MMS)

Table 2-35. Functional Immune Assays in Laboratory Animals Orally Exposed to Methylmercury During Adulthood

Species; duration	Dose (mg Hg/kg/day)	Mitogen	HG titers	AB production	PFA	NKC activity	Reference (compound)
Rat; 56 days	0.04	PHA: 0 Con A: ↑ (314)[a]	–	–	–	–	Ortega et al. 1997a, 1997b (MM2S)
Rat; 56 days	0.04	PHA: ↓ (56)[a]	–	–	–	–	Ortega et al. 1997a (MM3S)
Rat; 112 days	0.0004	Con A: ↓ (79)[a]	–	–	–	–	Ortega et al. 1997b (MMC)
Rat; 112 days	0.0004	Con A: ↓ (71)[a]	–	–	–	–	Ortega et al. 1997b (MM2S)
Rat; 112 days	0.04	Con A: ↓ (86)[a]	–	–	–	–	Ortega et al. 1997b (MMC)
Rat; 112 days	0.04	Con A: ↑ (200)[a]	–	–	–	–	Ortega et al. 1997b (MM2S)
Mouse; 21 days	0.08	–	SRBC: ↓ (23)[b] LPS: ↓ (31)[b]	LPS: ↓ (39)[b] [28 dpi]	PFA[c]: 1°:↓ (43)[b] 2°:↓ (19)[b]	–	Blakely et al. 1980 (MMC)
Mouse; 21 days	0.35	–	SRBC: ↓ (43)[b] LPS: ↓ (45)[b]	LPS: ↓ (53)[b] [28 dpi]	PFA[c]: 1°:↓ (56)[b] 2°:↓ (27)[b]	–	Blakely et al. 1980 (MMC)
Mouse; 21 days	1.7	–	SRBC: ↓ (36)[b] LPS: ↓ (45)[b]	LPS: ↓ (56)[b] [28 dpi]	PFA[c]: 1°:↓ (58)[b] 2°:↓ (24)[b]	–	Blakely et al. 1980 (MMC)
Mouse; 84 days	0.77	Con A Th: 0 Sp: ↑ (20)[b] LPS: 0	–	–	–	Bl: ↓ (75)[b] S: ↓ (44)[b]	Ilback 1991 (MM)
Rabbit; 98 days	0.05	–	–	Influenza: 0	–	–	Koller et al. 1977 (MMC)
Rabbit; 98 days	0.49	–	–	1°:↓ (50)[b] [7 dpi] 2°:↓ (50)[b] [24 dpi]	–	–	Koller et al. 1977 (MMC)

Table 2-35. Functional Immune Assays in Laboratory Animals Orally Exposed to Methylmercury During Adulthood

Species; duration	Dose (mg Hg/kg/day)	Mitogen	HG titers	AB production	PFA	NKC activity	Reference (compound)
Rabbit; 98 days	0.53	–	–	1°:↓ (75)[b] [7 dpi] 2°:↓ (50)[b] [24 dpi]	–	–	Koller et al. 1977 (MMC)

[a]Percent change compared to control, estimated from graphically presented data.
[b]Percent change compared to control, calculated from quantitative data.
[c]Primary (1°) response is production of IgM-producing cells in the spleen; secondary (2°) response is production of IgG-producing cells in the spleen.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; AB = antibody; Bl = blood; Con A = concanavalin A (T-cell mitogen); dpi = days post-infection; HG = hemagglutination; LPS = *Escherichia coli* lipopolysaccharide (B-cell mitogen); MM = methylmercury; MM2S = bis(methylmercury)sulfide; MM3S = tris(methylmercuric)sulphonium ion; MMC = methylmercuric chloride; MMS = methylmercury sulfide; NKC = natural killer cell; PFA = plaque-forming assay with SRBCs; PHA = phytohemagglutinin (T-cell mitogen); Sp = spleen; Th = thymus; SRBC = sheep red blood cell

Plasma IL-6 was elevated in rats exposed to ≥0.0004 mg Hg/kg/day as methylmercuric chloride or 0.004 mg Hg/kg/day as bis(methylmercury)sulfide for 8 weeks (Ortega et al. 1997b). With exposure for 16 weeks, plasma IL-6 levels were significantly elevated with exposure to ≥0.0004 mg Hg/kg/day as bis(methylmercury)sulfide (not dose-related) or 0.04 mg Hg/kg/day as methylmercuric chloride. These results are difficult to interpret due to lack of a clear dose- and duration-dependence.

Data for spleen and thymic weight and cellularity following developmental or adult exposure to methylmercury are presented in Table 2-36. There is limited evidence of increased thymus weight and/or cellularity in rodents following intermediate-duration developmental exposure to methylmercury (Thuvander et al. 1996; Tonk et al. 2010; Wild et al. 1997). In contrast, decreased thymus weight and cellularity were reported in a single intermediate-duration adult exposure study (Ilback et al. 1991). Available data are not adequate to assess dose- or duration-dependence of thymic changes for either exposure paradigms. No consistent, exposure-related changes in spleen weight or cellularity have been observed in rodents following developmental or adult exposure (see Table 2-36).

Table 2-36. Immune Organ Weight and Cellularity in Rodents Orally Exposed to Methylmercury

Species; duration	Dose (mg Hg/kg/day)	Spleen weight	Spleen cellularity	Thymus weight	Thymus cellularity	Reference (compound)
Developmental exposure[a]						
Rat; 15 days [PNDs 1–15]	0.37	Relative: ↓ (13)[b] [PND 15]	0	0	0	Ilback et al. 1991 (MM)
Rat; 26 days [GD 6–PND 10]	0.08	Relative: 0 [PNDs 21–70]	0	Relative: 0 [PNDs 21–70]	–	Tonk et al. 2010 (MMC)
Rat; 26 days [GD 6–PND 10]	0.3	Relative: ↓ (>5)[c] [PND 21]	0	Relative: 0 [PNDs 21–70]	–	Tonk et al. 2010 (MMC)
Rat; 26 days [GD 6–PND 10]	0.6–1.6	Relative: ↓ (>5)[c] [PNDs 21–42]	↑ (>5)[b] [PND 42]	Relative: ↑ (>5)[c] [PND 70]	–	Tonk et al. 2010 (MMC)
Rat; 105 days [8 weeks PM–PND 21] (W)	0.0006	Absolute ↑ (62)[d] [PND 42]	–	Absolute ↑ (105)[d] [PND 42]	–	Wild et al. 1997 (MMC)
Rat; 105 days [8 weeks PM–PND 21]	0.0003	Absolute 0 [PNDs 42–84]	–	Absolute ↑ (56)[d] [PND 42]	–	Wild et al. 1997 (MM2S)
Rat; 105 days [8 weeks PM–PND 21]	0.06	Absolute ↑ (122)[d] [PND 42]	–	Absolute ↑ (105)[d] [PND 42]	–	Wild et al. 1997 (MMC)
Rat; 105 days [11 weeks PM–GD 21]	0.37	0	0	0	0	Ilback et al. 1991 (MM)
Rat; 119 days [11 weeks PM–PND 15]	0.37	0	0	0	0	Ilback et al. 1991 (MM)
Mouse; 112 days [10 weeks PM–PND 15]	0.098	Absolute: ↑ (28)[b] [PND 10]	↑ (30)[b] [PND 10] ↑ (25)[b] [PND 22]	Absolute: 0 [PNDs 10–50]	↑ (33)[b] [PND 22]	Thuvander et al. 1996 (MMC)
Mouse; 112 days [10 weeks PM–PND 15]	0.98	0	0	0	0	Thuvander et al. 1996 (MMC)

Table 2-36. Immune Organ Weight and Cellularity in Rodents Orally Exposed to Methylmercury

Species; duration	Dose (mg Hg/kg/day)	Spleen weight	Spleen cellularity	Thymus weight	Thymus cellularity	Reference (compound)
Post-pubertal (adult) exposure						
Rat; 28 days	0.002–5.91	Relative: 0	–	–	–	Wildemann et al. 2015a (MMC)[e]
Rat; 730 days	0.006–0.16	Relative: 0	–	–	–	Verschuuren et al. 1976 (MMC)
Mouse; 84 days	0.77	Absolute: 0	0	Absolute: ↓ (22)[b]	↓ (50)[b]	Ilback 1991 (MM)

[a]Studies listed in LSE table under Development.
[b]Percent change compared to control, calculated from quantitative data.
[c]Dose-specific data not reported; data based on reported BMD_5 values.
[d]Percent change compared to control, estimated from graphically presented data.
[e]NOAEL for immune effects not included in LSE table; the only immune endpoint evaluated was spleen weight (endpoint assessment too limited for evaluation of adversity).

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; BMD = benchmark dose; GD = gestation day; LSE = Level of Significant Exposure; MM = methylmercury; MM2S = bis(methylmercury)sulfide; MMC = methylmercuric chloride; NOAEL = no-observed-adverse-effect level; PM = premating; PND = postnatal day

There is limited evidence for changes in subpopulations of immune cells in the thymus following developmental exposure to methylmercury. In a gestation plus lactation exposure study in wild-type mice, exposed offspring showed decreased number and percentages of CD8+ cells, CD4+ cells, and natural killer cells and increased ratio of CD4+/CD8+ cells in the spleen during the postweaning period (Tonk et al. 2010). Dose-specific data were not reported, but benchmark doses (BMDs) associated with a benchmark response (BMR) of 5% ranged from 0.14 to 0.52 mg Hg/kg/day. Another study reported a decreased percentage of CD4+ cells and CD4+CD8+ cells at PND 10 and an increased percentage of CD8+ cells at PNDs 22 and 50 in wild-type mouse offspring following maternal exposure to ≥0.098 mg Hg/kg/day and 0.98 mg Hg/kg/day, respectively, for 11 weeks premating through PND 15 (Thuvander et al. 1996).

No histopathological changes in the bone marrow, thymus, or spleen were observed in rats at chronic-duration methylmercury doses up to 0.18 mg Hg/kg/day (Verschuuren et al. 1976), or wild-type mice after intermediate- or chronic-duration doses up to 0.724 mg Hg/kg/day (Hirano et al. 1986; Mitsumori et al. 1990). In other species, no histopathological changes in the spleen were observed following exposure to methylmercury for intermediate-durations at dietary doses up to 1.1 mg Hg/kg/day in rabbits (Koller et al. 1977) or 0.176 mg Hg/kg/day in cats (Charbonneau et al. 1976), or chronic-durations at dietary doses up to 0.074 mg Hg/kg/day in cats (Charbonneau et al. 1976).

Predominant Mercury Form Unknown (General Populations). Studies of general populations have examined associations between mercury biomarkers and several immune endpoints including immunological diseases, ANAs, serum cytokines, and immune cell counts (Table 2-37). Studies used prospective and cross-sectional designs and evaluated effects in children and adults. A few studies examined the same endpoints (eczema, ANA titers, and cytokines), and the most common biomarker was BHg.

Table 2-37. Results of Epidemiological Studies Evaluating Exposure to Mercury (Predominant Mercury Form Unknown) and Immunological Effects in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Crowe et al. 2015 Cross-sectional; 52 patients with SLE (Northern Ireland)	UHg mean: 1.1 ng/g Cr HHg mean: 1.5 µg/g	SLE activity	0 (UHg, HHg)
		SLE damage	0 (UHg) ↓ (HHg)
Gallagher et al. 2013 Cross-sectional; males and females ages 12–85 (NHANES 2003–2004)	BHg mean, females ANA+: 1.30 µg/L ANA−: 1.47 µg/L BHg, males not reported	Serum ANA	0 (BHg, males and females)
Hui et al. 2016 Prospective; 407 children; cytokines measured at ages 6–9 years (China)	Cord BHg median: 9.2 µg/L	Plasma cytokines	
		IL-4	0 (cord BHg)
		IL-5	0 (cord BHg)
		IL-6	0 (cord BHg)
		IL-8	0 (cord BHg)
		IL-10	0 (cord BHg)
		IL-13	0 (cord BHg)
		TNF-α	0 (cord BHg)

Table 2-37. Results of Epidemiological Studies Evaluating Exposure to Mercury (Predominant Mercury Form Unknown) and Immunological Effects in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Kamycheva et al. 2017 Cross-sectional; 3,643 children and 11,040 adults (NHANES 2009–2012)	BHg mean, children CD+: 0.47 µg/L CD-: 0.64 µg/L BHg mean, adults CD+: 1.32 µg/L CD-: 1.64 µg/L	CD	↓ (BHg, children) 0 (BHg, adults)
Kim et al. 2015d Cross-sectional; 311 children (South Korea)	BHg median: 2.19 µg/L	Cell counts Total leukocytes Segmented leukocytes Lymphocytes Monocytes Basophils Eosinophils	 0 (BHg) 0 (BHg) ↑ (BHg) 0 (BHg) 0 (BHg) 0 (BHg)
Miyake et al. 2011 Prospective; 582 mother-child; maternal and child exposure and child outcomes assessed at age 29–39 months (Japan)	HHg median Mother: 1.52 µg/g Child: 1.38 µg/g	Eczema	0 (HHg, mother and child)
Monastero et al. 2017 Cross-sectional; 287 adults (Long Island, New York)	BHg median: 4.58 µg/L	Serum cytokines IL-1β IL-1ra IL-4 IL-10 IL-17 IFN-γ TNF-α	 0 (BHg) 0 (BHg) 0 (BHg) 0 (BHg) 0 (BHg) 0 (BHg) 0 (BHg)
		Serum ANA	0 (BHg)
Park and Kim 2011 Cross-sectional; 127 adults with lifetime prevalence of atopic dermatitis and 176 with atopic dermatitis diagnosed in the past year (Korea)	BHg tertiles T1: <3.56 µg/L T2: 3.56–6.04 µg/L T3: >6.04 µg/L	Atopic dermatitis (lifetime prevalence)	↑ (BHg, T3)
		Atopic dermatitis (1-year prevalence)	↑ (BHg, T3)

Table 2-37. Results of Epidemiological Studies Evaluating Exposure to Mercury (Predominant Mercury Form Unknown) and Immunological Effects in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Shaheen et al. 2004 Prospective; 1,755 newborns, assessed for eczema at 18–30 months of age (ALSPAC, United Kingdom)	Cord BHg Gmean: 0.0127 µg/L	Eczema	0 (cord BHg)
Somers et al. 2015 Cross-sectional; 1,352 females, ages 16–49 years (NHANES 1999–2004)	BHg quartiles (µg/L) Q1: <0.4 Q2: 0.4–0.8 Q3: 0.9–1.5 Q4: 1.6–32.8 UHg quartiles (µg/L) Q1: <0.0029 Q2: 0.0029–0.0063 Q3: 0.0063–0.0135 Q4: 0.0137–0.8873 HHg tertiles (µg/g) T1: <0.11 T2: 0.11–0.27 T3: 0.271–5.96	Serum ANA	↑ (BHg, Q4) 0 (UHg, Q4) ↑ (HHg, T3)
Stratakis et al. 2021 Cohort; mother-child pairs participating in the HELIX cohort; mean child age: 8.1 years; children were stratified into Group 1 (n=669; low risk for NAFLD) and Group 2 (n=123; high risk for NAFLD) (France, Greece, Lithuania, Norway, Spain, United Kingdom)	BHg median (maternal during pregnancy) Group 1: 1.8 µg/L Group 2: 2.7 µg/L	Serum Cytokines IL-1β IL-6 IL-8 TNF-α	 ↑ (BHg, Group 2) ↑ (BHg, Group 2) ↑ (BHg, Group 2) ↑ (BHg, Group 2)

↑ = positive association; ↓ = inverse association; 0 = no association; AD = atopic dermatitis; ALSPAC = Avon Longitudinal Study of Parents and Children; ANA = antinuclear antibodies; BHg = blood mercury; CD = celiac disease; CD+ = celiac disease seropositive; CD- = celiac disease seronegative; Gmean = geometric mean; HELIX = European Early-Life Exposome; HHg = hair mercury; IFN-γ = interferon-gamma; IL = interleukin; NAFLD = nonalcoholic fatty liver disease; NHANES = National Health and Nutrition Examination Survey; Q = quartile or quintile; SLE = systemic lupus erythematosus; T = tertile; Th1 = T-helper cell 1 (cell-mediated immunity); Th2 = T-helper cell 2 (humoral immunity); TNF-α = tumor necrosis factor-alpha

Epidemiological studies evaluating autoimmune diseases in general populations have investigated associations between mercury biomarkers and atopic dermatitis, eczema, SLE, and celiac disease seropositivity. Except for two studies on eczema, studies did not evaluate the same endpoints. Two

prospective studies in newborns that were followed through ages 18–39 months did not find associations between cord BHg or HHg and eczema (Miyake et al. 2011; Shaheen et al. 2004). Atopic dermatitis was positively associated with BHg in adults with a life-long prevalence of atopic dermatitis and adults with a diagnosis within the past year (Park and Kim 2011). No association was observed between urine mercury or hair mercury and SLE activity, although HHg was inversely associated with SLE damage (Crowe et al. 2015). A large cross-sectional study in NHANES children and adults found a negative association between BHg and celiac disease seropositivity in children and no association in adults (Kamycheva et al. 2017).

Three studies evaluated associations between mercury biomarkers and serum levels of ANA. A cross-sectional study of women reported positive associations between the highest BHg quartile and highest HHg tertile and serum ANA, but no association for the highest UHg quartile (Somers et al. 2015). The risks (OR) of a positive ANA were 2.51 (95% CI 1.04, 6.03) and 3.75 (95% CI 1.06, 13.28) for the fourth BHg quartile and the third HHg tertile, respectively. Study authors considered the positive association between mercury biomarkers and ANA titers to be indicative of subclinical autoimmunity, although the incidence of autoimmune disease in this population was not reported. In contrast, no associations were observed between BHg and positive ANA in other cross-sectional studies of men and women (Gallagher et al. 2013; Monastero et al. 2017).

Three studies examined the relationship between BHg and plasma cytokine levels in children (Hui et al. 2016; Monastero et al. 2017; Stratakis et al. 2021). A prospective study evaluated associations between maternal BHg and child plasma cytokine levels at age 8 years (Stratakis et al. 2021). Children were stratified into two groups: those at low risk and those at high risk for nonalcoholic fatty liver disease (NAFLD). This study found positive associations between maternal BHg and cytokine levels (IL-1β, IL-6, IL-8, and tumor necrosis factor-alpha [TNF-α]) in children with high risk of NAFLD. No associations were observed, except for a negative association between cord BHg and plasma IL-10 in a prospective study of children (Hui et al. 2016). A cross-sectional study evaluating immune cell counts in children reported a positive association between BHg and total lymphocyte count, but no associations for counts of total leukocytes, segmented leukocytes, monocytes, basophils, or eosinophils (Kim et al. 2015d). The clinical significance of these findings has not been established.

Several studies show that mercury induces dermal sensitization based on positive skin patch tests to elemental and/or inorganic mercuric salts; study results are summarized in Table 2-38. The specific form or forms of mercury that produced the initial sensitization cannot be determined. However, exposures

were most likely to a combination of elemental and methylmercury exposures; therefore, the study populations are classified as general populations. Studies were conducted in populations with known elemental mercury exposure (Kawahara et al. 1993), sensitivity to amalgam (Kawahara et al. 1993; Laine et al. 1997; Nordlind and Liden 1992; Skoglund and Egelrud 1991; Thanyavuthi et al. 2016; Tiwari et al. 2018), and general populations (Handley et al. 1993; Mori et al. 2007; Nonaka et al. 2011).

Table 2-38. Results of Skin Patch Tests to Mercury Compounds in General Populations

Reference and population	Challenge chemical	Result
Handley et al. 1993; 441 patients with suspected contact dermatitis (Northern Ireland)	$HgCl_2$, $HgNH_2Cl$, Hg^0	+ (14/441 patients to one or more compounds)
Kawahara et al. 1993; 12 male dental students (Japan)	$HgNH_2Cl$	+ (3/12 patients)
Koch and Bahmer 1999; 19 patients with oral lichenoid lesions (Germany)	$HgCl_2$ and $HgNH_2Cl$	+ (15/19 patients)
Laine et al. 1997; 118 patients with oral lichenoid lesions (Finland)	$HgNH_2Cl$	+ (80/118 patients)
Mori et al. 2007; 580 students (Japan)	$HgCl_2$	+ (55/580 subjects)
Nonaka et al. 2011; 930 adults (Japan)	$HgCl_2$	+ (94/930 subjects)
Nordlind and Liden 1992; 12 patients with oral lesions	$HgCl_2$, Hg^0	+ (5/12 patients)
Skoglund and Egelrud 1991; 24 patients with oral lesions	$HgNH_2Cl$	+ (8/12 patients)
Thanyavuthi et al. 2016; 53 patients with oral lichenoid lesions (Thailand)	Hg^0	+ (19/53 patients)
Tiwari et al. 2018; 68 patients with oral lichen planus (Australia)	Hg^0	+ (24/68 patients)

+ = positive skin patch test

In addition to studies showing positive skin patch to dermal mercury challenge, acrodynia, a syndrome that may involve a hypersensitivity reaction to mercury, is occasionally observed in infants and young children exposed to different forms of mercury (as reviewed by Jao-Tan and Pope 2006). Acrodynia, also known as “pink disease” due to characteristic pink coloration of toes and fingers, is of more historical interest, as it typically has been associated with mercury exposure through discontinued mercury-containing pharmaceuticals (e.g., teething and diaper powders, antihelminthics, ointments) and

preservatives. However, acrodynia has been observed following inhalation exposure to elemental mercury in accidental spills. Symptoms of acrodynia include pink, perspiring, swollen, and peeling hands and feet. Epidemiological studies on associations of acrodynia with environmental exposures to mercury were not identified.

Mechanisms of Action. Effects of mercury on the immune system are complex, as mercury has been shown to both stimulate and inhibit the immune system function (Havarinasab and Hultman 2005). Several mechanisms have been proposed for mercury-induced effects on immune function (Fournie et al. 2002; Havarinasab and Hultman 2005; Maqbool et al. 2017; Silbergeld et al. 2005; Vas and Monestier 2008). These include: (1) proliferation and activation of T and B cells, leading to increased serum IgG and IgE; (2) increased ANAs and ANoAs; (3) dysregulation of lymphocyte signal-transduction pathways; (4) altered gene expression of cytokines; (5) induction of protein kinase C (PKC), leading to phosphorylation of numerous proteins; (6) PKC-induced alteration of L-type calcium channels, resulting in increased intracellular calcium; (7) inhibition of nitric oxide production; (8) increased formation of ROS and lipid peroxidation; and (9) alteration of the intestinal microbiome (Khan and Wang 2020).

2.16 NEUROLOGICAL

Overview. Neurological effects of mercury exposure have been recognized for centuries, and occupational toxicity of mercury has a long history (Clarkson and Magos 2006). In the 19th century hatting industry, mercury was used to produce felt hats and workers in this industry commonly exhibited slurred speech, tremors, irritability, shyness, depression, and other neurological symptoms, a syndrome known as “Mad Hatter’s Disease” (NIOSH 2010). This section on neurological effects is divided into two sections: Section 2.16.1, Neurodevelopmental Effects; and Section 2.16.2, Neurological Effects in Adults. Data on neurodevelopmental and neurological effects of mercury are available from clinical case studies, epidemiology studies, and studies in animals. Epidemiological studies have been conducted in workers, general populations, and populations known to consume large amounts of fish, seafood, or marine mammals, in which dietary intake of methylmercury is expected to be the dominant source of mercury exposure. Neurotoxicity of mercury has been extensively studied in animal models.

The following summarizes results of epidemiological and animal studies on neurodevelopmental and neurological outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - Intermediate-duration exposures to mercury vapor (50–400 µg Hg/m^3) has produced cases of severe neurological and cognitive effects in children.
    - Studies of cognitive function in children exposed to elemental mercury released from mercury amalgam dental restorations have yielded mixed results. Most studies found no association between exposure (number or restorations or biomarkers) and cognition.
    - Studies of neurological function in adults have been conducted in workers in various industries who were exposed to mercury vapor. Collectively, these studies provide evidence for associations between exposure to mercury vapor and several categories of neurological effects, including tremor, vision, nerve conduction, motor speed and coordination, cognitive performance (memory, and integrative function), and subjective physiological symptoms (mood swings, irritability, nervousness, timidity, loss of confidence).
  - *Animal studies*
    - Limited neurodevelopmental studies in animals have reported altered learning and behavior (altered motor activity, impaired habituation) in monkeys, rats, and mice following gestational or early postnatal exposure to metallic mercury vapor.
    - Few studies have evaluated effects of exposure to elemental mercury and neurological outcomes in adult animals. Available data suggest impaired motor function and damage to the central nervous system, particularly the cerebellum.
- ***Inorganic mercury***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to inorganic mercury salts and neurological effects were identified.
    - Case studies of individuals acutely exposed to fatal or near-fatal levels of inorganic mercuric compounds reported disturbances of vision and behavior and seizures; at autopsy, brain abscesses in the cerebrum have also been observed.
  - *Animal studies*
    - Neurobehavioral changes are consistently reported in rodents following oral exposure to mercuric chloride during development, including hyperactivity, impaired motor coordination, impaired memory, and decreased sociability. There is limited evidence for altered neurophysiology at comparable doses (increased auditory thresholds, decreased peripheral nerve conduction, induction of seizure activity).

- Neurobehavioral changes (hyperactivity, impaired coordination, impaired learning and memory) have been reported in rodents following oral exposure to mercuric chloride during adulthood at doses similar to those associated with developmental findings; however, lower doses have not been evaluated in developmental studies.
- Overt signs of neurotoxicity (hindlimb crossing, ataxia, tremor, partial paralysis) and neuropathological changes to sensorimotor regions in the central nervous system (dorsal spinal route, cerebellum) have been reported in adult animals following oral exposure to mercuric chloride at doses higher than those associated with neurobehavioral changes.
- Oral exposure to mercuric sulfide can result in neurological effects in adult rodents at doses markedly higher than those associated with mercuric chloride toxicity, including impaired coordination, altered neurophysiology (decreased nerve conduction, increased auditory thresholds), and cerebellar damage.
- Available data following inhalation exposure to mercuric oxide are too limited to draw conclusions.

- ***Organic mercury***
  - *Epidemiology studies*
    - Severe neurodevelopmental effects occurred in association with maternal ingestion of methylmercury in seafood (congenital Minamata disease) and from ingestion of wheat contaminated with a methylmercury fungicide (Iraq outbreak). In both incidents, levels of exposure were sufficient to produce frank neurological effects in adults.
    - Cognitive and neurosensory effects have been observed in association with prenatal exposures to methylmercury in high fish and marine mammal consumers in the absence of evidence of maternal toxicity. Results of these studies have been inconsistent, with some studies finding associations between mercury exposure biomarkers (blood or hair mercury) and declines in tests of cognitive or neurosensory function, some studies finding improved function, and some studies finding no associations with mercury exposure biomarkers. Differences in outcomes may be due to differences in confounders and how they were controlled in regression models, and may also arise where groups (e.g., people of a specific sex or age) are differentially susceptible to mercury. Potential confounders include fish intake and related nutritional factors (e.g., 3-omega polyunsaturated long-chain fatty acids), co-exposure to other contaminants in fish or marine mammals (PCBs, selenium), and social variables affecting child development. Potential effect measure modifiers include genetic susceptibility factors.

- Studies of associations between exposure to methylmercury and neurological function in adults have also been conducted in populations that consume large amounts of fish or marine mammals. Collectively, these studies provide evidence for associations between exposure to methylmercury and decreasing performance on tests of fine motor coordination and speed, muscle strength, tactile sensation, color vision and visual contrast sensitivity, and memory and learning.

- *Animal studies*
  - Neurobehavioral and neurophysiological effects have been observed in multiple species following acute-, intermediate-, and chronic-duration exposure to methylmercury, including sensorimotor dysfunction (altered motor activity, impaired coordination, impaired reflexes), vision and hearing deficits, and impaired learning and memory. At higher doses, overt signs of neurotoxicity were observed (clumsiness, gross and fine motor incoordination, lethargy, hindlimb crossing, tremor, ataxia, partial paralysis).
  - Neuropathological changes were observed in both the central and peripheral nervous system, at doses above those associated with neurobehavioral changes. Central lesions were observed, primarily, in regions associated with sensorimotor and movement control (e.g., cerebellum, motor cortex, subcortical regions, dorsal ganglion, and nerve root of the spinal cord).
  - In both primates and rodents, developing animals are more sensitive to methylmercury-induced neurotoxic effects than adult animals.

- ***Predominant mercury form unknown (general populations)***
  - Studies of general populations, in which exposures to mercury derive from a variety of potential sources (e.g., mercury amalgam restoration, diet) have found inconsistent associations between biomarkers of exposure and performance on tests of cognitive function.
  - The different outcomes in cognitive development may reflect differences in how well confounders were adjusted for and whether effect measure modification was investigated. Potential confounders include fish consumption and related nutritional factors, and exposure to other chemicals (e.g., selenium, PCBs).
  - Few studies of neurological effects in general adult populations have been reported precluding conclusive statements.

Confounding Factors. Numerous factors can complicate interpretation of statistical associations between mercury exposure (or biomarkers of exposure) and neurological outcomes (Castoldi et al. 2008). These

include a variety of factors that can affect performance on tests of cognitive or neurosensory function that, if not homogenously distributed in the study population, can bias findings. These factors include (but are not limited to) child sex; birth weight; birth order; gestational age and child age; breastfeeding; maternal age, alcohol, and tobacco use, and medical history; parental education; caregiver general intelligence; family income; family language; home learning, and social stimulation; exposure to other neurotoxins (e.g., lead, PCBs); nutritional factors (e.g., fish consumption); history of neurological disease or head injuries; and genetic factors that may influence toxicity of mercury.

Some factors can introduce confounding bias because they are also associated with mercury exposure. For example, the dominant source of exposure to methylmercury in most populations is through consumption of contaminated fish. However, fish also contain nutrients that have been shown to be important modifiers of development. These include 3-omega LCPUFA, iodine, iron, selenium, and vitamin E (Cheatham 2008; Choi et al. 2008a; Muldoon et al. 2014). In populations in which consumption of marine mammals contributes to dietary mercury intake (e.g., Faroe Islands, Nunavik), dietary intake of PCBs and selenium, which accumulate in marine mammal tissue, can also be a source of confounding bias (Boersma and Lanting 2000; Park et al. 2010; Skroder et al. 2017). Unless otherwise specified, studies summarized in this section of the profile have considered potential confounders in assessments of associations of outcomes with mercury exposure.

2.16.1 Neurodevelopmental Effects

Elemental Mercury—Epidemiological Studies. Cases of severe neurological and cognitive effects in children exposed to elemental mercury vapor have been reported. Available epidemiological studies have focused on associations between exposures to elemental mercury released from mercury amalgam dental restorations and cognitive function in children. These studies have yielded mixed results. Most studies found no associations between exposure (number or restorations or biomarkers) and cognitive function.

Poisoning case studies. A case study of two children, ages 13 and 15 years, who were accidentally exposed to mercury vapor for a period of 3 months observed cognitive deficits that improved 1 year after exposure and treatment with a mercury complexing agent, 2,3-dimercaptosuccinic acid (DMSA) (Yeates and Mortensen 1994). Exposure resulted from vaporization of elemental mercury that had been spilled from a container in the residence. Exposure levels measured in the residence ranged from 50 to 400 µg Hg/m^3. At diagnosis, the 15-year-old patient had a urine mercury level of 1,314 µg Hg/L and blood mercury levels that ranged from 10 to 30 µg Hg/L. The 13-year-old patient had a urine mercury level of

624 µg Hg/L and a blood mercury level of 69 µg Hg/L. Both patients presented with rash (consistent with acrodynia, further discussed in Section 2.15, Immunological), anorexia, tremor, and paresthesia. Cognitive testing of the 15-year-old at diagnosis (Wechsler Intelligence Scale for Children, Revised [WISC-R]) indicated a full-scale IQ of 79 compared to a value of 101 measured at age 9 years, with the largest deficit on the digit span test of attention and short-term memory. Following DMSA chelation therapy and a period of 1 year following exposure, full-scale IQ increased to 93 with most of the improvement attributed to performance on the digit span test. Cognitive testing of the 13-year-old patient indicated a full-scale IQ of 79, which did not improve when retested 1 year later and after DMSA chelation therapy.

Exposures to mercury amalgam dental restorations. Studies evaluating effects of elemental mercury on neurological development include several longitudinal studies of associations between metrics of exposure from child or maternal mercury amalgam dental restorations and cognitive function and behavior, and one study that evaluated exposures to mercury in a gold mining community (Table 2-39). In the study populations, exposures included elemental mercury released from amalgams as well as exposures to other forms of mercury (e.g., dietary methylmercury). As a result of this mixed exposure, reported biomarkers such as urinary or hair mercury cannot be interpreted as specific metrics of exposures to amalgam mercury and most studies included an exposure metric directly related to amalgams such as number of amalgam surfaces, or compared outcomes between groups of people who had mercury amalgam restorations and groups with restorations made of other materials. In some studies, biomarkers more specific to methylmercury exposure, such as hair mercury, were used to adjust the models for potential confounding by methylmercury exposure (Bellinger et al. 2006, 2007a, 2008; Watson et al. 2011, 2012). This adjustment was particularly important in studies of the Seychelle Islands cohort, which had relatively high exposures to methylmercury (mean prenatal hair mercury 6–7 µg Hg/g; Watson et al. 2010, 2011). Some studies adjusted measurements of associations for exposures to lead (Bellinger et al. 2006, 2007a, 2008; Surkan et al. 2009); however, other potential chemical exposures associated with mercury exposure that might have contributed to outcomes were not considered. Most studies included analysis of covariates such as age, sex, race, birth weight, SES, caregiver education and/or IQ, and metrics of home environment as potential confounders.

Table 2-39. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) in Populations with Mercury Amalgam Dental Restorations and Neurodevelopmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Bellinger et al. 2006, 2007b, 2008; Surkan et al. 2009 Randomized clinical trial (NECAT); 534 children, 267 receiving amalgam fillings and 267 receiving resin fillings at age 6–10 years; neurological testing at 5 years following restoration; Boston, Massachusetts, Farmington, Maine	UHg mean Amalgam: 0.99 µg/g Cr No amalgam: 0.61 µg/g Cr HHg mean Female: 0.31 µg/g Male: 0.32 µg/g Amalgam surface-years mean: 31.7	IQ	0 (amalgam versus no amalgam) 0 (UHg, HHg) 0 (surface-years)
		Learning and memory	0 (amalgam versus no amalgam) 0 (UHg, HHg) 0 (surface-years)
		Visuomotor	0 (amalgam versus no amalgam) 0 (UHg, HHg) 0 (surface-years)
		Competence	0 (amalgam versus no amalgam)
		Internalization	↓ (amalgam versus no amalgam)
		Externalization	0 (amalgam versus no amalgam)
DeRouen et al. 2006 Randomized clinical trial; 507 children, 253 receiving amalgam fillings and 254 receiving resin fillings at age 8–10 years; annual neurological testing through 7 years following dental mercury amalgam or resin restorations; Portugal	UHg mean at baseline Amalgam: 1.8 µg/g Cr No amalgam: 1.9 µg/g Cr UHg mean at 2 years following restoration (peak exposure) Amalgam: 3.2 µg/g Cr No amalgam: 1.5 µg/g Cr	Learning and memory	0 (amalgam versus no amalgam)
		Attention	0 (amalgam versus no amalgam)
		Visuomotor	0 (amalgam versus no amalgam)
		Non-verbal IQ	0 (amalgam versus no amalgam)
Watson et al. 2011 Prospective cohort of 587 mother-child pairs recruited with follow-up at age 66 months; 249 mothers had amalgam restorations present during pregnancy; Seychelles	HHg mean Prenatal: 6.8 µg/g (based on Davidson et al. 1998) Amalgam group Number of maternal amalgam surfaces (mean): 5.12	General cognitive	0 (amalgam surfaces)
		Language	0 (amalgam surfaces)
		Reading and arithmetic	0 (amalgam surfaces)
		Visuomotor	0 (amalgam surfaces)
		Adaptive behavior	0 (amalgam surfaces)

Table 2-39. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) in Populations with Mercury Amalgam Dental Restorations and Neurodevelopmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Watson et al. 2012 Prospective cohort of 242 mother-child pairs recruited with follow-up at age 9 and 30 months; 196 mothers had amalgam restorations present during pregnancy; Seychelles	HHg mean Prenatal: 6.8 µg/g (based on Davidson et al. 1998) Amalgam group Number of maternal amalgam surfaces (mean): 8.49	Mental development index	0 (amalgam surfaces)
		Psychomotor development index	0 (amalgam surfaces)
Woods et al. 2012, 2014 Randomized clinical trial; 239 children, 121 boys and 118 girls, receiving amalgam fillings or resin fillings at age 8–12 years; neurological testing at 7 years following restoration; Portugal Note: Subjects included children from a dental amalgam clinical trial (DeRouen et al. 2006) with CPOX4 genotyping; amalgam status was not reported.	UHg mean at baseline Boys: 1.65 µg/g Cr Girls: 1.98 µg/g Cr UHg mean at 2 years following restoration (peak exposure) Boys: 2.17 µg/g Cr Girls: 2.86 µg/g Cr UHg mean at 7 years following restoration Boys: 1.25 µg/g Cr Girls: 1.77 µg/g Cr	Attention	Boys: ↓ (cumulative UHg) Girls: 0 (cumulative UHg)
		Visual-spatial	Boys: ↓ (cumulative UHg) Girls: 0 (cumulative UHg)
		Learning and memory	Boys: ↓ (cumulative UHg) Girls: 0 (cumulative UHg)
		Motor	Boys: 0 (cumulative UHg) ↑ (cumulative UHg and CPOX4 genotype) Girls: 0 (cumulative UHg)
Woods et al. 2013, 2014 Randomized clinical trial; 239 children, 120 boys and 119 girls, receiving amalgam fillings or resin fillings at age 8–12 years; neurological testing at 7 years following restoration; Portugal Note: Subjects included children from a dental amalgam clinical trial (DeRouen et al. 2006) with MT1M and MT2A genotyping; amalgam status was not reported.	UHg mean at baseline Boys: 1.68 µg/g Cr Girls: 1.97 µg/g Cr UHg mean at 2 years following restoration (peak exposure) Boys: 2.18 µg/g Cr Girls: 2.86 µg/g Cr UHg mean at 7 years following restoration Boys: 1.26 µg/g Cr Girls: 1.76 µg/g Cr	Visual spatial	Boys: 0 (cumulative UHg) ↑ (cumulative UHg and MT2A genotype) Girls: 0 (cumulative UHg)
		Learning and memory	Boys: 0 (cumulative UHg) ↑ (cumulative UHg and MT1M genotype) ↑ (cumulative UHg and MT2M genotype) Girls: 0 (cumulative UHg)

Table 2-39. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) in Populations with Mercury Amalgam Dental Restorations and Neurodevelopmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Ye et al. 2009 Cross-sectional cohort of 403 children ages 7–11 years; 198 with amalgam fillings and 205 without amalgam fillings; Shanghai	UHg median Amalgam: 1.6 µg/g Cr No amalgam: 1.4 µg/g Cr	CBCL	0 (amalgam versus no amalgam)
		EPQ	0 (amalgam versus no amalgam)
		Academic math score	0 (amalgam versus no amalgam)
		Academic language	0 (amalgam versus no amalgam)

↑ = positive association; ↓ = inverse association; 0 = no association; CBCL = Child Behavior Checklist; Cr = creatinine; CPOX = coproporphyrinogen; EPQ = Eysenck Personality Questionnaire; HHg = hair mercury; IQ = intelligence quotient; MT = metallothionein; NECAT = New England Children's Amalgam Trial; UHg = urine mercury

Outcomes were based on a variety of tests that measured various domains of cognitive function, including verbal and non-verbal IQ, learning and memory, visual-spatial and visual-motor function, nerve conduction velocity, and psychosocial behavior. In some studies, as many as 20–30 different tests were administered, introducing the potential for random outcomes of "significant" associations based on p-levels. Therefore, interpretation of these studies requires consideration of the overall outcomes and consistencies or inconsistencies in outcomes across tests of similar domains of cognitive function. Most studies did not find consistent evidence for associations between exposures to mercury from amalgams and cognitive function (Bellinger et al. 2006, 2007b, 2008; DeRouen et al. 2006; Surkan et al. 2009; Watson et al. 2011, 2012). The exception were studies reported by Woods et al. (2012, 2013), which found decreased performance on some tests of attention, learning and memory, and visuomotor function in association with increased cumulative urinary mercury, based on analysis of data from a mercury amalgam random clinical trial (DeRouen et al. 2006). Woods et al. (2012, 2013) also found interactions between cumulative urinary mercury and genotypes for coproporphyrinogen (CPOX), an enzyme in the heme metabolism pathway, and metallothionein (MT), an inducible metal binding protein. Cumulative urinary mercury was used as the exposure metric, without adjustment for other potential sources of urinary mercury unrelated to amalgams. The highest mean urinary mercury levels were observed in the amalgam group in the 2-year follow-up, 3.2 µg Hg/g creatinine, compared to the baseline (prior to restorations), 1.8 µg Hg/g creatinine (DeRouen et al. 2006). This suggests that more than half of the urinary mercury may have derived from sources other than amalgam mercury. Adjustments for other potential contributors to cognitive performance outcomes were not reported. An analysis of data from

this same study compared cognitive performance in restoration groups and did not find differences in performance between mercury amalgam and resin restoration groups (DeRouen et al. 2006).

Elemental Mercury—Animal Studies. Neurodevelopmental studies have found altered learning and behavior in monkeys, rats, and mice following gestational or early postnatal exposure to metallic mercury vapor; however, data are limited and/or inconsistent between studies and testing paradigms. One study reported neurodevelopmental effects in squirrel monkeys following gestational exposure to metallic mercury vapor. Long-term impairment in operant training performance in a lever-press paradigm was observed in monkey offspring at 0.8–4 years of age following intermittent exposure to 0.5 or 1 mg Hg/m^3 (5 days/week; 4 or 7 hours/day) during the last two-thirds or more of the gestation period (Newland et al. 1996). No difference in sensitivity to reinforcer ratios was identified in the steady state, but there was much more variability in the steady-state performance of exposed monkeys, with exposed monkeys producing smaller or slower transitions than controls. The magnitude and stability of lever-press durations for controls and exposed monkeys were indistinguishable early in the study, but at the end, the exposed monkeys had longer lever-press durations and the session-to-session variability was much greater. One monkey's exposure began during the third week of gestation (earlier than any of the others) and its behavior was so erratic that some of the analyses could not be accomplished. The median maternal blood mercury levels were 0.025–0.09 µg Hg/g at 0.5 mg Hg/m^3 and 0.12–0.18 µg Hg/g at 1 mg Hg/m^3. Offspring blood mercury levels were not reported.

Alterations in neurobehavior have been observed in rats and mice following gestational or early postnatal exposure to metallic mercury vapor, including altered motor activity, impaired spatial learning, and decreased habituation to a novel environment. However, findings have been inconsistent between studies and different testing paradigms.

Increased motor activity (total, horizontal, and vertical) was reported in 4-month-old male rat offspring following intermittent exposure to 1.8 mg Hg/m^3 during GDs 14–19 (Fredriksson et al. 1996). Exposure to the same vapor level during GDs 11–14 plus GDs 17–20 resulted in decreased motor activity in 3-month-old male and female rat offspring (Danielsson et al. 1993). When rats were postnatally exposed to 0.05 mg Hg/m^3 during PNDs 11–17 for 1–4 hours/day, total and vertical (rearing) activity was increased in 4-month-old males exposed for 1 hour/day and 2-month-old males exposed for 4 hours/day, but decreased in 4-month-old males exposed for 4 hours/day; vertical activity was decreased in each group of rats (Fredriksson et al. 1992). No changes were observed in motor activity in 2-month-old males exposed for 1 hour/day. In mice, total motor activity was decreased in 11-week-old females following

continuous exposure to 0.188 mg Hg/m^3 from PND 2 to 28 (Yoshida et al. 2018); no changes were observed in female mice exposed to 0.03 mg Hg/m^3 during GDs 0–18 or 0.057 mg Hg/m^3 during PNDs 1–20 (Yoshida et al. 2011, 2013).

Impaired spatial learning was observed in male and female rats following gestational exposure to 1.8 mg Hg/m^3 (GDs 14–19 or GDs 11–14 plus GDs 17–20) or postnatal exposure to 0.05 mg Hg/m^3 (PNDs 11–17) when evaluated using the radial arm maze at 4–6 months of age, as indicated by increased latency to finish and increased number of errors (Danielsson et al. 1993; Fredriksson et al. 1992, 1996). Impaired spatial learning was also observed in male rat offspring exposed to 1.8 mg Hg/m^3 during GDs 14–19 (1.5 hours/day) when evaluated using a swim maze at 4.5 months of age (increased latency to escape) (Fredriksson et al. 1996). However, no deficits in the swim maze were observed in male or female rat offspring exposed to 1.8 mg Hg/m^3 during GDs 11–14 plus GD 17–20 (1 or 3 hours/day) when evaluated at 7 and 15 months of age (Danielsson et al. 1993) or male rats exposed to 0.05 mg Hg/m^3 on PNDs 11–17 (1 hour/day) when evaluated at 5 months (Fredriksson et al. 1992). In mice, no changes in spatial learning were observed in female mice at 2–15 months of age following gestational or postnatal exposures up to 0.03 or 0.188 mg Hg/m^3, respectively (Yoshida et al. 2011, 2013, 2018).

Decreased habituation, as indicated by sustained activity in a novel environment over time as opposed to expected decreases in exploratory behavior, was observed in male and female rat offspring following exposure to 1.8 mg Hg/m^3 during GDs 11–14 plus GDs 17–20 (3 hours/day) (Danielsson et al. 1993). Similar effects were not noted when exposure was only 1 hour/day.

No changes in passive avoidance learning were observed in female mice at 2–15 months of age following gestational or postnatal exposures up to 0.03 or 0.188 mg Hg/m^3, respectively (Yoshida et al. 2011, 2013, 2018). No changes in sensory evoked potentials (visual, auditory, cortical and cerebellar somatosensory, or peripheral nerve) were observed in adult offspring of rats exposed to metallic mercury vapor at 4 mg Hg/m^3 for 2 hours/day during GDs 6–15 (Herr et al. 2004).

No exposure-related changes in reflex ontogeny (e.g., surface righting, negative geotaxis) were observed in rats following acute gestational inhalation exposure to 1.8 mg Hg/m^3 for 1–5 hours/day (Danielsson et al. 1993; Fredriksson et al. 1996).

Inorganic Mercury—Animal Studies. Several studies have evaluated potential neurodevelopmental effects of gestational and/or early postnatal exposure to mercuric chloride in rats and mice. While only a limited number of studies evaluated each endpoint, available data suggest potential associations between developmental exposure to mercuric chloride and hyperactivity, impaired motor coordination, impaired memory, and decreased sociability in rodents. Studies evaluating electrophysiological endpoints are limited and reported mixed findings.

Increased motor activity during open field testing have been reported in male ICR mice following exposure to a gavage dose of 0.4 mg Hg/kg/day throughout gestation and lactation, during GD 1–PND 70, or postnatally only from PNDs 21–70 (Huang et al. 2011). Effects were most prominent with exposure during GD 1–PND 70. Increased stereotypical behavior during open field testing was observed in both groups with post-weaning exposure. Increased locomotor activity was also observed in autoimmune susceptible mouse offspring exposed to 2.7 mg Hg/kg/day during GD 8–PND 21 via maternal drinking water, but not similarly exposed wild-type mice (Zhang et al. 2011). Another drinking water study did not observe overall increases in locomotor activity in male Swiss mice following drinking water exposure to 3.3 mg Hg/kg/day during GD 0–PND 70; however, the time spent in the periphery of the open field was significantly increased, suggesting increased anxiety (Malqui et al. 2018). Increased anxiety was confirmed in these mice using the elevated plus maze. In contrast, decreased anxiety was observed in the elevated plus maze in PND 63 female rat offspring following maternal exposure to ≥6.1 mg Hg/kg/day during GDs 1–21 (Chehimi et al. 2012).

Impaired motor coordination in the rotarod test was observed in PND 70 male mice following exposure to 0.4 mg Hg/kg/day via gavage during GD 1–PND 70 or PNDs 21–70 (Huang et al. 2011). No effects on motor coordination were observed in similarly exposed mice during GD 1–PND 21 only (Huang et al. 2011). In rats, sensorimotor development and balance and motor coordination (while walking on the rim of a beaker at PNDs 17–20) were normal in offspring following maternal drinking water exposure to doses up to 3.8 mg Hg/kg/day during GD 1–PND 21 (Oliveira et al. 2016). However, dose-related delays in sensorimotor development were observed in female rat offspring following maternal exposure to ≥6.1 mg Hg/kg/day during GDs 1–21, including delayed rooting reflex, vibrissae placing response, righting reflex, grip strength, and negative geotaxis (Chehimi et al. 2012).

Decreased sociability, particularly decreased preference for a novel stranger, was observed in PND 70 mice exposed to ≥2.7 mg Hg/kg/day during both gestational and postnatal periods (Malqui et al. 2018; Zhang et al. 2013). These findings may be secondary to increased anxiety, supported by increased self-

grooming (stereotypical behavior) during sociability testing at 3.3 mg Hg/kg/day (Malqui et al. 2018). Alternatively, decreased preference for novelty may be due to impaired memory since performance was also impaired in mice exposed to 3.3 mg Hg/kg/day in the Y-maze spontaneous alternation and object recognition tests (Malqui et al. 2018).

One study reported impaired auditory function (increased auditory thresholds) in male mice following exposure to a gavage dose of 0.4 mg Hg/kg/day throughout gestation and lactation, during GD 1–PND 70, or postnatally only from PNDs 21–70 (Huang et al. 2011). Effects were most prominent with exposure during GD 1–PND 70.

No exposure-related changes in electrophysiological recordings, including spontaneous and evoked sensory potentials (somatosensory, visual, and acoustic) and tail nerve conduction velocity and refractory period, were observed in adult male rat offspring following exposure during gestation or gestational plus lactation at maternal doses up to 1.6 mg Hg/kg/day during GDs 5–15 (Papp et al. 2005). However, when offspring exposed during gestation and lactation were additionally exposed postweaning (PNDs 29–84), dose-related decreases in peripheral sensory nerve conduction velocity were observed at doses ≥0.4 mg Hg/kg/day, and decreased spontaneous sensory cortex potentials were observed at ≥0.8 mg Hg/kg/day (Papp et al. 2005). In another study, induction of epileptiform activity was promoted in PND 90 rat offspring following gestational and lactational exposure to 0.6 mg Hg/kg/day; no changes in epileptiform activity were observed at PND 28 and baseline cortical activity was comparable to control at both time points (Szász et al. 2002).

No changes in reflex ontogeny were observed in rat offspring following drinking water exposure to doses up to 3.8 mg Hg/kg/day during GD 0–PND 21 (Oliveira et al. 2016). No other identified studies specifically evaluated reflex ontogeny following developmental exposure to mercuric chloride.

Organic Mercury—Epidemiological Studies. Human epidemiological studies provide strong support for the developing nervous system being a sensitive target of methylmercury. Severe neurodevelopmental effects occurred in association with maternal ingestion of methylmercury in seafood (congenital Minamata disease) (Harada 1995) and from ingestion of wheat contaminated with a methylmercury fungicide (Iraq outbreak) (Amin-Zaki et al. 1974). In both incidents, exposure levels were sufficient to produce severe neurological effects in adults.

Studies of lower levels of prenatal exposures have largely focused on populations consuming large amounts of marine fish or mammals. In these populations, the dominant source of the mercury body burden derives from consumption of methylmercury in fish or marine mammals, providing a strong basis for use of blood or hair mercury as a biomarker of methylmercury exposure. Results of these studies have been inconsistent, with some studies finding associations between mercury exposure biomarkers (blood or hair mercury) and declines in tests of cognitive or neurosensory function, and other studies finding improved function or no associations with mercury. Differences in outcomes may be due to differences in confounders and how they were controlled in regression models. These variables include fish intake and related nutritional factors (e.g., 3-omega polyunsaturated long-chain fatty acids), co-exposure to other contaminants in fish or marine mammals (selenium, PCBs), and social variables affecting child development. In addition, genetic susceptibility factors may act as effect measure modifiers, impacting the associations observed between mercury and a health outcome.

Epidemiological studies have evaluated neurodevelopmental effects in the following populations with high dietary methylmercury exposure, relative to most general populations: Minamata, Japan; Iraq; Seychelle Islands; Faroe Islands; North Island, New Zealand; Nunavik region of arctic Canada; Amazon River basin, Madeira, and Portugal. Meta-analyses of the studies of high fish consumers have estimated effect sizes for prenatal methylmercury exposure and IQ (e.g., Axelrad et al. 2007a, 2007b; Cohen et al. 2005; Ryan 2008).

Minamata, Japan. Discharges of wastewater from an acetaldehyde production facility into the Shiranui Sea located in the Kumamato Prefecture of Japan, that occurred in the mid-1950s resulted in exposure of pregnant women to methylmercury ingested in locally contaminated fish and shellfish (Harada 1995). Severe neuromotor and cognitive impairments resembling cerebral palsy were observed in infants exposed prenatally (Harada 1995). Patients diagnosed with congenital Minamata disease showed a common set of signs which included severe cognitive impairments, primitive reflex, cerebellar ataxia, disturbances in physical growth and nutrition, dysarthria (speech and vocalization impairment), limb deformities, hyperkinesia (restlessness), hypersalivation, strabismus (abnormal eye alignment), paroxysmal symptoms, and pyramidal symptoms (Harada 1995). Measurements of mercury in blood and hair were not made until several years following the period of most intense exposure and, therefore, do not provide reliable estimates of exposures that may have contributed to congenital Minamata disease. Methylmercury levels in umbilical cord tissue of congenital Minamata disease patients ranged from 0.15 to 4.65 µg Hg/g dry weight (Harada et al. 1999). Long-term follow-up of congenital Minamata disease patients have observed neuromotor and cognitive impairments as adults, including hand tremor,

postural sway, low scores on cognitive processing speed, and more rapid declines in cognitive function with age (Iwata et al. 2016; Yorifuji et al. 2015, 2016, 2018). The follow-up studies have included small numbers of subjects (<20), limiting the power to associate clinical outcomes with measures of exposure. In a study of 22 congenital Minamata disease patients (age range 42–57 years), low performance on the digit symbol-coding test of the Wechsler Adults Intelligent Scale III were observed in subjects from pregnancies in which cord tissue methylmercury levels ranged from 0.1 to 2 µg Hg/g dry weight (Yorifuji et al. 2015). In a study of 18 congenital Minamata disease patients (mean age 50 years), low scores on tests of fine motor control were observed in subjects from pregnancies who had a mean umbilical cord tissue level of 0.7 µg Hg/g dry weight (Yorifuji et al. 2016).

Iraq. An outbreak of methylmercury poisoning occurred in Iraq in 1971–1972 as a result of widespread consumption of wheat that had been treated with a methylmercuric fungicide (Al-Mufti et al. 1976; Bakir et al. 1973; Clarkson et al. 1976). Approximately 6,500 cases of mercury poisoning occurred, with approximately 459 related deaths (Clarkson et al. 1976). Sixty-five days after exposure, blood mercury levels in poisoning cases ranged from 10 to 3,000 µg Hg/L (Clarkson et al. 1976). Cases of neurological abnormalities in infants exposed prenatally were reported which included impaired motor function, hyperreflexia, and delayed attainment of development milestones (walking, speech) and, at the highest exposure levels, seizures (Amin-Zaki et al. 1974, 1978, 1981; Marsh et al. 1987). Blood mercury levels in infant cases ranged from approximately 10 to 1,600 µg Hg/L (Amin-Zaki et al. 1981). Prenatal exposures were reconstructed from segmental analysis of single maternal hair strands and used to derive prenatal dose-response relationships for neurodevelopmental outcomes (Cox et al. 1989; Crump et al. 1995; Marsh et al. 1987). Cox et al. (1989) constructed prenatal mercury dose response models based on observations of 83 mother-infant pairs (Marsh et al. 1987). The dose metric used in these models was the estimated maximum hair mercury level during gestation. Outcome metrics were attainment of developmental milestones (age of walking) or scores from a clinical examination for signs of neurological abnormalities (e.g., muscle tone, reflexes). Based on a threshold model (“hockey-stick” model), Cox et al. (1989) concluded that the best estimate of the threshold for delayed walking (not walking by age 18 months) was 7.3 µg Hg/g hair (95% CL: 0, 13.6). However, confidence limits on the threshold estimate were sensitive to the estimated background response (probability of delay in walking when there is no prenatal exposure to mercury). For the upper 95% limit on the estimated background response (0.04), the threshold was estimated to be 9 µg Hg/g (95% CL: 4, 190). The best estimate of the threshold for an abnormal score on neurological examination (score >3 of 11) was 10 µg Hg/g (95% CL: 9, 287). Based on a logit model applied to the same data, hair mercury levels of 5 and 50 µg Hg/g were associated with excess risks of 2.5 and 19%, respectively, for delayed walking, and 2.3 and 13%, respectively for

abnormal neurological signs (Cox et al. 1989). Data from 81 mother-infant pairs were analyzed using an outcome metric that was a composite score for delayed walking (age >18 months), delayed talking (age >24 months), and neurological signs (score >3 of 11; Marsh et al. 1987). An analysis of covariance showed an increase in composite score with increasing hair mercury levels (range 1–674 µg Hg/g) with a higher slope for males compared to females. In males, when stratified by maximum prenatal hair mercury, scores were 2.6-fold higher in children from pregnancies in which hair mercury ranged from 23 to 72 µg Hg/g (score 1.14), compared to pregnancies in which hair mercury was 1 µg Hg/g (score 0.43).

Crump et al. (1995) utilized data on 81 mother-infant pairs (Marsh et al. 1987) to estimate BMDs for delayed walking (age >18 months), delayed talking (age >24 months), and neurological signs score (score >3 of 11). The lower confidence limits on the BMDs (BMDLs) were 73 µg Hg/g for delayed walking, 54 µg Hg/g for delayed talking, and 80 µg Hg/g for neurological signs, when the background response probability was 0.05 and the quantal BMR was 0.1. The large differences in the dose-response thresholds estimated by Cox et al. (1989) and Crump et al. (1995) demonstrate the importance of model selection in estimating a statistically based NOAEL from these data.

Seychelle Islands. Two prospective studies of methylmercury and neurodevelopmental outcomes have been conducted in the Republic of Seychelles: the Seychelles Child Development Study (SCDS) and the Seychelles Child Development Nutrition Study (SCDNS). A summary of the major outcomes of the Seychelles studies are presented in Table 2-40. Oceanic fish consumption, typically consumed at every meal, is the major contributor to methylmercury exposure in the Seychelle population. Maternal fish intake in the SCDNS cohort was estimated from a food use questionnaire and 4-day diet diary. The median was 77 g Hg/day (range 0–346 g Hg/day) (Davidson et al. 2008b). Marine mammals were not consumed and there were no other local sources of PCB exposure (Shamalaye et al. 2004). PCBs were not detectable in cohort serum samples (Davidson et al. 1998).

Table 2-40. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Prospective Birth Cohorts in the Seychelle Islands

Reference, age at follow-up	Biomarker	Outcome evaluated	Result[a]
SCDS (listed in order of follow-up age)			
Myers et al. 1995 SCDS follow-up at age 6.5 months (n=779)	HHg median Maternal: 5.9 µg/g	DDST	0 (HHg, maternal)
Davidson et al. 1999 SCDS follow-up at age 6.5 months (n=740)	HHg median Maternal: 5.9 µg/g	FTII (2 metrics)	0 (HHg, maternal) 0 (HHg, maternal with maternal x caregiver intelligence and x family income) [b]
Axtell et al. 1998; Myers et al. 1997 SCDS follow-up at age 19 months (n=738)	HHg median Maternal: 5.8 µg/g	Age of talking	0 (HHg, maternal)
		Age of walking	0 (HHg, maternal) ↑ (HHg, maternal ≤7 µg/g) ↓ (HHg, maternal >7 µg/g)
Davidson et al. 1995, 1999 SCDS follow-up at age 19 months (n=738)	HHg median Maternal: 5.9 µg/g	BSID MDI	0 (HHg, maternal) ↑ (HHg, maternal with caregiver intelligence and x family income)[b]
		BSID PDI	0 (HHg, maternal)
Davidson et al. 1995, 1999 SCDS follow-up at age 29 months (n=736)	HHg median Maternal: 5.9 µg/g	BSID MDI	0 (HHg, maternal)
		BSID PDI	0 (HHg, maternal)
		BSID IBR	0 (HHg, maternal) 0 (HHg, maternal with maternal x caregiver intelligence and x family income)[b]
Axtell et al. 2000; Davidson et al. 1998 SCDS follow-up at age 66 months (n=711)	HHg mean Maternal: 6.8 µg/g Child (age 66 months): 6.5 µg/g	BVMGT	0 (HHg, maternal) 0 (HHg, child, females) ↓ (HHg, child, males)
		CBCL	0 (HHg, maternal) ↑ (HHg, maternal ≤15 µg/g) ↓ (HHg, maternal >15 µg/g) 0 (HHg, child)
		MSCA GCI	0 (HHg, maternal) 0 (HHg, child) ↑ (HHg, child ≤10 µg/g) ↓ (HHg, child >10 µg/g)
		PLS	↑ (HHg, maternal) ↓ (HHg, maternal ≤10 µg/g) ↑ (HHg, maternal >10 µg/g) ↑ (HHg, child)
		WJTA	0 (HHg, maternal) ↑ (HHg, child)

Table 2-40. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Prospective Birth Cohorts in the Seychelle Islands

Reference, age at follow-up	Biomarker	Outcome evaluated	Result[a]
Myers et al. 2000 SCDS follow-up at age 66 months (n=711)	HHg mean Maternal: 6.8 µg/g Child (age 66 months): 6.5 µg/g	CBCL (10 subscales)	0 (HHg, maternal) 0 (HHg, child)
Palumbo et al. 2000 SCDS follow-up at age 66 months (n=711)	HHg mean Maternal: 6.8 µg/g Child (age 66 months): 6.5 µg/g	MSCA verbal	0 (HHg, maternal)
		MSCA perceptual	0 (HHg, maternal) 0 (HHg, child)
		MSCA memory	0 (HHg, maternal) ↑ (HHg, child)
		MSCA quantitative	0 (HHg, maternal) 0 (HHg, child)
		MSCA motor	0 (HHg, maternal) 0 (HHg, child)
Strain et al. 2021 SCDS follow-up at age 7 years (n=1,237)	HHg mean Maternal: 3.91 µg/g	BNT	0 (HHg, maternal)
		CBCL	0 (HHg, maternal)
		CELF-5	0 (HHg, maternal)
		KBIT-2	0 (HHg, maternal)
		SCQ	0 (HHg, maternal)
		SRS-2	0 (HHg, maternal)
		WJTA-III	0 (HHg, maternal)
Myers et al. 2003; Huang et al. 2005 SCDS follow-up at age 9 years (n=643)	HHg mean Maternal: 6.9 µg/g	BOT	0 (HHg, maternal)
		BNT	0 (HHg, maternal)
		CVLT	0 (HHg, maternal)
		CBCL	0 (HHg, maternal)
		CTRS (hyperactivity index)	↓ (HHg, maternal) ↑ (HHg, maternal, ≤5 µg/g) ↓ (HHg, maternal, >5 µg/g)
		Finger tapping	0 (HHg, maternal)
		GPB (dominant hand)	0 (HHg, maternal) ↓ (HHg, maternal, ≤10 µg/g) ↑ (HHg, maternal, >10 µg/g)
		GPB (non-dominant hand)	↑ (HHg, maternal, males) ↓ (HHg, maternal, ≤5 µg/g, males) ↑ (HHg, maternal, >5 µg/g, males) 0 (HHg, maternal, females)
		HAPDT	0 (HHg, maternal)
		Trail making	0 (HHg, maternal)
		VMI	0 (HHg, maternal)

Table 2-40. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Prospective Birth Cohorts in the Seychelle Islands

Reference, age at follow-up	Biomarker	Outcome evaluated	Result[a]
		WJTA	0 (HHg, maternal)
		WISC-III FSIQ	0 (HHg, maternal)
		WRAML	0 (HHg, maternal)
van Wijngaarden et al. 2009 SCDS follow-up at age 9 years (n=643)	HHg mean Maternal: 6.9 µg/g (as reported by Myers et al. 2003)	OR for total abnormal cases any domain (1st or 99th test score)	0 (maternal Hg)
		OR for abnormal cognition cases	0 (maternal Hg)
		OR for abnormal motor function cases	0 (maternal Hg)
Davidson et al. 2010 SCDS follow-up at age 9 years (n=437–456 for academic achievement scores; 225 for SACMEQ)	HHg mean Maternal: 6.89 µg/g Child (age 9 years): 6.09 µg/g	Mathematics score	0 (HHg, maternal) ↑ (HHg, child; female) 0 (HHg, child; male)
		Social studies score	0 (HHg, maternal) ↓ (HHg, child)
		English language score	0 (HHg, maternal) 0 (HHg, child)
		French language score	↓ (HHg, maternal) ↑ (HHg, child; female) 0 (HHg, child; male)
		Kreol language score	0 (HHg, maternal) 0 (HHg, child)
		Science score	0 (HHg, maternal) 0 (HHg, child)
		SACMEQ: Reading comprehension	0 (HHg, maternal) ↑ (HHg, child; female) ↓ (HHg, child; male)
		SACMEQ: Mathematics	0 (HHg, maternal) 0 (HHg, child; female) ↓ (HHg, child; male)
Davidson et al. 2006a SCDS longitudinal analysis, age 19 months to 9 years (n=738, 736, 735, 711, and 643 at 19, 29, 66, and 107 months, respectively)	HHg mean Maternal: 6.8 µg/g Child (age 66 months): 6.5 µg/g Child (age 107 months): 6.1 µg/g	Global cognition based on BSID MDI, MSCA GCI, WISC-III FSIQ, WJTA, WRAML	0 (HHg, maternal) ↑ (HHg, child, males at 66 months) ↓ (HHg, child, females at 107 months)

Table 2-40. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Prospective Birth Cohorts in the Seychelle Islands

Reference, age at follow-up	Biomarker	Outcome evaluated	Result[a]
van Wijngaarden et al. 2013 SCDS follow-up at age 10 years (n=537)	HHg mean Maternal: 6.8 µg/g	TSRSS for ASD (5 metrics)	0 (HHg, maternal)
Davidson et al. 2008a SCDS follow-up at age 11 years (n=613)	HHg mean Maternal: 6.83 µg/g Child (age 11 years): 6.97 µg/g	BVMGT	0 (HHg, maternal) 0 (HHg, child)
Davidson et al. 2010 SCDS follow-up at age 17 years (n=351–384)	HHg mean Maternal: 6.89 µg/g Child (age 17 years): 8.00 µg/g	Seychelles academic achievement scores (6 subjects)	0 (HHg, maternal) 0 (HHg, child)
Davidson et al. 2011; Huang et al. 2018 SCDS follow-up at age 17 years (n=462)	HHg mean Maternal: 6.89 µg/g Child (age 17 years): 7.98 µg/g	CANTAB (4 tests)	↓ (HHg, maternal; IED shift) ↓ (HHg, maternal, ≤12 µg/g; IED shift) 0 (HHg, maternal; all other tests) 0 (HHg, child)
		CVLT (2 tests)	0 (HHg, maternal) ↑ (HHg, maternal, ≤8 µg/g; calculation) 0 (HHg, child)
		WJTA (6 tests)	↑ (HHg, maternal; calculation) ↑ (HHg, maternal, ≤15 µg/g; calculation) 0 (HHg, maternal, >15 µg/g; calculation) ↓ (HHg, child; passage comprehension)
		Behavioral endpoints (6 endpoints)	↓ (HHg, maternal; substance use, male) ↓ (HHg, maternal; incidents/year) ↑ (HHg, maternal; referrals/year) 0 (HHg, child)
Orlando et al. 2014 SCDS follow-up at age 19 years (n=517)	HHg mean Maternal: 6.89 µg/g Child (age 19 years): 10.32 µg/g	Pure tone hearing	0 (HHg, maternal)
		Auditory brainstem response	0 (HHg, maternal)
		Otoacoustic emissions	0 (HHg, maternal)

Table 2-40. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Prospective Birth Cohorts in the Seychelle Islands

Reference, age at follow-up	Biomarker	Outcome evaluated	Result[a]
van Wijngaarden et al. 2017 SCDS follow-up at age 22 years (n=571)	HHg mean Maternal: 6.83 µg/g Child (age 22 years) 5.17 µg/g	CANTAB (7 tests, 23 metrics)	↑ (HHg, maternal, reaction time) ↑ (HHg, maternal, delayed match to sample) 0 (HHg, maternal, all other tests) ↑ (HHg, child, IED shift) 0 (HHg, child, all other tests)
		BNT	0 (HHg, maternal) 0 (HHg, child)
		Profile of mood states (2 metrics)	0 (HHg, maternal) 0 (HHg, child)
		Healthy behavior (4 metrics)	0 (HHg, maternal) 0 (HHg, child)
van Wijngaarden et al. 2017 SCDS follow-up at age 24 years (n=577)	HHg mean Maternal: 6.80 µg/g Child (age 24 years): 4.95 µg/g	Stroop interference	0 (HHg, maternal) 0 (HHg, child)
		Barkley ADHD rating (4 metrics)	0 (HHg, maternal 0 (HHg, child)
		Visual attention (5 metrics)	0 (HHg, maternal) 0 (HHg, child)
		Auditory attention (5 metrics)	↓ (HHg, maternal, mean response time) 0 (HHg, child)
		Finger tapping (2 metrics)	0 (HHg, maternal) 0 (HHg, child)
		Healthy behavior (3 metrics)	0 (HHg, maternal) 0 (HHg, child)
SCDNS			
Davidson et al. 2008b SCDNS follow-up at age 5 months (n=215)	HHg mean Maternal: 5.7 µg/g	FTII (2 metrics)	0 (HHg, maternal)
		VEXP (2 metrics)	0 (HHg, maternal)
Davidson et al. 2008b SCDNS follow-up at age 9 months (n=226)	HHg mean Maternal: 5.7 µg/g	FTII (2 metrics)	0 (HHg, maternal)
		VEXP (2 metrics)	0 (HHg, maternal)
		BSID MDI	0 (HHg, maternal)
		BSID PDI	0 (HHg, maternal)
Strain et al. 2015 SCDNS follow-up at age 20 months (n=1,265)	HHg mean Maternal: 3.92 µg/g	BSID MDI	0 (HHg, maternal)
		BSID PDI	0 (HHg, maternal)
		CDI	0 (HHg, maternal)
		BSID IBR	0 (HHg, maternal)

Table 2-40. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Prospective Birth Cohorts in the Seychelle Islands

Reference, age at follow-up	Biomarker	Outcome evaluated	Result[a]
Davidson et al. 2008b SCDNS follow-up at age 25 months (n=218)	HHg mean Maternal: 5.7 µg/g	DSA (4 metrics)	0 (HHg, maternal)
Davidson et al. 2008b SCDNS follow-up at age 30 months (n=228)	HHg mean Maternal: 5.7 µg/g	BSID MDI	0 (HHg, maternal)
		BSID PDI	↓ (HHg, maternal)
Strain et al. 2012 SCDNS follow-up at age 5 years (n=225)	HHg mean Maternal: 5.7 µg/g	Finger tapping (2 metrics)	0 (HHg, maternal)
		PLS (3 metrics)	0 (HHg, maternal)
		WJTA	0 (HHg, maternal)
		KBIT (2 metrics)	0 (HHg, maternal)
		CBCL	0 (HHg, maternal)

[a]Interpretation of neurobehavioral test scores:
Age of talking or walking: increased age = delay in development
Barkley ADHD: higher score = lower performance
BNT: higher score = higher performance
BOT: higher score = higher performance
BVMGT: higher score = lower performance
CANTAB: higher score = higher performance
CVLT: higher score = higher performance
FTII: higher score = higher performance
BSID IBR: higher score = higher performance
BSID MDI: higher score = higher performance
BSID PDI: higher score = higher performance
BVMGT: higher score = lower performance
CBCL: higher score = lower performance
CDI: higher score = higher performance
CELF-5: higher score = higher performance
CTRS: higher score = lower performance
CVLT: higher score = higher performance
DDST: milestones evaluated against a standard; below standard = delayed development
DSA: higher score = higher performance
Finger tapping: higher score = higher performance
GPB: higher score = lower performance
HAPDT: higher score = higher performance
KBIT-2: higher score = higher performance
MSCA: higher score = higher performance
PLS: higher score = higher performance
SCQ: higher score = higher performance
SRS-2: higher score = higher performance
Stroop interference: higher score = higher performance
TSRSS: higher score = higher performance
VEXP: higher score = higher performance
WJTA: higher score = higher performance
WRAML: higher score = higher performance

Table 2-40. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Prospective Birth Cohorts in the Seychelle Islands

Reference, age at follow-up	Biomarker	Outcome evaluated	Result[a]

[b]This study examined potential effect modification from caregiver intelligence, family income, and home environment on the association between maternal hair mercury and neurodevelopmental outcomes.

↑ = positive association; ↓ = inverse association; 0 = no association; x represents interaction; ADHD = Attention Deficit/Hyperactivity Disorder; ASD = autism spectrum disorder; BNT = Boston naming test; BOT = Bruininks-Oseretsky Test of Motor Proficiency; BSID = Bayley Scales of Infant Development; BVMGT = Bender Visual Motor Gestalt Test; CANTAB = Cambridge Neuropsychological Test Automated Battery; CBCL = Child Behavior Checklist; CDI = MacArthur-Bates Communicative Development Inventories; CELF-5 = Clinical Evaluation of Language Fundamentals; CTRS = Connors' Teacher Rating Scale; CVLT = California Verbal Learning Test; DDST = Denver Developmental Screening Test; DSA = Delayed Spatial Alternation; FSIQ = full scale intelligence quotient; FTII = Fagan Test of Infant Intelligence; GPB = grooved pegboard; HAPDT = Haptic Discrimination Test; HHg = hair mercury; IBR = Infant Behavior Record; IED = Intradimensional-extradimensional discrimination; KBIT = Kauffman Brief Intelligence Test; MDI = BSID Mental Development Index; MSCA GCI = McCarthy Scales of Children's Abilities Global Cognition Index; OR = odds ratio; PDI = BSID Psychomotor Development Index; PLS = Preschool Language Scale; SACMEQ = Southern and Eastern African Consortium for Monitoring Educational Quality; SCDNS = Seychelles Child Development Nutrition Study; SCDS = Seychelles Child Development Study; SCQ = Social Communication Questionnaire; TSRSS = Total Social Responsiveness Social Scores; VEXP = Visual Expectation Paradigm; VMI = Visual Motor Integration; WISC-III = Wechsler Intelligence Scales for Children, 3rd edition; WJTA = Woodcock-Johnson Test of Achievement; WRAML = Wide Range Assessment of Memory and Learning

The SCDS included a cohort of 779 mother-infant pairs (6 months post-partum), recruited in 1989–1990. Neurodevelopmental outcomes were initiated at age 6 months and have continued through age 24 years (Myers et al. 1995; van Wijngaarden et al. 2017). The primary methylmercury exposure metric has been average maternal gestational hair mercury level. Methylmercury accounted for >80% of total mercury in hair (Cernichiari et al. 1995). Annual median maternal hair mercury levels measured over the period 1986–1989 ranged from 5.9 to 8.2 μg Hg/g; the highest observed value was 36 μg Hg/g (Cernichiari et al. 1995). The main cohort followed from age 6 months and later had a median prenatal maternal level of 5.9 μg Hg/g (range 0.5–26.7 g Hg/day) (Myers et al. 1995). Approximately half of the maternal hair mercury levels were ≤6 μg Hg/g, while the highest 15% (approximately 95 women) were >12 μg Hg/g; therefore, power to discern significant associations was higher at hair mercury levels <12 μg Hg/g. Neurodevelopmental outcomes were assessed using a variety of tests, which changed as the children aged. These included tests of learning and memory, visual-motor function, auditory function, developmental milestones (e.g., age of waking, age of talking), intellectual achievement, and behavior (e.g., signs of attention deficit/hyperactivity disorder or autism spectrum disorder; referrals for substance use, mental health, antisocial behavior, or self-injury). Outcome associations were adjusted for covariates that included (in most studies): child sex, birth weight, birth order, gestational age, medical history, and breastfeeding; maternal age, alcohol and tobacco use, and medical history; and parental education,

caregiver general intelligence (Raven's Progressive Matrices), family income, family language, home learning, and social stimulation (Home Observation Measurement of the Environment; HOME score).

In addition to the SCDS, a second prospective study, the SCDNS, evaluated associations between prenatal mercury exposure (maternal hair mercury), nutrition, and cognitive outcomes (Davidson et al. 2008b; Strain et al. 2008). This study included 300 pregnant women recruited in 2001, with follow-up of infants and children from age 5 months to age 5 years. As in the SCDS, the highest hair mercury during pregnancy was used as the exposure metric. Mean prenatal maternal HHg level was 5.7 µg/g (range 0.2–18.5 µg/g). Mean maternal fish consumption was 77 g/day (range 0–346 g/day), estimated based on a food use questionnaire and 4-day diet recall (Davidson et al. 2008b). Prenatal maternal nutritional variables associated with child development were assessed in regression models of mercury exposure and developmental outcomes. These included arachidonic acid (AA), choline, Ω-3 and Ω-6 LCPUFAs, docosahexaenoic acid (DHA), thyroid hormone status, and iron status. Neurodevelopmental outcomes were assessed from tests of learning and memory, visual-motor function, and behavior.

Seychelles Child Development Study (SCDS). In general, the SCDS has not found consistent evidence for associations between exposure to methylmercury and neurodevelopmental outcomes at any age thus far studied. This conclusion is supported by cross-sectional follow-ups of the cohort from ages 6.5 months to 24 years (Davidson et al. 1995, 1998, 1999, 2008a, 2010, 2011; Huang et al. 2005; Myers et al. 1995 1997, 2000, 2003; Orlando et al. 2014; Palumbo et al. 2000; van Wijngaarden et al. 2009, 2013, 2017), longitudinal analyses of individual outcome metrics (Axtell et al. 1998; Davidson et al. 1998; Myers et al. 1997), and longitudinal analysis of metrics of global cognition based on aggregation of outcome metrics (Davidson et al. 2006a). Accounting for error in measuring hair mercury levels (and other covariates) had no appreciable effect on dose-response models assessed at age 66 months (Huang et al. 2003).

Although linear regression models consistently found no association between exposure (maternal or child hair mercury) and cognitive development, nonlinear models of cognitive test scores suggested that performance improved or declined in association with prenatal maternal hair mercury or child hair mercury, depending on the hair level (Axtell et al. 1998, 2000; Davidson et al. 1998, 2006a; Huang et al. 2005, 2007, 2018; Myers et al. 1997, 2003). For some outcomes, performance declined at lower hair mercury levels (e.g., ≤7 µg Hg/g), but improved at higher levels; and, for some outcomes, the opposite pattern was observed. At age 66 months, lower performance was not evident in a subgroup of the cohort that had a mean hair mercury level of 15.3 µg Hg/g (>85th percentile) (Davidson et al. 1998). It is uncertain if these nonlinear patterns reflect actual dose-level effects or differential statistical power across

the hair mercury range; or, possibly, random outcomes from the numerous (>20) tests evaluated (Axtell et al. 2000; Davidson et al. 2006b; Huang et al. 2005, 2007). Age of walking increased with increasing prenatal maternal hair mercury over the range of 1–7 µg Hg/g, however; the effect size was <1 day and the association was not evident at higher levels of hair mercury (Axtell et al. 1998). Aggregating scores of cognitive performance into metrics of global cognitive function (Davidson et al. 2006a) or dichotomizing test scores into a binomial metric (benchmark response) also revealed no associations in cognitive development and prenatal maternal hair mercury <20 µg Hg/g (Crump et al. 2000; van Wijngaarden et al. 2006, 2009).

Further complicating the interpretation of associations with mercury exposure were interactions between social variables (e.g., HOME score, caregiver intelligence, SES) and prenatal mercury exposure (Davidson et al. 2004; Huang et al. 2007, 2018; Love et al. 2017). For example, when assessed at age 9 years, performance on tests of motor skills improved in association with increasing maternal mercury in approximately half of children who had an average HOME score; however, performance declined in response to hair mercury in children who had below average HOME scores (Huang et al. 2007). Given the large number of potential effect modifiers on the cognitive outcomes assessed, the possibility of non-homogeneous susceptibility to methylmercury exposures has been considered in the SCDS (Engstrom et al. 2016; Huang et al. 2007, 2018; Love et al. 2017). The number of maternal mercury amalgam restorations was not associated with performance on tests of cognitive abilities (Watson et al. 2011).

BMD modeling of data from follow-ups up to age 66 months (Crump et al. 2000) and 9 years (van Wijngaarden et al. 2006) evaluated dose-response models for more than 20 cognitive performance endpoints. Based on endpoints measured in follow-ups through age 66 months, the mean BMDL for 144 endpoints was 25 µg Hg/g (range 19–30 µg Hg/g) maternal hair mercury, when the background response probability was 0.05 and the quantal benchmark response was 0.1 (Crump et al. 2000). Based on the follow-up at age 9 years, the mean BMDL for 26 endpoints was 20.1 µg Hg/g (range 17.2–22.5 µg Hg/g) hair mercury (van Wijngaarden et al. 2006).

Seychelles Child Development Nutrition Study (SCDNS). The SCDNS found an association between increasing maternal hair mercury and decreasing psychomotor development index (PDI of the Bayley Scales of Infant Development) when assessed at age 30 months (Davidson et al. 2008b). However, the mercury association was modified by an interaction with maternal omega-3 fatty acid status (Strain et al. 2008). Increasing maternal serum omega-3 levels (or decreasing omega-6/omega-3 ratio) was associated with increases in PDI at age 9 months and the association persisted when maternal hair mercury was

included in the model. At age 30 months, the association between PDI and maternal omega-3 levels was not evident (Strain et al. 2008). At age 5 years, increasing maternal DHA and Ω-3 LCPUFA continued to be associated with improved performance on the preschool language scale, whereas no association was found with hair mercury (Strain et al. 2012). Analysis of the data from the follow-ups at ages 9 and 30 months showed that increasing maternal DHA levels were associated with improved PDI and mental development index (MDI) scores; however, the benefit of increasing maternal DHA (increasing scores) was attenuated with increasing maternal hair mercury. Neurobehavioral endpoints were re-examined at age 7 years in a second cohort from the SCDNS (Strain et al. 2021). The study did not find associations between maternal mercury hair levels (mean 2.91 µg/g; range 0.01, 31.66) and scores of tests that evaluated executive function, cognition, and linguistic skills. The study found improved scores in association with maternal serum omega-3 levels and no interaction between serum omega-3 levels and maternal hair mercury. These observations suggest that nutritional benefits of the relatively high fish consumption of the cohort may have weakened possible associations between measured neurodevelopmental outcomes and prenatal mercury exposure.

Faroe Islands. A prospective study of methylmercury and neurodevelopmental outcomes has been conducted in the Faroe Islands (Faroes study). A summary of the major outcomes of the Faroes study are presented in Table 2-41. Consumption of marine fish and mammals (e.g., pilot whale) is the major contributor to methylmercury exposure in the Faroes population (Grandjean et al. 1992). The Faroes study included a cohort of 1,022 singleton births pairs recruited in 1986–1987. Assessment of neurodevelopmental outcomes began with pediatric observations at age 2 weeks and cognitive function testing conducted periodically, with the most recent follow-up at age 22 years (Steuerwald et al. 2000; Oulhote et al. 2017b). The primary methylmercury prenatal exposure metric has been total mercury in cord blood, which was predominantly (>80%) methylmercury (Grandjean et al. 1992). Maternal hair mercury was also measured and used as an exposure metric in some analyses. The median cord blood mercury concentration was 24 µg Hg/L and interquartile range (IQR) was 13–40 µg Hg/L; approximately 25% of the cord mercury levels were >40 µg Hg/L (Grandjean et al. 1992). Cord blood mercury levels (µg Hg/L) were approximately 5 times maternal hair mercury levels measured at parturition (median 4.5 µg Hg/g, IQR: 2.5, 7.7) (Grandjean et al. 1992). Based on a dietary survey, the average daily consumption in the Faroe Island population was 72 g fish/day and 12 g whale/day (Grandjean et al. 1992). Mercury levels in blood and hair were correlated with the number of fish meals per week and number of whale meals per week and were not correlated with number of mercury amalgam dental restorations (Grandjean et al. 1992; Weihe et al. 1996). Although both fish and whale consumption correlated with blood mercury levels, the largest fraction of the variance in blood and hair mercury levels was explained

by variance in consumption of pilot whale, whereas fish consumption was a less important explanatory variable.

Table 2-41. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Prospective Birth Cohort in the Faroe Islands

Reference (listed in order of age at follow-up)	Biomarker	Outcome evaluated	Result[a]
Steuerwald et al. 2000 Follow-up at age 2 weeks (n=182)	BHg geometric mean Cord: 20.4 µg/L	Neurologic optimality score	↓ (BHg, cord)
Grandjean et al. 1995 Follow-up at age 12 months (n=583)	BHg median Cord: not reported HHg geometric mean: Maternal: 4.47 µg/g Child (age 12 months): 0.9–1.3 µg/g	Age of sitting	0 (BHg, cord) 0 (HHg, maternal) ↓ (HHg, child) ↓ (duration of nursing)
		Age of crawling	0 (BHg, cord) 0 (HHg, maternal) ↓ (HHg, child) ↓ (duration of nursing)
		Age of standing	0 (BHg, cord) 0 (HHg, maternal) ↓ (HHg, child) ↓ (duration of nursing)
Grandjean et al. 1997, 1998, 1999, 2003 Follow-up at age 7 years (n=917)	BHg geometric mean Cord: 22.9 µg/L HHg geometric mean Maternal: 4.27 µg/g Low-level mercury exposure considered maternal HHg <10 µg/g	VEPL	0 (BHg, cord)
		BAEPL	↑ (BHg, cord)
		Postural sway	0 (BHg, cord)
		HRV	0 (BHg, cord)
		NES FTT	↓ (BHg, cord) 0 (BHg, cord; low-level only)
		NES HECT	0 (BHg, cord) 0 (BHg, cord; low-level only)
		NES CPT (reaction time)	↑ (BHg, cord) ↑ (BHg, cord; low-level only)
		WISC-R (digit span)	↓ (BHg, cord) ↓ (BHg, cord; low-level only)
		WISC-R (similarities)	0 (BHg, cord) 0 (BHg, cord; low-level only)
		WISC-R (block design)	0 (BHg, cord) 0 (BHg, cord; low-level only)
		BVMGT (copy)	0 (BHg, cord) 0 (BHg, cord; low-level only)
		BVMGT (reproduction)	0 (BHg, cord) ↓ (BHg, cord; low-level only)
		BNT	↓ (BHg, cord) ↓ (BHg, cord; low-level only)

Table 2-41. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Prospective Birth Cohort in the Faroe Islands

Reference (listed in order of age at follow-up)	Biomarker	Outcome evaluated	Result[a]
		CVLT	↓ (BHg, cord) ↓ (BHg, cord; low-level only)
		NVAPMS	0 (BHg, cord) 0 (BHg, cord; low-level only
		CBCL	0 (BHg, cord)
Yorifuji et al. 2013 Follow-up age at 7 years (n=139)	BHg geometric mean Cord: 22.8 μg/L HHg geometric mean Maternal: 4.6 μg/g	VEPL	0 (BHg, cord) ↑ (HHg, maternal)
Grandjean et al. 2014 Follow-up at age 7 years (n=694)	BHg geometric mean Cord: 22.3 μg/L Child (age 7 years): 8.36 μg/L	NES FTT	↓ (BHg, cord) 0 (BHg, child)
		NES HECT	↑ (BHg, cord) 0 (BHg, child)
		NES CPT (reaction time)	↑ (BHg, cord) 0 (BHg, child)
		WISC-R (digit span)	0 (BHg, cord) 0 (BHg, child)
		WISC-R (similarities)	0 (BHg, cord) 0 (BHg, child)
		WISC-R (block design)	0 (BHg, cord) 0 (BHg, child)
		BVMGT (copy)	0 (BHg, cord) 0 (BHg, child)
		BVMGT (reproduction)	0 (BHg, cord) ↓ (BHg, child)
		BNT	↓ (BHg, cord) 0 (BHg, child)
		CVLT	0 (BHg, cord) 0 (BHg, child)
Debes et al. 2006 Follow-up at age 14 years (n=860)	BHg geometric mean Cord: 22.5 μg/L HHg geometric mean Maternal: 4.21 μg/g	NES FTT	↓ (BHg, cord) ↓ (HHg, maternal)
		CATSYS FTT (reaction time)	0 (BHg, cord) ↑ (HHg, maternal)
		NES CPT (reaction time)	↑ (BHg, cord) ↑ (HHg, maternal)
		Digit span	0 (BHg, cord) 0 (HHg, maternal)
		Spatial span	↑ (BHg, cord) ↑ (HHg, maternal)

Table 2-41. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Prospective Birth Cohort in the Faroe Islands

Reference (listed in order of age at follow-up)	Biomarker	Outcome evaluated	Result[a]
		ST-BI copying	0 (BHg, cord) 0 (HHg, maternal)
		WISC-R (block design)	0 (BHg, cord) 0 (HHg, maternal)
		WISC-R (similarities)	0 (BHg, cord) 0 (HHg, maternal)
		BNT	↓ (BHg, cord) 0 (HHg, maternal)
		CVLT	0 (BHg, cord) 0 (HHg, maternal)
Julvez et al. 2010; Debes et al. 2006 Follow-up at age 14 years (n=860)	BHg geometric mean Cord: 22.5 µg/L Child (age 7 years): 9.00 µg/L Child (age 14 years): 4.08 µg/L HHg geometric mean Maternal: 4.21 µg/g Child (age 7 years): 2.99 µg/g Child (age 14 years): 0.92 µg/g	NES CPT (reaction time during 1–2 minutes of testing)	0 (BHg, cord) 0 (BHg, child) 0 (HHg, maternal) 0 (HHg, child)
		NES CPT (reaction time during 3–6 minutes of testing)	↑ (BHg, cord) 0 (BHg, child) ↑ (HHg, maternal) 0 (HHg, child)
		NES CPT (reaction time during 7–10 minutes of testing)	↑ (BHg, cord) 0 (BHg, child) ↑ (HHg, maternal) 0 (HHg, child)
		NES CPT (reaction tine during 3–10 minutes of testing)	↑ (BHg, cord) 0 (BHg, child) ↑ (HHg, maternal) 0 (HHg, child)
Murata et al. 2004a Follow-up at age 14 years (n=859)	BHg geometric mean: Cord: 22.6 µg/L HHg median Maternal: 4.22 µg/g Child (age 14 years): 0.96 µg/g	BAEPL	↑ (BHg, cord) ↑ (HHg, maternal) ↑ (HHg, child)

Table 2-41. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Prospective Birth Cohort in the Faroe Islands

Reference (listed in order of age at follow-up)	Biomarker	Outcome evaluated	Result[a]
Debes et al. 2016 Follow-up at age 22 years (n=814)	BHg geometric mean Cord: 22.91 µg/L Child (age 22 years): 2.53 µg/L HHg geometric mean Maternal: 4.24 µg/g Child (age 22 years): 0.68 µg/g	WJTA (concept formation)	0 (BHg, cord) 0 (HHg, maternal)
		WJTA (synonyms, antonyms)	↓ (BHg, cord) ↓ (HHg, maternal)
		WJTA (numbers reversed)	0 (BHg, cord) 0 (HHg, maternal)
		WJTA (word memory)	0 (BHg, cord) 0 (HHg, maternal)
		WJTA (spatial)	0 (BHg, cord) 0 (HHg, maternal)
		WMS (spatial span)	0 (BHg, cord) 0 (HHg, maternal)
		WISC-R (block design)	0 (BHg, cord) 0 (HHg, maternal)
		CVLT	0 (BHg, cord) 0 (HHg, maternal)
		WFRT	0 (BHg, cord) 0 (HHg, maternal)
		RSPM	↓ (BHg, cord) ↓ (HHg, maternal)
		BNT	↓ (BHg, cord) 0 (HHg, maternal)
		NES CPT (reaction time)	0 (BHg, cord) 0 (HHg, maternal)
		NES (finger tapping)	0 (BHg, cord) 0 (HHg, maternal)

[a]Interpretation of neurobehavioral test scores:
Age of crawling, sitting or walking: increased age = delay in development
BAEPL: higher score = lower performance
BVMGT: higher score = lower performance
BNT: higher score = higher performance
CATSYS FTT: higher score = higher performance
CBCL: higher score = lower performance
CTRS: higher score = higher behavioral problems
CVLT: higher score = higher performance
Digit span: higher score = higher performance
HRV: higher score = lower performance
NES CPT: longer response time = lower performance
NES FTT: higher score = higher performance
NES HECT: higher score = higher performance
Neurologic optimality score: higher score = higher performance
NVAPMS: higher score = more negative mood

Table 2-41. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Prospective Birth Cohort in the Faroe Islands

Reference (listed in order of age at follow-up)	Biomarker	Outcome evaluated	Result[a]
Postural sway: higher score = lower performance RSPM: higher score = lower performance Spatial span: higher score = higher performance ST-BI copying: higher score = higher performance ST-BT block design: higher score = higher performance VEPL: higher score = lower performance WFRT: higher score = higher performance WISC-R: higher score = higher performance WJTA: higher score = higher performance WMS: higher score = higher performance			

↑ = positive association; ↓ = inverse association; 0 = no association; BAEPL = Brainstem auditory evoked potential latencies; BHg = blood mercury; BVMGT = Bender Visual Motor Gestalt Test; BNT = Boston naming test; CATSYS FTT = Catsys (equipment name) Finger Tapping Test; CBCL = Child Behavior Checklist; CTRS = Connors' Teacher Rating Scale; CVLT = California Verbal Learning Test; HHg = hair mercury; HRV = heart rate variability; NES CPT = Neurobehavioral Evaluation Systems Continuous Performance Test; NES HECT = Neurobehavioral Evaluation Systems Hand Eye Coordination Test; NES FTT = Neurobehavioral Evaluation Systems Finger Tapping Test; NVAPMS = Nonverbal Analogue Profile of Mood States; RSPM = Raven Standard Progressive Matrices; ST-BI = Stanford-Binet; VEPL = visual evoked potential latencies; WFRT = Warrington's Face Recognition Test; WISC-R = Wechsler Intelligence Scale for Children, Revised; WJTA = Woodcock-Johnson Test of Achievement; WMS = Wechsler Memory Scale

Neurodevelopmental outcomes were assessed using a variety of tests that changed as the children aged. These included tests of learning and memory, visual-motor function, auditory function, autonomic nervous function, developmental milestones (e.g., sitting, crawling, standing), intellectual achievement, and behavior. Outcome associations were adjusted for covariates that included (in most studies, depending on the outcome measured): child age, sex, and birth weight; breastfeeding; maternal age, alcohol and tobacco use, and medical history; and caregiver general intelligence (Raven's Progressive Matrices).

The Faroe Islands study found associations between prenatal (cord) blood mercury and decreasing performance on tests of cognitive function assessed at age 7 years (Grandjean et al. 1997, 1998, 2003, 2014), 14 years (Debes et al. 2006; Julvez et al. 2010), and 22 years (Debes et al. 2016). The associations were not consistently observed in all tests of cognitive function, and tended to cluster in domains of fluid reasoning (e.g., identifying rules for visual similarities and differences), comprehension and knowledge (e.g., naming, word synonyms and antonyms), decision and reaction speed, and motor coordination (Debes et al. 2016). For example, tests that consistently showed associations with cord mercury included the Boston Naming Test, Woodcock-Johnson test of synonyms and antonyms, Neurobehavioral Evaluation Systems Continuous Performance Test Hit Reaction Time latencies, and Neurobehavioral

Evaluation Systems Finger Tapping test. At ages 7 and 14 years, the size of the effect was estimated to be approximately 5–10% of the test score SD per doubling of cord blood mercury (Debes et al. 2006; Grandjean et al. 1997, 1999). Latencies of brainstem auditory evoked potentials measured at age 7 or 14 years increased in association with increasing prenatal or child hair mercury levels (Grandjean et al. 1997; Murata et al. 2002, 2004a). BMD modeling was applied to auditory evoked potentials observed at age 7 and 14 years (Murata et al. 2002, 2004a). At age 7 years, estimated BMDLs ranged from 7 to 9 µg Hg/g maternal hair mercury when the background response probability was 0.05 and the quantal BMR was 0.05; and from 12 to 14 µg Hg/g when the BMR was 0.1. At age 14 years, the BMDL was 10 µg Hg/g for BMR 0.1 and 0.05 background response. When the data from the 7-year follow-up of the Faroes study was combined with the data from the Madeira Portugal study (described below), the BMDL (BMR 0.1) ranged from 16 to 17 µg Hg/g hair (Murata et al. 2002).

A variety of factors have been explored to assess potential bias in the associations observed in the Faroe Islands study. Exposure measurement error based on estimation of biomarker imprecision was estimated to exceed laboratory measurement error, which would tend to attenuate dose-slopes and bias estimates of effect sizes downward (Grandjean and Budtz-Jorgensen 2007; Grandjean et al. 2004b). The observed associations with cognitive test outcomes persisted after excluding subjects who had large variability in hair mercury levels during pregnancy (Grandjean et al. 2003). Postnatal hair mercury levels correlated with duration of breastfeeding; however, breastfeeding was not a significant explanatory variable for cognitive test outcomes in the cohort (Grandjean et al. 1995; Jensen et al. 2005). Blood selenium levels correlated with blood mercury levels and whale consumption (Grandjean et al. 1992); however, prenatal selenium level (cord blood) was not a significant explanatory variable for cognitive test outcomes in the cohort (Choi et al. 2008b). Cord blood PCB concentration correlated with blood mercury levels; however, associations between cord blood mercury levels and cognitive tests scores persisted after adjustment for cord blood PCB concentrations (Grandjean et al. 1997). Adjustment for cord serum Ω-3 LCPUFA strengthened associations between prenatal mercury exposure and cognitive test scores or brainstem evoked potential latencies (Yorifuji et al. 2013). Improved cognitive performance was associated with higher aerobic capacity (maximum oxygen utilization; VO_{2Max}); however, the association was attenuated with increasing prenatal mercury exposure (Oulhote et al. 2017b).

North Island New Zealand. A prospective study of methylmercury exposure and neurodevelopmental outcomes was conducted in North Island, New Zealand (Kjellstrom et al. 1989). The original cohort consisted of 10,930 children and mother pairs recruited in 1978. Consumption of marine fish was the major contributor to methylmercury exposure in this population. The prenatal exposure metric was that

average total mercury in maternal hair during pregnancy. A subset of 935 high consumer subjects was selected based on consumption >3 fish meals per week. Hair mercury levels in this group ranged from 0.24 to 86.4 µg Hg/g. A high exposure subset of 73 high consumers was selected based on hair mercury level >6 µg Hg/g, from which 38 were tested at age 4 years, along with a set of 31 matched referents from mothers who consumed no more than one fish meal per week and matched for maternal ethnic group, age, residence time in New Zealand, tobacco smoking, and child birth date and sex. Assessment of neurodevelopmental outcomes occurred at age 4 and 6 years. Mean hair mercury was 8.8 µg Hg/g (range 6.0–86.4 µg Hg/g) in the high exposure group and 1.9 µg Hg/g (range 0.5–6.1 µg Hg/g) in the reference group. At age 4 years, children were assessed for performance on the Denver Developmental Screening Test (DDST; function, language, and personal-social behavior), Sheridan-Gardiner Letter Matching Test or Miniature Toy Test (vision), and tactile sensory function (touch, temperature), and the parent was surveyed with a questionnaire on child health and neurological signs (Kjellstrom et al. 1986). The OR for abnormal or questionable scores on the DDST at age 4 years (n=31, relative matched referents) was 6.5 ($p<0.005$). Performance of high-exposure children on vision and sensory function tests were not different from matched referents.

At age 6 years, 61 children in the high-exposure group were re-evaluated along with a set of 3 referent groups (n=58–60), each matched with the high-exposure group for maternal ethnic group, age, residence time in New Zealand, tobacco smoking, and child birth date and sex (Kjellstrom et al. 1989). Geometric mean maternal hair mercury level was 8.3 µg Hg/g (range 6–86 µg Hg/g) in the high-exposure group (follow-up Group 1). Hair mercury levels in the three referent groups were as follows: Group 2 (consumed >3 fish meals per week): 4.5 µg Hg/g (range 3– 6 µg Hg/g); Group 3 (consumed >3 fish meals per week): 2.0 µg Hg/g (range 0.1–3 µg Hg/g), and Group 4 (consumed ≤3 fish meals per week): 2.0 (µg Hg/g (range 0.1– 3 µg Hg/g). Geometric mean cord blood lead levels in the four groups were as follows: Group 1: 4.9 µg Pb/L (geometric standard deviation [GSD] 1.4); Group 2: 5.5 µg Pb/dL (GSD 1.3); Group 3: 6.5 µg Pb/dL (GSD 1.4); and Group 4: 5.7 µg Pb/dL (GSD 1.2). The study did not evaluate associations between blood lead levels and outcomes. Children were assessed for performance academic attainment, language development, motor coordination, intelligence, and behavior. Language development was assessed from performance on the Test of Language Development (TOLD; phonology, syntax, semantics) and Peabody picture vocabulary test (word knowledge). Intelligence was assessed using the McCarthy scales and Weschler Intelligence Scale for Children (WISC). Outcome associations were adjusted for significant covariates; variables explored included maternal ethnic group, age, smoking and alcohol consumption, residence time in New Zealand, social class, language spoken at home, siblings, duration of breastfeeding, and child sex, birth weight, maturity at birth, and Apgar score. Maternal hair

mercury was associated with lower scores on the TOLD spoken language quotient (β -5.48, p=0.0064), WISC full-scale IQ (β -4.41, p=0.019), and McCarthy perceptual scale (β -4.23, p=0.0034). When the high-exposure group (Group 1) was split into two maternal hair mercury categories, 6–<10 or ≥10 μg Hg/g, a larger fraction of variance in the TOLD and WISC tests were explained by the higher hair mercury category. Performance on TOLD spoken language quotient was inversely associated with hair mercury in the lower hair mercury category, whereas performance on both the TOLD spoken language quotient and WISC full scale was inversely associated with hair mercury ≥10 μg Hg/dL. Children scored as having an abnormal Denver test at age 4 years had lower WISC full scale IQ scores at age 6 years.

Crump et al. (1998) analyzed data on 237 children from the original North Island New Zealand study (age 6–7 years) to estimate BMDLs for cognitive outcomes. The cohort included 61 children born to mothers who consumed fish more than 3 times per week and who had hair mercury levels ≥6 μg Hg/g, matched to 176 control children from mothers who had hair mercury levels <6 μg Hg/g (matched for ethnicity, place of residence of mother, and maternal smoking). Outcome measures used in the analysis were the scores on a subset of 5 of the 26 tests administered in the original study: TOLD (spoken language quotient), Wechsler Intelligence Scale (performance and full sale IQ), and McCarthy Scales of Children's Abilities (perceptual and motor). Estimated BMDLs for the five tests ranged from 7.4 to 10 μg Hg/g when the background response probability was 0.05 and the quantal BMR was 0.1.

Nunavik region of arctic Canada. A prospective study of methylmercury exposure and neuro-developmental outcomes was conducted in the Nunavik region of arctic Canada (Nunavik study). A summary of the major outcomes of the Nunavik study are presented in Table 2-42. Consumption of marine fish and mammals was the major contributor to methylmercury exposure in the Nunavik population (Blanchet and Rochette 2008). The Nunavik study included a cohort of pregnant women recruited in 1995–2001, as part of the Nunavik Environmental Contaminants and Child Development Study (NECCDS), Arctic Cord Blood Monitoring Program (Muckle et al. 1998), and Nunavik Preschool Study (Saint-Amour et al. 2006). Assessment of neurodevelopmental outcomes began at age 6.5 months with periodic follow-ups, the most recent at age 11 years (Boucher et al. 2010, 2012a, 2012b, 2014, 2016; Despres et al. 2005; Ethier et al. 2012; Jacobson et al. 2015).

Table 2-42. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Prospective Birth Cohort in the Nunavik Region of Arctic Canada

Reference (listed in order of age at follow-up)	Biomarker	Outcome evaluated[a]	Result
Boucher et al. 2010 Follow-up at age 11 years (n=118)	BHg mean Cord: 21.5 µg/L Child (11 years): 4.69 µg/L	Auditory oddball test	0 (BHg, cord) 0 (BHg, child)
		Test EEG ERP amplitude	↓ (BHg, cord) 0 (BHg, child)
		Test EEG ERP latency	↑ (BHg, cord) 0 (BHg, child)
Boucher et al. 2012a Follow-up at age 11 years (n=196)	BHg mean Cord: 21.2 µg/L Child (11 years): 4.6 µg/L	Go/no go test	0 (BHg, cord) 0 (BHg, child)
		Test EEG ERP amplitude	0 (BHg, cord) 0 (BHg, child)
		Test EEG ERP latency	0 (BHg, cord) 0 (BHg, child)
Boucher et al. 2012b Follow-up at age 11 years (n=279)	BHg mean Cord: 21.6 µg/L Child (11 years): 4.6 µg/L	TRF internalizing	0 (BHg, cord) 0 (BHg, child)
		TRF externalizing	0 (BHg, cord) 0 (BHg, child)
		TRF attention	0 (BHg, cord) 0 (BHg, child)
		ADHD inattentive	↑ (BHg, cord)
		ADHD hyperactive-impulsive	↑ (BHg, cord)
		ODD or CD	0 (BHg, cord)
Boucher et al. 2014 Follow-up at age 6.5 and 11 months (n=94)	BHg mean Cord: 22.5 µg/L	FTII	0 (BHg, cord)
		A not B test	↓ (BHg, cord)
		BSID MDI	0 (BHg, cord)
		BSID PDI	0 (BHg, cord)
Boucher et al. 2016 Follow-up at age 11 years (n=265)	BHg mean Cord: 21.4 µg/L Child (11 years): 4.8 µg/L	SAFB	0 (BHg, cord) 0 (BHg, child)
		NES FTT	0 (BHg, cord) ↓ (BHg, child)
		ST-BI copying	0 (BHg, cord) 0 (BHg, child)
Despres et al. 2005 Follow-up at age 4–6 years (n=110)	BHg mean Cord: 22.2 µg/L	Reaction time	0 (BHg, cord)
		Postural sway	0 (BHg, cord)
		Alternating movements	0 (BHg, cord)
		Pointing tremor	↑ (BHg, cord)
Ethier et al. 2012 Follow-up at age 11 years (n=149)	BHg mean Cord: 21 µg/L Child (11 years): 5 µg/L	VEP amplitude	↑ (BHg, cord)
		VEP latency	↑ (BHg, cord)

Table 2-42. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Prospective Birth Cohort in the Nunavik Region of Arctic Canada

Reference (listed in order of age at follow-up)	Biomarker	Outcome evaluated[a]	Result
Jacobson et al. 2015 Follow-up at age 11 years (n=282)	BHg mean Cord: 21.8 µg/L Child (11 years): 4.7 µg/L	WISC-IV (FSIQ)	↓ (BHg, cord) 0 (BHg, child)

[a]Interpretation of neurobehavioral test scores:
A not B test: higher score = higher performance
BSID MDI: higher score = higher performance
BSIS PDI: higher score = higher performance
CD: higher score = more behavioral problems
NES FTT: higher score = higher performance
NES FTT: higher score = higher performance
ODD: higher score = more behavioral problems
SAFB: higher score = higher performance
ST-BI copying: higher score = higher performance
TRF: higher score = more behavioral problems
WISC-IV: higher score = higher performance

↑ = positive association; ↓ = inverse association; 0 = no association; ADHD = attention deficit/hyperactivity disorder; BHg = blood mercury; BSID = Bayley Scales of Infant Development; CD = Conduct Disorder; EEG ERP = electroencephalogram event related potential; FSIQ = full scale intelligence quotient; FTII = Fagan Test of Infant Intelligence; MDI = BSID Mental Development Index; NES = Neurobehavioral Evaluation Systems; FTT = Finger Tapping Test; ODD = Oppositional Deviant Disorder; PDI = BSID Psychomotor Development Index; SAFB = Santa Ana Form Board; ST-BI = Stanford-Binet; TRF = Teacher Report Form; VEP = visual evoked potential; WISC-IV = Wechsler Intelligence Scale for Children, 4th edition

The primary methylmercury prenatal exposure metric has been total mercury in cord blood. Based on results from the Arctic Cord Blood Monitoring Program, the geometric mean (GM) cord blood mercury concentration was 23 µg Hg/L and the IQR was 12–27 µg Hg/L (Muckle et al. 2001). Cord blood mercury levels (µg Hg/L) were approximately 5 times maternal hair mercury levels measured during the third trimester (GM 4.4 µg Hg/g; IQR 2.4, 6.0) (Muckle et al. 2001). Based on a dietary survey of Nunavik population, the average daily consumption was approximately 50 g/day of fish and 22 g/day of marine mammals (Blanchet and Rochette 2008).

Neurodevelopmental outcomes were assessed using a variety of tests that changed as the children aged. These included tests of learning and memory, visual-motor function, auditory function, and behavior problems (e.g., attention deficit/hyperactivity disorder). Outcome associations were adjusted for covariates that included (in most studies, depending on the outcome measured): sex; age at testing; cord and current blood lead, selenium, DHA, and PCBs; SES; maternal marital status; education; caregiver general intelligence (Raven's Progressive Matrices); tobacco smoking and marijuana use during pregnancy; and HOME score.

The Nunavik study found associations between increasing prenatal (cord) blood mercury and slower reaction times in tests of visual and auditory information processing tasks (Boucher et al. 2010, 2014, 2016; Ethier et al. 2012), pointing tremor (Despres et al. 2005), full scale IQ (Jacobson et al. 2015), and higher symptom scores for attention deficit/hyperactivity disorder (Boucher et al. 2012b). In some studies of information processing, increased latency of electrophysiological (e.g., EEG) event response potentials were evident, suggesting a possible effect of exposure on behavioral reaction time (Boucher et al. 2010, Ethier et al. 2012). At age 11 years, the size of the mercury effect on IQ (WISC) was a decrease of 4.8 points in children whose cord blood mercury had been ≥7.5 µg Hg/L, compared to children whose cord blood mercury had been <7.5 µg Hg/L (Jacobson et al. 2015).

A variety of factors have been explored to assess potential bias in the associations observed in the Nunavik study. Cord blood mercury was correlated with cord PCB, lead, selenium, and DHA levels (Boucher et al. 2010). Cord PCB levels were independently associated with many of the outcomes measured. In some studies, associations with cord mercury were no longer evident when cord or child blood PCB levels were included as covariates (Boucher et al. 2012a, 2016; Despres et al. 2005). Cord PCBs and lead interacted with cord mercury in explaining variance in some cognitive outcomes (Boucher et al. 2012a). Nutrients such as cord blood DHA and selenium tended to strengthen associations between cord mercury levels and response latency and IQ outcomes (Boucher et al. 2010; Jacobson et al. 2015). When stratified by breastfeeding duration, children who were breastfed for <3 months tended to show stronger associations with cord mercury levels (Boucher et al. 2010). These observations suggest that associations between cognitive performance outcomes and prenatal mercury exposures can be modified by co-exposure to other agents that may independently affect cognitive performance (e.g., PCBs, lead, nutrients).

Amazonian riverine populations. Studies of methylmercury exposure and neurodevelopmental outcomes have been conducted in populations living in Amazon River basins (Amazonian studies). These include several cross-sectional studies of children from birth cohorts who resided in various river basins, with neurodevelopmental assessments in infancy and various later ages, with the oldest cohort being 14 years of age (Chevrier et al. 2009; Cordier et al. 2002; Dorea et al. 2012, 2014; dos Santos Freitas et al. 2018; Hoshino et al. 2015; Marques et al. 2007, 2015; Reuben et al. 2020). Exposure to methylmercury in these populations derived primarily from methylation of inorganic mercury released to local aquatic ecosystems from alluvial gold mining (Marques et al. 2007). A summary of the major outcomes of the Amazonian studies are presented in Table 2-43.

Table 2-43. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Amazonian River Basin Studies

Reference, study type, and population	Biomarker	Outcome evaluated	Result[a]
Hoshino et al. 2015 Cross-sectional cohort of 58 individuals (age range 1–47 years); Brazil	HHg median 10.91 µg/g	Tympanometry	0 HHg
		Acoustic reflexes	0 HHg
		Pure tone audiometry	0 HHg
		Transient otoacoustic emissions	0 HHg
Marques et al. 2007 Prospective study of birth cohort, follow-up at age 6 months (n=100); Brazil	HHg median Maternal: 5.40 µg/g Child (birth): 1.59 µg/g Child (6 months): 1.81 µg/g	GDS	0 (HHg, birth) 0 (HHg, 6 months)
Marques et al. 2015 Prospective study of birth cohort, follow-up at age 6 months (n=294), Brazil	HHg median (female, male) Child (birth): 0.79, 0.81 µg/g Child (6 months): 0.98, 0.97 µg/g	BSID MDI	0 (HHg, birth) 0 (HHg, 6 months)
		BSID PDI	0 (HHg, birth) 0 (HHg, 6 months)
Marques et al. 2015 Prospective study of birth cohort, follow-up at age 24 months (n=294); Brazil	HHg median (female, male) Child (birth): 0.79, 0.81 µg/g Child (6 months): 0.98, 0.97 µg/g Child (24 months): 1.75, 1.72 µg/g	BSID MDI	0 (HHg, birth) 0 (HHg, 6 months) 0 (HHg, 24 months)
		BSID PDI	0 (HHg, birth) 0 (HHg, 6 months) 0 (HHg, 24 months)
Dorea et al. 2012 Cross-sectional cohort study of children, 1–6 months of age (n=281); Brazil	HHg mean (infant) Itapua: 3.95 µg/g Bom Futuro: 1.85 µg/g Porto Velho: 3.84 µg/g	GDS	0 (HHg, current age)
Cordier et al. 2002 Cross-sectional cohort of children age 5–12 years (n=378); French Guiana	HHg geometric mean (maternal) Upper Maroni: 12.7 µg/g Camopi: 6.7 µg/g Awala: 2.8 µg/g	ST-BI copying	↓ (HHg, maternal)
		NES FTT	0 (HHg, maternal)
		Leg coordination	0 (HHg, maternal)
		Digit span (forward)	0 (HHg, maternal)
Chevrier et al. 2009 Pooled analysis of children, age 7 to 12 years (n=395); Brazil, French Guiana	HHg mean Maternal: 10.3 µg/g Child: 9.8 µg/g	ST-BI copying error	↑ (HHg, maternal) ↑ (HHg, child)
Dorea et al. 2014 Cross-sectional cohort study of children, 12–24 months of age (n=299); Brazil	HHg median (infant) Itapua: 3.5 µg/g Bom Futuro: 2.2 µg/g	GDS	0 (HHg, infant)
		Age of talking	0 (HHg, current age)
		Age of walking	0 (HHg, current age)

Table 2-43. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurodevelopmental Effects—Amazonian River Basin Studies

Reference, study type, and population	Biomarker	Outcome evaluated	Result[a]
dos Santos Freitas et al. 2018 Cross-sectional cohort study of children, 7–14 years of age (n=176); Brazil	HHg mean (child) Tapajos basin: 4.5 µg/g Tocantins basin: 0.49 µg/g	Color vision	0 (HHg, current age)
Reuben et al. 2020 Longitudinal cohort study of children, 5–12 years of age (n=163); Peru	HHg mean (child) 2.06 µg/g	Visual-motor integration	0 (HHg, child)
		Cognitive ability	↓ (HHg, child)

[a]Interpretation of neurobehavioral test scores:
BSID MDI: higher score = higher performance
VISI PDI: higher score = higher performance
Digit span: higher score = higher performance
GDS: higher score = higher performance
NES FTT: higher score = higher performance
ST-BI copying: higher score = higher performance
ST-BI copying error: higher error score = lower performance

↑ = positive association; ↓ = inverse association; 0 = no association; BSID = Bayley Scales of Infant Development; HHg = hair mercury; GDS = Gesell Developmental Scales; MDI = BSID Mental Development Index; NES FTT = Neurobehavioral Evaluation System Finger Tapping Test; PDI = BSID Psychomotor Development Index; ST-BI = Stanford-Binet Bead Memory test

The primary methylmercury prenatal exposure metric in these studies has been total mercury in hair. In riverine populations in the Madeira Basin, the median maternal hair mercury level was 12 µg Hg/g (range 1– 131 µg Hg/g) and correlated with newborn hair mercury (median 3 µg Hg/g; range 0.1–19 µg Hg/g) (Marques et al. 2013a). In the Madeira Basin population, the median number of fish meals per week was 5 (range 0–7) and number of fish meals per week correlated with maternal hair mercury (Marques et al. 2013b). Neurodevelopmental outcomes were assessed using a variety of tests that changed as the children aged. These included developmental milestones (e.g., age of talking and walking) and tests of learning and memory, vision, and visual-motor function. Outcome associations were adjusted or stratified for covariates that included (in most studies, depending on the outcome measured): sex, age at testing, breastfeeding, SES, maternal marital status, education, general intelligence caregiver general intelligence (Raven's Progressive Matrices), tobacco smoking, and HOME score.

Studies of Amazonian populations have found associations between prenatal (maternal) or child hair mercury levels and performance on tests of cognitive ability (Chevrier et al. 2009; Cordier et al. 2002;

Reuben et al. 2020). A study of families residing in an artisanal and small-scale gold mining region of Amazonian Peru evaluated associations between child (mean age 8 years; N=163) hair mercury and visual-motor coordination, general cognitive ability, and physical health (Reuben et al. 2020). The mean hair mercury was 2.06 µg Hg/g (range 0.08, 14.61). Increasing hair mercury was associated with decreasing scores of the Spanish language Woodcock-Johnson Tests of Cognitive Abilities (β = -2.59 points per ln[µg Hg/g hair], 95% CI -4.52, -0.66). In a pooled analysis of children, age 7–12 years, from Amazonian Brazil and French Guiana, the size of the association was an increase of 1.2 in error score on the Stanford-Binet copying test for an increase in child hair mercury concentration of 10 µg Hg/g (Chevrier et al. 2009). In a population from Amazonian Brazil, age 5–12 years, the effect was a decrease of 2.98 in performance score on the on the Stanford-Binet copying test for an increase in child hair mercury concentration of 10 µg Hg/g (Cordier et al. 2002). Scores on other tests of cognitive development were not associated with mercury exposure, including Bayley Scales of Infant Development at age 6–12 months (Marques et al. 2015), Gesell Development Scales at age 6–20 months (Dorea et al. 2012, 2014; Marques et al. 2015), age of talking or walking (Dorea et al. 2014), various tests of visual-motor coordination at age 5–12 years (Cordier et al. 2002), or color vision at age 7–14 years (dos Santos Freitas et al. 2018). The above studies did not explore the potential impacts of other exposures (e.g., lead, PCBs) or nutritional factors that may have also correlated with fish consumption.

Madeira, Portugal. Cognitive function was studied in a cross-sectional cohort of 149 mothers and children who resided in Madeira, a fishing village in Portugal (Murata et al. 1999a, 2004b). Fish consumption was a major contributor to exposure to methylmercury in this population. Maternal fish consumption ranged from <1 meal per week (25%) to ≥5 meals/week and correlated with maternal hair mercury levels (22%; Murata et al. 1999a). Increasing maternal hair mercury levels (median 9.6 µg Hg/g) was associated with delays in brainstem auditory and visual evoked potentials measured at age 7 years. Murata et al. (2002) estimated BMDLs (BMR 0.1) of 14 and 19 µg Hg/g hair for the increased latency of auditory evoked potentials. When the data from the Madeira cohort were combined with the data from the 7-year follow-up of the Faroe Islands study, BMDL estimates (BMR 0.1) ranged from 16 to 17 µg Hg/g hair (Murata et al. 2002).

Artisanal gold mining. Studies have been conducted of neurodevelopment outcomes in populations exposed to mercury released from artisanal gold mining operations (Counter 2003; Counter et al. 1998, 2002, 2006, 2012; Ramirez et al. 2000, 2003; Reuben et al. 2020). In artisanal mining, gold is extracted from a substrate (e.g., pulverized ore, sediment, soil) by mixing the substrate with elemental mercury to form mercury-gold amalgam. The amalgam is washed, sedimented, and roasted to vaporize the elemental

mercury out of the amalgam. This process can result in direct exposures of mine workers to mercury vapor. Exposures of the general population to methylmercury can also occur as a result of methylation of inorganic mercury released to local aquatic ecosystems (Ramirez et al. 2000). Although human exposures to wastes from artisanal goldmines can be a mixture of elemental mercury, inorganic mercuric mercury, and methylmercury, studies of neurodevelopmental outcomes in children residing near gold mine operations are included in the discussion of epidemiological studies of methylmercury because methylmercury is likely to have been a major source of exposures in these populations (Counter et al. 1998; Ramirez et al. 2000).

A prospective study examined developmental milestones and cognitive performance in children from a birth cohort of 78 pregnancies in an area in Philippines where mercury amalgam was used to extract gold from ore (Tagum study) (Ramirez et al. 2000, 2003). In a subset of the cohort (n=12), the mean cord blood mercury level was 53 µg Hg/L (range 20–130 µg Hg/L). The mean level in fetal meconium (n=36) was 49 µg Hg/L (range 20–200 µg Hg/L). The follow-up conducted at age 2 years (n=48) evaluated cognitive performance based on a cognitive adaptive test (CAT), clinical linguistic auditory milestone scale (CLAMS), and full-scale developmental quotient (FSDQ), and compared outcomes to a control group (from Saranggani, a coastal area not impacted by gold mining waste). Mean blood mercury levels in the children were higher in the control group (3.25 µg Hg/L) compared to the children from the Tagum region (2.6 µg Hg/L); however mean hair mercury levels were higher in the Tagum area (1.28 µg Hg/g) compared to the control group (0.66 µg Hg/g). Mean scores on CAT, CLAMS, and FSDQ were lower in the exposed group. ORs (not adjusted for potential covariates) for “abnormal scores” with the control group (n=88) as the reference, were 4.8 (95% CI 2.03, 11.4) for CLAMS, 1.26 (95% CI 0.32, 1.97) for CAT, and 3.10 (95% CI 0.85, 11.2) for FSDQ. Adjusted ORs were not reported, although a comparison of means between the exposed and control groups were reported for various SES and childcare variables.

A study of families living in an artisanal and small-scale gold mining area of Peru evaluated performance in children at mean age 8 years (n=163; Reuben et al. 2020). The study evaluated associations between child hair mercury level and visual-motor integration, cognitive ability, and physical health. The mean hair mercury was 2.06 µg Hg/g (range 0.08, 14.61). Decreasing general cognitive ability, measured by a Spanish-language Woodcock-Johnson Tests of Cognitive Abilities, was associated with increasing hair mercury after adjustment for potential confounding variables (β, -2.59 points per ln µg/g; 95% CI -4.52, -0.66).

Several cross-sectional studies of children residing near gold mining operations in Ecuador have been conducted (Counter et al. 1998, 2002, 2006, 2012). These studies were largely ecological in design in that they compared mean outcomes between children who resided near gold mines and had higher mercury levels than a control group that did not reside near goldmines. In general, associations between outcomes and blood mercury (or hair mercury levels) were not adjusted for potential covariates. In a population from the Nambija gold mining area, the mean blood mercury level (n=77; mean age 9 years) was 18 µg Hg/L (range 2–89 µg Hg/L) (Counter et al. 2002). Brainstem auditory evoked responses in children who had blood mercury levels >20 µg Hg/L (median) showed longer latencies than in children who had blood mercury levels <20 µg Hg/L (Counter 2003). Children from the Nambija and Portovelo mining areas had lower scores on the Raven's Coloured Progressive Matrices (RCPM), a test of visual-spatial processing, than children from other areas (e.g., Peru, Puerto Rico, United States) (Counter et al. 2006). RCPM scores were also lower among children who had blood mercury levels >5 µg Hg/L or hair mercury levels >2 µg Hg/g compared to children who had lower mercury levels (Counter et al. 2006). Increasing brainstem-mediated acoustic stapedius reflex thresholds in children correlated with increasing blood mercury (Counter et al. 2012).

Meta-analyses. Cohen et al. (2005) conducted a meta-analysis of outcomes of the Faroe Islands study, Seychelles Child Development Study, and North Island New Zealand study. Outcomes from various domains of cognitive function were aggregated into a weighted IQ metric and the meta outcome was expressed as the change in IQ points as a fraction of the outcome SD per 1 µg Hg/g increase in maternal hair mercury. The meta average effect size was a decrease in 0.043 SD per µg Hg/g. For a SD of 15 IQ points, the meta estimate corresponds to approximately 0.7 IQ points per µg Hg/g (range 0–1.5 IQ points per µg Hg/g). A follow-up to the Cohen et al. (2005) meta-analysis included outcomes from the Faroe Islands study at age 7 years, Seychelles Child Development Study at age 9 years, and North Island New Zealand study at age 6 years (Axelrad et al. 2007a, 2007b; Ryan 2008). The meta estimate for the effect size was -0.18 IQ points per increase of 1 µg Hg/g hair (95% CI -0.378, -0.009). Murata et al. (2002) pooled data on auditory evoked potentials observed at age 7 years in the Faroe Islands and Madeira Portugal studies and estimated BMDLs (BMR 0.1) that ranged from 16 to 17 µg Hg/g hair.

Organic Mercury—Animals Studies. Numerous studies have identified the nervous system as a target of methylmercury toxicity in nonhuman primates and rodents following developmental exposures. Collectively, these studies provide conclusive evidence that methylmercury is associated with adverse neurodevelopmental effects. Neurodevelopmental are observed at doses at or below those associated with adverse neurological effects of exposure during adulthood.

Neurodevelopmental effects have been reported in macaque monkeys following prenatal and/or postnatal exposure to methylmercury compounds (Table 2-44). The most sensitive effects were impaired spatial visual discrimination and progressive hearing loss at doses ≥0.01 mg Hg/kg/day (Burbacher et al. 2005; Rice 1998a; Rice and Gilbert 1992); no changes in temporal visual discrimination or peripheral vision were observed at 0.05 mg Hg/kg/day (Rice and Gilbert 1982, 1990). Mild deficits in operant training were observed in adult monkeys exposed to 0.04–0.08 mg Hg/kg/day during gestation; however, a NOAEL/LOAEL determination cannot be made because the study authors combined all exposed monkeys for data presentation and analysis (Gilbert et al. 1996). In other studies, no impairments in operant training were observed following pre- and postnatal exposure to 0.05 mg Hg/kg/day (Rice 1998b; Rice and Gilbert 1982; Rice and Hayward 1999). Overt clinical signs of neurotoxicity were observed at developmental exposures ≥0.05 mg Hg/kg/day (Rice and Gilbert 1990; Willes et al. 1978) and diffuse neuronal degeneration in the cerebral cortex (especially the calcarine, insular, pre-, and postcentral gyri, and occipital lobe), cerebellum, basal ganglia, thalamus, amygdala, and lateral geniculate nuclei were observed at developmental exposures of 0.5 mg Hg/kg/day (Willes et al. 1978).

Table 2-44. Neurodevelopmental Effects[a] in Male and Female Primates Following Oral Exposure to Methylmercury Compounds

Species (sex), exposure duration, and time of examination	Overt clinical signs[b]	Learning/ Memory[b]	Auditory function[b]	Visual function[b]	Neuro-pathology[b]	Reference (compound)
Macaca fascicularis; up to 29 days from birth; examined 2 weeks post-exposure	+ L: 0.5 (8.0–9.4)	–	–	–	+ L: 0.5 (8.0–9.4)	Willes et al. 1978 (MMC)
M. fascicularis; 165 days during gestation; examined at 8–15 years	–	↓ L: 0.04–0.08[c] (1.04–2.45)	–	↓ L: 0.04–0.08[c] (1.04–2.45)	–	Burbacher et al. 2005; Gilbert et al. 1996 (MMH)
M. fascicularis; up to 1,460 days from birth to age 4 years; examined at 3–5.5 years	–	0 N: 0.05 (0.6–0.9)	–	↓ L: 0.05 (0.6–0.9)	–	Rice and Gilbert 1982; Rice and Gilbert 1990 (MMC)

Table 2-44. Neurodevelopmental Effects[a] in Male and Female Primates Following Oral Exposure to Methylmercury Compounds

Species (sex), exposure duration, and time of examination	Overt clinical signs[b]	Learning/ Memory[b]	Auditory function[b]	Visual function[b]	Neuro-pathology[b]	Reference (compound)
M. fascicularis; up to 1,625 days from gestation through age 4 years; examined at 4–19 years	+ L: 0.05 (0.8)	0 N: 0.05 (0.8)	↓ L: 0.01 (0.21)	↓ L: 0.01 (0.21)	–	Rice 1998a; Rice and Gilbert 1990 (MMC)

[a]Studies with exposure prior to puberty only, including studies that evaluate adult animals after developmental exposure. These findings are listed under "Develop" in the LSE table.
[b]NOAEL (N) or LOAEL (L) for dose administered in mg Hg/kg/day (blood level in mg Hg/L).
[c]Study authors combined dose groups for data presentation and analysis; NOAEL/LOAEL determinations could not be made.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; + = present; Develop = developmental; LOAEL = lowest-observed-adverse-effect level; LSE = Levels of Significant Exposure; MMC = methylmercuric chloride; MMH = methylmercury hydroxide; NOAEL = no-observed-adverse-effect level

Eighteen studies have evaluated neurobehavioral effects in rodents following acute developmental exposure to methylmercury compounds during gestation or early postnatal periods (see Table 2-45). Reported exposure-related effects included decreased motor activity and coordination, impaired learning and memory, delayed or altered reflexes, and altered nocturnal rhythms; findings for anxiety were inconsistent (some reported an increase, others a decrease). In most acute-duration neurodevelopmental studies in rodents, no overt clinical signs of neurotoxicity were reported. Exceptions were "abnormal" walking posture and transient lethargy and ataxia observed in neonatal mice following a single exposure to 16 mg Hg/kg/day during gestation or early postnatal development (Inouye et al. 1985; Post et al. 1973). In rats, the most sensitive effect was impaired operant conditioning (associative learning) following exposure to 0.008 mg Hg/kg/day during GDs 6–9 (Bornhausen et al. 1980). In mice, the most sensitive effects were noted at a comparable gestational dose of 0.009 mg Hg/kg/day (during GDs 8–18), and included hypoactivity, impaired motor coordination, impaired spatial learning, and increased anxiety (Montgomery et al. 2008).

Table 2-45. Neurobehavioral Effects in Rodents Following Acute Oral Exposure to Methylmercury Compounds During Development

Species; duration	Motor activity, coordination[a]	Anxiety[a]	Associative learning[a]	Spatial/ working learning and memory[a]	Other[a]	Reference (compound)
Gestational exposure						
Rat; 1 day, GD 15	0 (N: 6.4)	–	↓ (L: 6.4)	–	–	Cagiano et al. 1990; Zanoli et al. 1994 (MMC)
Rat; 1 day, GD 8 or 15	↓ (L: 7)	0 (N: 7)	↓ (L: 7)	↓ (L: 7)	Reflexes, ASR, PPI 0 (N: 7)	Carratu et al. 2006, 2008 (MM)
Rat; 4 days, GDs 6–9	–	–	↓ (L: 0.008)	–	–	Bornhausen et al. 1980 (MMC)
Rat; 4 days, GDs 6–9	↓ (L: 4)	–	0 (L: 4)	↓ (L: 4)	ASR ↑ (L: 4)	Stoltenburg-Didinger and Markwort 1990 (MMC)
Rat; 4 days, GDs 6–9	0 (N: 1.9)	–	–	0 (N: 1.9)	Reflexes 0 (N: 1.9)	Fredriksson et al. 1996 (MM)
Mouse; 1 day, GD 8	0 (N: 5)	–	↓ (L: 3)	0 (N: 5)	–	Hughes and Annau 1976 (MMH)
Mouse; 1 day, GD 13, 14, 15, 16, or 17	↓ (L: 16)	–	–	–	Righting reflex ↓ (L: 16)	Inouye et al. 1985 (MMC)
Mouse; 3 days, GDs 7–9	0 (N: 5)	0 (N: 5)	–	↓ (L: 3)	–	Dore et al. 2001 (MMC)
Mouse; 3 days, GDs 12–14	↓ (L: 3)	0 (N: 5)	–	↓ (L: 5)	–	Dore et al. 2001 (MMC)
Mouse; 3 days, GDs 12–14	↓ (L: 3)	↓ (L: 3)	–	↓ (L: 3)	Altered nocturnal rhythm (L: 3)	Kim et al. 2000 (MM)
Mouse; 11 days, GDs 8–18	↓ (L: 0.009)	↑ (L: 0.009)	–	↓ (L: 0.009)	–	Montgomery et al. 2008 (MMC)
Postnatal exposure						
Rat; 1 day, PND 15 or 21	0 (N: 16)	–	–	0 (N: 16)	–	Post et al. 1973 (MMC)
Rat; 10 days, PNDs 14–23	↓ (L: 0.6)	0 (N: 0.6)	↓ (L: 0.6)	–	Nociception 0 (N: 0.6)	Coluccia et al. 2007 (MMC)
Mouse; 1 day PND 10	↓ (L: 0.37)	–	–	↓ (L: 0.37)	–	Fischer et al. 2008 (MMC)

Table 2-45. Neurobehavioral Effects in Rodents Following Acute Oral Exposure to Methylmercury Compounds During Development

Species; duration	Motor activity, coordination[a]	Anxiety[a]	Associative learning[a]	Spatial/ working learning and memory[a]	Other[a]	Reference (compound)
Mouse; 5 days, PNDs 29–33	↓ (L: 0.2)	–	–	–	–	Bellum et al. 2007 (MMC)

[a]NOAEL (N) or LOAEL (L) dose in mg Hg/kg/day for endpoint category

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; ASR = acoustic startle reflex; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; MM = methylmercury; MMC = methylmercuric chloride; MMH = methylmercury hydroxide; NOAEL = no-observed-adverse-effect level; PND = postnatal day; PPI = paired-pulse inhibition

Twenty-four studies have evaluated neurobehavioral effects in rodents following intermediate-duration developmental exposure during gestation and/or early postnatal periods (see Table 2-46). Reported exposure-related effects included decreased motor coordination, impaired learning and memory, and delayed reflex ontogeny; findings for motor activity were inconsistent (some reported increases, others decreases). In most studies, no overt clinical signs of neurotoxicity were reported in intermediate-duration neurodevelopmental studies in rodents. An exception was hindlimb crossing and paralysis observed in neonatal rats following direct exposure to 4 mg Hg/kg/day from PND 1 to 30 (Sakamoto et al. 2002). The most sensitive neurobehavioral effects following intermediate-duration developmental exposure were observed in mice following exposure to 0.02 mg Hg/kg/day during gestation and/or early postnatal development, including altered motor activity and impaired motor coordination (Huang et al. 2011). Impaired hearing, as indicated by decreased auditory brainstem responses, was also observed at this exposure level. The only other neurophysiological study identified in rodents following developmental exposure reported elevated epileptiform activity following maternal exposure to 0.3 mg Hg/kg/day for 7–8 weeks premating through PND 21; baseline cortical activity was comparable (Szász et al. 2002).

Table 2-46. Neurobehavioral Effects in Rodents Following Intermediate Oral Exposure to Methylmercury Compounds During Development

Species; duration	Motor activity[a]	Motor coordination[a]	Associative learning (OC, AA, PA)[a]	Spatial/ working learning, and memory[a]	Other[a]	Reference (compound)
Gestational exposure						
Rat; 25 days, PM–GD 19	–	–	↓ (L: 0.8)	0 (N: 0.8)	–	Kakita et al. 2000 (MMC)
Rat; 49–56 days, PM–GD 20 (G)	0 (N: 1)	–	–	–	FOB, ASR 0 (N: 1)	Beyrouty et al. 2006 (MMC)
Mouse (C57) 19 days, GD 0–18 (diet)	M: ↑; F: ↓ (L: 0.9)	–	0 (N: 0.9)	↓ (L: 0.9)	Anxiety ↓ (L: 0.9)	Yoshida et al. 2011 (MM)
Gestational plus postnatal exposure						
Rat; 22 days, GD 7–PND 7	↑ (L: 0.5)	–	–	–	–	Giménez-Llort et al. 2001 (MMH)
Rat; 22 days, GD 7–PND 7	↓ (L: 0.474)	–	–	0 (N: 0.474)	–	Rossi et al. 1997 (MMH)
Rat; 35 days, GD 7–PND 21	–	–	–	–	Reflex ontogeny ↓ (L: 1.9)	Sitarek and Gralewicz 2009 (MMC)
Rat; 38 days, GD 5–PND 21	↓ (L: 0.4)	–	↓ (L: 0.2)	↓ (L: 0.2)	–	Albores-Garcia et al. 2016 (MMC)
Rat; 42 days, GD 1–PND 21	↑ (L: 0.23)	↓ (L: 0.23)	–	0 (N: 0.23)	Reflex ontogeny ↓ (L: 0.23)	Cheng et al. 2015; Fujimura et al. 2012 (MM)
Rat; 60 days, PM–PND 21	↑ (L: 0.74)	–	↓ (L: 0.74)	0 (N: 0.74)	–	Elsner 1991 (MMC)
Rat; 70–91 days, PM–PND 16	–	–	↓ (L: 0.045)	–	Reflex ontogeny (N: 0.6)	Newland and Reile 1999; Newland and Rasmussen 2000; Newland et al. 2004 (MMC)
Rat; 111 days PM–PND 55	–	↓ (L; 0.5)	↓ (L: 0.5)	0 (N: 0.5)	–	Sakamoto et al. 2002 (MM)
Mouse; 35 days, GD8–PND 21	0 (N: 0.06)	–	–	–	–	Zhang et al. 2011 (MM)
Mouse[b]; 35 days, GD 8–PND 21	↑ (L: 0.06)	–	–	–	–	Zhang et al. 2011 (MM)

Table 2-46. Neurobehavioral Effects in Rodents Following Intermediate Oral Exposure to Methylmercury Compounds During Development

Species; duration	Motor activity[a]	Motor coordination[a]	Associative learning (OC, AA, PA)[a]	Spatial/ working learning, and memory[a]	Other[a]	Reference (compound)
Mouse; 41 days, GD 2–PND 21	↓ (L: 0.9)	0 (N: 1.7)	–	↓ (L: 0.9)	–	Goulet et al. 2003 (MMC)
Mouse; 63–70 days, PM–PND 13	–	↓ (L: 0.2)	0 (N: 0.6)	↓ (L: 0.2)	–	Weiss et al. 2005 (MMC)
Mouse; 70, PM–PND 21	↓ (L: 0.02)	0 (N: 0.02)	–	–	–	Huang et al. 2011 (MM)
Mouse; 119 days, PM–PND 70	↓ (L: 0.02)	↓ (L: 0.02)	–	–	–	Huang et al. 2011 (MM)
Postnatal exposure						
Rat; 30 days, PNDs 1–30	–	↓ (L: 4)	↓ (L: 0.8)	–	–	Sakamoto et al. 2004 (MMC)
Mouse; 21 days, PNDs 1–21	↓ (L: 4.7)	↓ (L: 4.7)	–	–	–	Franco et al. 2006 (MMC)
Mouse; 27 days, PNDs 2–28	↓ (L: 0.9)	–	0 (N: 0.9)	0 (N: 0.9)	Anxiety 0 (N: 0.9)	Yoshida et al. 2018 (MMC)
Mouse; 49 days, PNDs 21–70	↑ (L: 0.02)	↓ (L: 0.02)	–	–	–	Huang et al. 2011 (MM)

[a]NOAEL (N) or LOAEL (L) dose in mg Hg/kg/day for endpoint category.
[b]Autoimmune susceptible mouse strain.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; AA = active avoidance learning, ASR = acoustic startle reflex; F = female; FOB = functional observation battery; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; M = male; MM = methylmercury; MMC = methylmercuric chloride; MMH = methylmercury hydroxide; NOAEL = no-observed-adverse-effect level; OC = operant conditioning; PA = passive avoidance learning; PM = premating; PND = postnatal day;

Evaluation of the oral neurodevelopmental database indicates that of the sensitive effects identified following acute and intermediate-duration exposure to methylmercury compounds (see Tables 2-45 and 2-46), the most consistently reported findings included impaired operant conditioning in rats, impaired spatial learning and memory in mice, motor incoordination in rats and mice, and hearing deficits in mice. Additional details on neurobehavioral testing and dose-response information for these consistently observed and sensitive neurodevelopmental effects in rodents following developmental exposure to methylmercury can be found in Table 2-47. Dose-related impairments in operant conditioning in rats were consistently observed following developmental exposure to oral doses ≥0.008 mg Hg/kg/day (Bornhausen et al. 1980; Elsner 1991; Newland and Rasmussen 2000; Newland et al. 2004). When

assessed using the Morris water maze, impaired spatial learning and/or memory was consistently observed in C57BL/6 mice following gestational exposure to oral doses ≥0.009 mg Hg/kg/day (Kim et al. 2000; Montgomery et al. 2008; Yoshida et al. 2011). In NMRI mice, impaired spatial learning in the Morris water maze was observed following early postnatal exposure to oral doses ≥0.37 mg Hg/kg/day (Fischer et al. 2008). No changes in spatial learning were observed in BALB/c or CFW mice exposed to doses up to 3 or 5 mg Hg/kg/day, respectively, during gestation (Hughes and Annau 1976; Kim et al. 2000). Based on reported findings in the T-maze and radial arm maze following oral methylmercury exposure (Dore et al. 2001; Fischer et al. 2008; Goulet et al. 2003; Weiss et al. 2005; Yoshida et al. 2018), these tests appear to be less sensitive and/or less consistent measures of methylmercury-induced spatial learning impairments in mice compared to the Morris water maze. In rats, dose- and duration-dependent motor coordination impairments were observed during rotarod testing, with impairments reported following postnatal-only exposure to 4 mg Hg/kg/day (Sakamoto et al. 2004) and gestation plus postnatal exposure to ≥0.23 mg Hg/kg/day (Cheng et al. 2015; Fujimura et al. 2012; Sakamoto et al. 2002); no changes were observed following a single exposure to 7 mg Hg/kg/day during gestation (Carratu et al. 2006). Findings in the rotarod test were less consistent in mice, with varying findings between different strains and exposure paradigms (Bellum et al. 2007; Dore et al. 2001; Franco et al. 2006; Goulet et al. 2003; Huang et al. 2011; Montgomery et al. 2008). Data for other measures of coordination in mice (footprint analysis, vertical pole) are limited (Bellum et al. 2007; Montgomery et al. 2008; Weiss et al. 2005). One study evaluated auditory function in mice following developmental exposure to 0.02 mg Hg/kg/day throughout gestation and lactation, during GD 1–PND 70, or postnatally only from PND 21–70 (Huang et al. 2011). Observed hearing deficits were similar in the GD 1–PND 21 and PND 21–70 groups, and markedly worse in the group with exposure during GD 1–PND 70.

Table 2-47. Neurological Effects[a] in Primates Following Oral Exposure to Methylmercury Compounds

Species (sex); exposure duration	Overt clinical signs[b]	Learning/ Memory[b]	Auditory function[b]	Visual function[b]	Neuro-pathology[b]	Reference (compound)
M. fascicularis (F); 150 days	0 N: 0.04 (NR)	–	–	–	–	Petruccioli and Turillazzi 1991 (MMC)
Marmoset (M); up to 242 days	+ L:0.5 (~10)	–	–	–	+ L:0.5 (~10)	Eto et al. 2001 (MM)
M. fascicularis (F); up to 395 days	+ L: 0.08 (1.56–2.209)	–	–	–	–	Burbacher and Mottet 1988; Burbacher et al. 1984, 2005 (MMH)

Table 2-47. Neurological Effects[a] in Primates Following Oral Exposure to Methylmercury Compounds

Species (sex); exposure duration	Overt clinical signs[b]	Learning/ Memory[b]	Auditory function[b]	Visual function[b]	Neuro-pathology[b]	Reference (compound)
M. fascicularis (F); up to 548 days	0 N: 0.05 (1.1–2)	–	–	–	+ L: 0.05 (1.1–2)	Charleston et al. 1994, 1995, 1996; Vahter et al. 1994 (MMH)
M. fascicularis (M, F): up to 2,555 days (from birth)[c]	+ L: 0.05 (0.6–0.9)	0	↓ L: 0.05 (0.6–0.9)	0	–	Rice 1998b, 1989c; Rice and Gilbert 1992; Rice and Hayward 1999 (MMC)

[a]Studies with exposure in post-pubertal animals, including macaque monkey studies that include exposures, beginning during early neonatal periods and continuing through puberty (which occurs at ~5 years of age).
[b]NOAEL (N) or LOAEL (L) for dose administered in mg Hg/kg/day (blood level in mg Hg/L).
[c]Findings in studies with exposure extending from birth through adulthood may be due to developmental exposure, post-pubertal exposure, or both.

↓ = decreased; 0 = no change; – = not assessed; + = present; F = female; LOAEL = lowest-observed-adverse-effect level; M = male; MM = methylmercury; MMC = methylmercuric chloride; MMH = methylmercury hydroxide; NOAEL = no-observed-adverse-effect level; NR = not reported

Pathological changes in the rat brain have been reported following developmental exposure to methylmercury at doses above those associated with neurobehavioral and neurophysiological effects, primarily in regions associated with motor and movement control. An acute gestational exposure study observed dendritic spine abnormalities in the somatosensory cortex in rat offspring at 4 mg Hg/kg/day (Stoltenburg-Didinger and Markwort 1990). Exposure throughout gestation in rats resulted in widespread neuronal degeneration (pyknosis, shrinkage of perikaryon, eosinophilic changes), decreased cell numbers in amygdala and hippocampus, and reactive gliosis at 0.8 mg Hg/kg/day (Kakita et al. 2000). Focal cerebellar dysplasia, including heterotopic location of Purkinje cells and granule cells, and reactive gliosis were observed in rats following exposure to 0.5 mg Hg/kg/day throughout gestation, lactation, and postweaning until PND 55 (Sakamoto et al. 2002). Widespread neuronal damage in the central nervous system was also observed in rats exposed to 4 mg Hg/kg/day from PND 1 to 30 (Sakamoto et al. 2004).

Pathological changes in regions of the brain associated with motor and movement control have also been observed in mice following developmental exposure to methylmercury at doses above those associated with neurobehavioral and neurophysiological effects. Findings in acute gestational exposure studies included altered cerebellar development in mouse offspring at ≥1 mg Hg/kg/day (Inouye et al. 1985; Khera and Tabacova 1973) and a reduction in the size of "nucleus caudatus putamen" in mouse offspring

at 16 mg Hg/kg/day (Inouye et al. 1985). Additionally, cerebellar inflammation was observed in an autoimmune susceptible mouse strain in offspring following maternal exposure to 0.06 mg Hg/kg/day during gestation and lactation (Zhang et al. 2011). Inflammation was not observed in similarly exposed wild-type mice.

Cerebellar damage has also been observed in hamsters following gestational exposure to methylmercury (no other neurological endpoints evaluated in hamsters). Exposure to 1.6 mg Hg/kg/day on GD 10 or GDs 10–15 resulted in degenerative changes in the cerebellum of hamster offspring examined between PND 1 and 25 (Reuhl et al. 1981a) or PND 275 and 300 (Reuhl et al. 1981b). In neonates, findings were most pronounced from PND 1 to 15, and included accumulation of lysosomes and areas of floccular cytoplasmic degradation in neuroblasts of the granular layer, pyknotic nuclei in the external granular layer, swollen developing dendrites packed with degenerating cytoplasmic material, and large aggregates of irregular debris, lysosomes, and large lipid droplets in astrocytes and perivascular macrophages. In older hamsters, findings included focal astrogliosis in the molecular layer, residual bodies in the perikarya and dendrites of granule and Purkinje neurons (sequalae of neonatal injuries), and degenerative changes of myelinated axons.

Predominant Mercury Form Unknown (General Populations). A large number of studies have been conducted on neurodevelopmental outcomes in general populations (Table 2-48). Most studies of general populations found no associations or inconsistent associations across outcome measures and biomarkers of exposure. These inconsistences may relate to the relatively low exposures in most of these populations (maternal or cord blood mercury <10 µg Hg/L; hair mercury <2 µg Hg/g), which may be near or below toxic thresholds, as well as other variables that may have affected outcomes and were not adequately controlled in models of association. These variables include multiple sources of exposure (e.g., diet, mercury amalgam dental restorations), fish consumption rates and related nutritional variables, and exposure to other chemicals (e.g., lead, PCBs).

In general populations, blood and hair mercury will be more greatly affected by exposures to other forms of mercury (e.g., mercury from amalgams) than in high fish consuming populations in which methylmercury is the dominant contributor to mercury body burden. Therefore, general population studies that estimated oral intake of methylmercury directly are stronger designs for the purpose of dose-response assessments of methylmercury. One study found associations between methylmercury intake and language proficiency (Vejrup et al. 2016, 2018).

Table 2-48. Results of Epidemiological Studies Evaluating General Population Exposure to Mercury (Predominant Mercury Form Unknown) and Neurodevelopmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result[a]
Al-Saleh et al. 2016 Cross-sectional cohort of 944 mother-infant pairs evaluated at age 3–12 months; Saudi Arabia	BHg median Maternal: 0.635 µg/L HHg median Maternal: 0.118 µg/g Child: 0.101 µg/g HMeHg Maternal: 0.132 µg/g Child: 0.091 µg/g	DDST-II	↓ (HMeHg, maternal) 0 (HHg, maternal) 0 (BHg, maternal) 0 (HMeHg, child) 0 (HHg, child)
		PEDS	0 (HMeHg, maternal) ↓ (HHg, maternal) 0 (BHg, maternal) 0 (HMeHg, child) 0 (HHg, child)
Barbone et al. 2019 Prospective cohort of mother-infant pairs, follow-up at 18 months (n=1,308); Mediterranean Europe (Italy, Slovenia, Croatia, Greece)	BHg median Maternal: 0.0024 µg/g Cord: 0.0036 µg/g HHg median Maternal: 0.704 µg/g	BSID cognitive composite score	0 (BHg, cord) 0 (BHg, maternal) 0 (HHg, maternal)
		BSID language composite score	0 (BHg, cord) ↑ (HHg, maternal)
		BSID motor composite score	0 (BHg, cord) 0 (BHg, maternal) 0 (HHg, maternal)
		BSID receptive communication	0 (BHg, cord) 0 (BHg, maternal) ↑ (HHg, maternal)
		BSID expressive communication	0 (BHg, cord) 0 (BHg, maternal) 0 (HHg, maternal)
Cheuk and Wong 2006 Case-control study of 52 ADHD cases and 59 controls, age <18 years; Hong Kong	BHg geometric mean Child case: 3.65 µg/L Child control: 2.33 µg/L	ADHD	↑ (BHg, child >5.8 µg/L)
Choi and Park 2017 Cross-sectional study 853 adolescents (mean age 15 years) and 5,187 adults (mean age 45 years) (Republic of Korea; KNHANES 2010–2012)	BHg geometric mean Adults: 3.58 µg/L Adolescents: 2.03 µg/L	Speech-frequency hearing	0 (BHg)
		High-frequency hearing	0 (BHg)
Daniels et al. 2004 Prospective cohort of mother-infant pairs, follow-up at age 15–18 months (n=1,054); United Kingdom	Cord tissue mercury median Wet weight: 0.01 µg/g Dry weight: 0.04 µg/g	MSCA	0 (Hg, cord tissue)
		DDST	0 (Hg, cord tissue)

Table 2-48. Results of Epidemiological Studies Evaluating General Population Exposure to Mercury (Predominant Mercury Form Unknown) and Neurodevelopmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result[a]
Freire et al. 2010 Prospective study of mother-child-infant pairs, follow-up at age 4 years (n=72); Spain	HHg mean Child (age 4 years): 0.96 µg/g	MSCA cognitive	↓ (HHg, child≥1 ug/g)
		MSCA quantitative	0 (HHg, child ≥1 ug/g)
		MSCA memory	↓ (HHg, child ≥1 ug/g)
		MSCA verbal	↓ (HHg, child ≥1 ug/g)
		MSCA performance	0 (HHg, child ≥1 ug/g)
		MSCA motor	0 (HHg, child ≥1 ug/g)
Golding et al. 2016a Prospective birth cohort (ALSPAC) at ages 4–17 years (n=2,776); United Kingdom	BHg median Maternal: 1.86 µg/g	Hyperactivity	0 (BHg)
		Conduct problems	↓ (BHg)
		Emotional problems	↓ (BHg)
		Peer problems	↓ (BHg)
		Prosocial	0 (BHg)
Golding et al. 2016b Prospective birth cohort (ALSPAC) at ages 6–42 months (n=3264); United Kingdom	BHg median Maternal: 1.86 µg/g	DDST (6 months)	↑ (BHg)
		DDST (18 months)	↑ (BHg)
		DDST (30 months)	0 (BHg)
		DDST (42 months)	↑ (BHg)
Golding et al. 2017 Prospective birth cohort (ALSPAC) at age 8 years (n=4,285); United Kingdom	BHg median Maternal: 1.86 µg/g	WISC-III (verbal)	0 (BHg)
		WISC-III (PIQ)	0 (BHg)
		WISC-III (FSIQ)	0 (BHg)
Golding et al. 2018 Prospective birth cohort (ALSPAC) at age 9–11 years (n=2,800); United Kingdom	BHg median Maternal: 1.86 µg/g	Signs of autism	0 (BHg)
Gustin et al. 2017 Cross-sectional cohort of 1,434 children, age 10 years; Bangladesh	HHg median Child: 0.674 µg/g	WISC-IV	0 (HHg, child)
		SDQ (behavior difficulties)	↓ (HHg, child)
Ha et al. 2009 Cross-sectional cohort of 1,778 children, mean age 7 years; Republic of Korea	BHg geometric mean Child: 2.4 µg/L	ADHD symptoms	0 (HHg, child)

Table 2-48. Results of Epidemiological Studies Evaluating General Population Exposure to Mercury (Predominant Mercury Form Unknown) and Neurodevelopmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result[a]
Hu et al. 2016 Prospective cohort of mother-infant pairs, follow-up at age 12 months (n=410); China	BHg geometric mean Maternal: 0.72 µg/L Cord: 1.2 µg/L	GDS gross motor	0 (BHg, maternal) 0 (BHg, cord)
		GDS fine motor	0 (BHg, maternal) 0 (BHg, cord)
		GDS adaptive	0 (BHg, maternal) ↑ (BHg, cord)
		GDS language	0 (BHg, maternal) 0 (BHg, cord)
		GDS social	0 (BHg, maternal) ↑ (BHg, cord)
Hertz-Piccioto et al. 2010 Case-control study of 332 autism cases at ages 2–5 years; California	BHg median Autism: 0.19 µg/L Controls: 0.28 µg/L	Autism	0 (child BHg)
Jedrychowski et al. 2006 Prospective cohort of mother-infants, follow up at age 12 months (n=233); Poland	BHg geometric mean Maternal: 0.55 µg/L Cord: 0.88 µg/L	BSID PDI or MDI	↓ (BHg, maternal ≥0.5 ug/g) ↓ (BHg, cord ≥0.8 ug/g)
Jedrychowski et al. 2007 Prospective cohort of mother-infant pairs, follow-up at age 12 months (n=374), 24 months (n=353), and 36 months (n=270); Poland	BHg, “high” exposure Cord: >0.90 µg/L (n=177)	BSID PDI or MDI 12 months	↓ (BHg, cord)
		BSID PDI or MDI 24 months	0 (BHg, cord)
		BSID PDI or MDI 36 months	0 (BHg, cord)
Jeong et al. 2017 Prospective cohort of mother-infant pairs, follow-up at age 60 months (n=553); Republic of Korea	BHg geometric mean Maternal: 3.14 µg/L	WPPSI-RK (FSIQ)	↓ (BHg, maternal)
		WPPSI-RK (VIQ)	↓ (BHg, maternal)
		WPPSI-RK (PIQ)	0 (BHg, maternal)
Julvez et al. 2013 Prospective cohort (ALSPAC) of mother-infant pairs, follow-up at age 8 years (n=843); United Kingdom	Cord tissue mercury mean Dry weight: 0.026 µg/g	WISC-III (FSIQ)	0 (Hg, cord tissue)
		WISC-III (VIQ)	0 (Hg, cord tissue)
		WISC-III (PIQ)	0 (Hg, cord tissue)

Table 2-48. Results of Epidemiological Studies Evaluating General Population Exposure to Mercury (Predominant Mercury Form Unknown) and Neurodevelopmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result[a]
Kim et al. 2018 Prospective cohort of mother-infant pairs, follow-up at age 6 months (n=662), 12 months (n=595), 24 months (n=523), and 36 months (n=438); Republic of Korea	BHg geometric mean Maternal (late pregnancy): 3.0 µg/L Cord: 5.1 µg/L	BSID 6 months	0 (BHg, maternal) 0 (BHg, cord)
		BSID 12 months	0 (BHg, maternal) 0 (BHg, cord)
		BSID 24 months	0 (BHg, maternal) 0 (BHg, cord)
		BSID 36 months	0 (BHg, maternal) 0 (BHg, cord)
Lam et al. 2013 Prospective cohort of mother-infant pairs, follow-up at age 8 years (n=608); Hong Kong	BHg median Cord: 9.21 µg/L	WISC-HK (picture arrangement)	↓ (BHg, cord)
		WISC-HK (total)	0 (BHg, cord)
		HKLLT (recall)	↓ (BHg, cord)
		TEACH	0 (BHg, cord)
		BNT	0 (BHg, cord)
		GPB	0 (BHg, cord)
Lederman et al. 2008 Prospective cohort of mother-infant pairs, follow-up at ages 12, 24, and 36 months (n=280); New York	BHg mean Cord: 7.82 µg/L Maternal: 2.32 µg/L	BSID MDI, 12 months	0 (BHg, cord)
		BSID PDI, 12 months	0 (BHg, cord)
		BSID MDI, 24 months	0 (BHg, cord)
		BSID PDI, 24 months	0 (BHg, cord)
		BSID MDI, 36 months	0 (BHg, cord)
		BSID PDI, 36 months	↓(BHg, cord)
		WPPSI-R IQ, 48 months	↓(BHg, cord)
Llop et al. 2012 Prospective cohort of mother-infant pairs (n=1683) follow-up at age 14 months; Spain	BHg geometric mean Cord: 8.4 µg/L	BSID MDI	0 (BHg, cord)
		BSID PDI	0 (BHg, cord)
McKean et al. 2015 Case-control study of 164 autism cases at ages 2–5 years; California	BHg median Neonatal autism: 3.41 µg/L Neonatal controls: 3.48 µg/L	Autism	0 (child BHg)

Table 2-48. Results of Epidemiological Studies Evaluating General Population Exposure to Mercury (Predominant Mercury Form Unknown) and Neurodevelopmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result[a]
Murata et al. 2004b Cross-sectional cohort of 327 mother-child pairs, age 7 years; Japan	HHg mean Maternal: 1.63 µg/g Child: 1.65 µg/g	BAEPL	0 (HHg, maternal)
Oken et al. 2008 Prospective cohort of mother-infant pairs, follow-up at age 38 months (n=341); Massachusetts	EHg mean Maternal: 3.8 ng/g	PPVT	↓ (EHg, maternal)
		WRAVMA	↓ (EHg, maternal)
Oken et al. 2016 Prospective cohort of mother-infant pairs, follow-up at 8 years (n=872); Massachusetts	EHg mean Maternal: 4.0 ng/g	KBIT	0 (EHg, maternal)
		WRAVMA	0 (EHg, maternal)
		WRAML	0 (EHg, maternal)
Orenstein et al. 2014 Prospective cohort of mother-infant pairs, follow-up at age 8 years (n=393); Massachusetts	HHg mean Maternal: 0.6 µg/g	WRAML verbal	0 (HHg, maternal)
		WRAML visual	↓ (HHg, maternal)
		WRAML learning	0 (HHg, maternal)
Rothenberg et al. 2016b Prospective cohort of 270 mother-infant pairs, follow-up at age 12 months; China	HHg geomean Maternal: 0.47 µg/g HMeHg geomean Maternal: 0.26 µg/g (65%, range 30–108)	BSID MDI	↓ HHg
		BSID PDI	0 HHg
Ryu et al. 2017 Prospective cohort of mother-infant pairs, follow-up at 5 years (n=458); Republic of Korea	BHg geometric mean Maternal (late pregnancy): 3.30 µg/L Cord: 5.52 µg/L Child (age 3 years): 2.16 µg/L	SRS (autistic behaviors)	In male children: ↑ (BHg, maternal) ↑ (BHg, cord) 0 (BHg, child) In female children: 0 (BHg, maternal) 0 (BHg, cord) 0 (BHg, child)
Sagiv et al. 2012 Prospective study of mother-infant pairs, follow-up at age 8 years (n=421); Massachusetts	HHg median Maternal: 0.45 µg/g	CTRS (impulsive/ hyperactive)	↑ (HHg, maternal)
		NES CPT	0 (HHg, maternal)
		WISC -III (processing speed)	↓ (HHg, maternal)

Table 2-48. Results of Epidemiological Studies Evaluating General Population Exposure to Mercury (Predominant Mercury Form Unknown) and Neurodevelopmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result[a]
Skogheim et al. 2021 Case-control study of mother-infant pairs, age >2 years (n=705 ADHD cases, 397 ASD cases, 1034 controls); Norway	BHg geomean Maternal: 1.17	ADHD	↓(BHg, maternal)
		ASD	↑ (BHg <1 µg/L, maternal) 0 (BHg >1 µg/L, maternal)
Snoj Tratnik et al. 2017 Prospective study of mother-infant pairs, follow-up at age 18 months (n=361); Slovenia	BHg geomean Cord: 2.06 µg/L HHg geomean Maternal: 0.361 µg/g	BSID III Cognitive	0 (BHg, cord) 0 (HHg, maternal)
		Language	0 (BHg, cord) 0 (HHg, maternal)
		Motor	0 (BHg, cord) 0 (HHg, maternal)
		Fine motor	↓(BHg, cord) 0 (HHg, maternal)
		Gross motor	0 (BHg, cord) 0 (HHg, maternal)
Stewart et al. 2003 Prospective study of mother-infant pairs, follow-up at age 38 months (n=194) and 54 months (n=197); New York	HHg median Maternal: 0.50 µg/g	MSCA 38 months	↓ (HHg, maternal, prenatal PCB detected)
		MSCA 54 months	0 (HHg, maternal)
Taylor et al. 2018a Prospective study (ALSPAC) of mother-infant pairs, follow-up at age 7 years (n=1,558); United Kingdom	BHg median Maternal: 2.23 µg/L	ALSPAC CT (5 subtests)	0 (BHg, maternal)
		DCD	0 (BHg, maternal)
Valent et al. 2013 Prospective cohort of mother-infant pairs, follow-up at age 18 months (n=606), Italy	BHg median Maternal: 0.00235 µg/g Cord: 0.00397 µg/g HHg median Maternal: 0.788 µg/g	BSID composite scores (cognitive, language, motor, social-emotional, adaptive behavior)	0 (HHg, maternal) 0 (BHg, maternal 0 (BHg, cord)
Vejrup et al. 2016 Prospective cohort (MoBa) of mother-infant pairs, follow-up at age 3 years (n=46,750); Norway	Dietary fish mercury median Maternal: 1.3 µg/day Maternal: 0.14 µg/kg/week	DBGR (speech)	↓ (maternal dietary fish mercury >2.6 µg/day)
		ASQ (language)	↓ (maternal dietary fish mercury >2.6 µg/day)

Table 2-48. Results of Epidemiological Studies Evaluating General Population Exposure to Mercury (Predominant Mercury Form Unknown) and Neurodevelopmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result[a]
Vejrup et al. 2018 Prospective cohort (MoBa) of mother-infant pairs, follow-up at age 5 years (n=38,581); Norway	BHg median (n=2,232) Maternal: 1.03 µg/L Dietary fish mercury median Maternal: 0.15 µg/kg/week	ASQ (language)	0 (BHg, maternal) ↓ (maternal dietary seafood >400 µg/week)
		SLAS (language)	0 (BHg, maternal) ↓ (maternal dietary seafood >400 µg/week)
		Language 20	0 (BHg, maternal) ↓ (maternal dietary seafood >400 µg/week)
Wu et al. 2014 Prospective cohort of mother-infant pairs, follow-up at age 3 days (n=418); China	BHg median Maternal: 5.00 µg/L Cord: 7.62 µg/L HHg median Maternal: 1.08 µg/g	NBNA (total)	↑ (BHg, cord)
		NBNA (behavior)	0 (BHg, cord)
		NBNA (passive muscle tone)	↑ (BHg, cord)
		NBNA (active muscle tone)	↑ (BHg, cord)
Xu et al. 2016 Prospective cohort of mother-infant pairs, follow-up at age 5 weeks (n=344); Ohio	BHg geometric mean Maternal: 0.6 µg/L Cord: 0.72 µg/L	NICU NNS	0 (HHg, maternal) 0 (HHg, cord)
Yau et al. 2014 Retrospective cohort of 84 autism cases and 49 developmental delay cases at age 3–4 years; California	Serum mercury geometric mean Maternal autism: 0.48 µg/L Maternal control: 0.32 µg/L BHg geometric mean Neonatal autism: 3.52 µg/L Neonatal control: 2.85 µg/L	Autism	0 (maternal serum Hg) 0 (child BHg)

[a]Interpretation of neurobehavioral test scores:
ADHD: higher score = more behavioral problems
ASD: higher score = more behavioral problems
ALSPAC CT: higher score = higher performance
ASQ: higher score = more behavioral problems
BNT: higher score = higher performance
BSID: higher score = higher performance
CPT: longer response time = lower performance
CTRS: higher score = lower performance
DBGR: higher score = higher performance
DCD: higher score = more behavioral problems
DDST-II: milestones evaluated against a standard; below standard = delayed development
GDS: higher score = higher performance
GPB: higher score = lower performance

Table 2-48. Results of Epidemiological Studies Evaluating General Population Exposure to Mercury (Predominant Mercury Form Unknown) and Neurodevelopmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result[a]
HKLLT: higher score = higher performance KBIT: higher score = higher performance Language 20: higher score = higher performance MSCA: higher score = higher performance MSCA: higher score = higher performance NBNA: higher score = higher performance NICU NNS: higher score = higher performance PEDS: higher score = higher performance PPRVT: higher score = higher performance SDQ: higher score = more behavioral problems SLAS: higher score = higher performance SRS: higher score = more behavioral problems TEACH: higher score = higher performance WISC-III: higher score = higher performance WPPSI-RK: higher score = higher performance WRAVMA: higher score = higher performance			

↑ = positive association; ↓ = inverse association; 0 = no association; ADHD = Attention Deficit/Hyperactivity Disorder; ALSPAC = Avon Longitudinal Study of Parents and Children; ASD = Autism Spectrum Disorder; ASQ = Ages and Stages Communication Scale; BAEPL = brainstem auditory evoked potential latencies; BHg = blood mercury; BNT = Boston naming test; BSID = Bayley Scales of Infant Development; CTRS = Connors' Teacher Rating Scale; DBGR = Dale and Bishop Grammar Rating; DDST = Denver Developmental Screening Test; EHg = erythrocyte mercury; FSIQ = full scale intelligence quotient; GDS = Gesell Development Schedules; GPB = grooved pegboard; HHg = hair mercury; HKLLT = Hong Kong List Learning Test; HMeHg = hair methylmercury; KBIT = Kauffman Brief Intelligence Test; KNHANES = Korea National Health and Nutrition Examination Survey; MDI = BSID Mental Development Index; MoBa = Norwegian Mother and Child Cohort Study; MSCA = McCarthy Scales of Children's Abilities; NBNA = Neonatal Behavioral Neurological Assessment; NES CPT = Neurobehavioral Evaluation Systems Continuous Performance Test; NICU NNS = Neonatal Intensive Care Unit Network Neurobehavioral Scale; PDI = BSID Psychomotor Development Index; PEDS = Parents Evaluation of Developmental Status; PIQ = Performance Intelligence Quotient; PPVT = Peabody Picture Vocabulary Test; SDQ = Strengths and Difficulties Questionnaire; SLAS = Speech and Language Assessment Scale; SRS = Social Responsiveness Scale; TEACH = Test for Everyday Attention for Children; VIQ = Verbal Intelligence Quotient; WISC-III = Wechsler Intelligence Scale, 3rd Edition; WISC-IV = Wechsler Intelligence Scale, 4th Edition; WISC-HK = Wechsler Intelligence Scale, Hong Kong; WPPSI-R = Wechsler Preschool and Primary Scale Intelligence, Revised; WPPSI-RK = Wechsler Preschool and Primary Scale Intelligence, Revised, Korean; WRAML = Wide Range Assessment of Memory and Learning; WRAVMA = Wide Range Assessment of Visual Motor Abilities

General populations are exposed to a mixture of elemental, inorganic, and organic mercury. The relative contribution from each form of mercury in the studied populations is likely to vary with diet, number and state of mercury amalgam dental restorations, and extent of occupational exposures. Given the uncertainty in the source of exposure to mercury, the biomarkers used to represent exposure (e.g., total hair mercury, total blood mercury) cannot be confidently attributed to any specific form of mercury (see Section 3.3.1, Biomarkers of exposure).

A possible exception is a large prospective study conducted in Norway (Vejrup et al. 2016, 2018). This study examined a birth cohort consisting of 46,750 mother-infant pairs recruited during the period 1999–

2008. Dietary intake of mercury from fish consumption was estimated in each mother based on outcomes of a food frequency questionnaire completed during pregnancy and a survey of mercury levels in fish consumed by Norwegians (Jenssen et al. 2012). Median mercury intake from consumption of fish was estimated to be 0.14 µg Hg/kg/week (range 0.0–1.68 µg Hg/kg/week). The 90th percentile was 0.29 µg Hg/kg/week. (Vejrup et al. 2016). The median intake of fish and seafood was 32 g/day (range 0–292 g/day) (Vejrup et al. 2016). Since dietary intakes of mercury in fish (which is dominated by methylmercury) were estimated, this study did not use biomarkers for the dose metrics.

The Norwegian study evaluated language proficiency and communication skills using parent-administered questionnaires. This study found associations between increasing dietary intake of mercury in fish with decreasing performance on language proficiency tests administered at ages 3 and 5 years. These associations persisted after adjustment for known important confounders related to fish consumption, including fish consumption rate (adjustment strengthened the association with mercury), 3-omega LCPUFA consumption, and exposure to PCBs (Vejrup et al. 2016). The language outcomes associated with mercury intake (>0.29 µg Hg/kg/week) were described as "unintelligible speech" (OR 2.28; 95% CI 1.31, 3.99) on the Dale and Bishop Grammar Rating and "weak communication development" on the Ages and Stages Communication Scale (OR 1.29; 95% CI 1.00, 1.67). Estimates of ORs were adjusted for parity, parental education, pre-pregnancy BMI, bilingual parents, and child age.

In a follow-up at age 5 years, children were assessed with three outcome tests: Ages and Stages Communication Scale, Speech and Language Assessment Scale, and Twenty Statements about Language-Related Difficulties (Vejrup et al. 2018). No associations were observed with mid-pregnancy maternal blood mercury concentrations in a subcohort of the main cohort (2,232 subjects) in which blood mercury levels were measured (median 1.0 µg Hg/L; range 0–14 µg Hg/L). However, in the full cohort (n=38,397) among women who consumed <400 g fish/week, both fish consumption and mercury intake were associated with improvement of scores (negative error scores) in the Ages and Stages Communication Scale (adjusted β -0.16; 95% CI -0.3, -0.02) and Speech and Language Assessment Scale (-0.22; 95% CI -0.4, -.01).

When Vejrup et al. (2018) confined the analyses to matched siblings, dietary fish mercury intake at the 90th percentile level (>3.18 µg Hg/day) was associated with decreasing performance on the Speech and Language Assessment Scale (adjusted β 0.1; 95% CI 0.1, 0.2) but not on the Ages and Stages Communication Scale or Language-Related Difficulties scale. These results suggest that fish intake was a confounding variable in this study (correlation between dietary fish mercury intake and fish intake was

0.88) and may have attenuated associations between dietary methylmercury intake and delays in attainment of language skills. The absence of an association with maternal blood mercury may represent variance in blood mercury levels that is unrelated to dietary methylmercury intake (e.g., mercury from amalgam restorations).

Results from other smaller studies that have examined associations between mercury exposure biomarkers and language proficiency have been inconsistent (Barbone et al. 2019; Freire et al. 2010; Hu et al. 2016; Jeong et al. 2017; Julvez et al. 2013, Lederman et al. 2008; Orenstein et al. 2014; Rothenberg et al. 2016b; Snoj Tratnik et al. 2017; Valent et al. 2013). A prospective study conducted in the Republic of North Korea (553 mother-infant pairs) found associations between increasing maternal blood mercury (median 3.1 µg Hg/L) and verbal proficiency at age 5 years, which persisted when adjusted for blood lead and maternal fish consumption (Jeong et al. 2017). The effect size was estimated to be a 2.48 verbal IQ points (95% CI 0.72, 4.2) and 2.40 points in total IQ (95% CI 0.51, 4.27) per doubling of maternal blood mercury. The Barbone et al. (2019) meta-analysis of populations in Mediterranean Europe (1,308 mother infant pairs) found an association between increasing prenatal (cord) blood mercury (median 3.6 µg Hg/L) and improved language performance at age 18 months, based on scores on the Bayley Scales of Infant Development. Mercury levels in the Barbone et al. (2019) study were similar to the Jeong et al. (2017) study (described above), which found an association between prenatal blood mercury and declining language proficiency. Other studies found declines in language or verbal performance (Freire et al. 2010) or no association (Hu et al. 2016; Julvez et al. 2013; Orenstein et al. 2014) with mercury exposure biomarkers.

Several studies measured cognitive performance with the Bayley Scales of Infant Development at various ages, allowing comparison of the same outcomes across studies (Barbone et al. 2019; Jedrychowski et al. 2006, 2007; Kim et al. 2018; Lederman et al. 2008; Llop et al. 2012; Rothenberg et al. 2016b; Snoj Tratnik et al. 2017; Valent et al. 2013). Two of these studies found an inverse association with cord blood mercury (0.9 µg Hg/L) at age 12 months (Jedrychowski et al. 2006; Rothenberg et al. 2016b); one study found a positive association with cord blood mercury (median 3.6 µg Hg/L) at age 18 months (Barbone et al. 2019); one study found an inverse association with cord blood mercury (mean 7.8 µg Hg/L) at age 36 months, but not at younger ages (Lederman et al. 2008); and five studies found no association with cord or maternal blood mercury levels (median range >0.9–8.4 µg Hg/L) at ages 12–36 months (Jedrychowski et al. 2007; Kim et al. 2018; Llop et al. 2012; Snoj Tratnik et al. 2017; Valent et al. 2013).

For example, when Jedrychowski et al. (2006) did not adjust for fish consumption or exposure to lead or PCBs, an inverse association was observed. When Jedrychowski et al. (2007) did adjust for fish consumption, there was no association. However, this was not the case for Rothenberg et al. (2016b) where the inverse association was strengthened after adjustment for maternal fish and shellfish consumption, rice consumption, and total energy intake. Other studies that found no association adjusted their regression models for fish consumption (Kim et al. 2018; Llop et al. 2012; Valent et al. 2013) and PCB and lead exposure (Llop et al. 2012). The inverse association observed in the Rothenberg et al. (2016b) study was strengthened after adjustment for maternal fish and shellfish consumption, rice consumptions, and total energy intake. Studies that found no association adjusted their regression models for fish consumption (Jedrychowski et al. 2007; Kim et al. 2018; Llop et al. 2012; Valent et al. 2013) and PCB and lead exposure (Llop et al. 2012).

Exposure to PCBs was found to be an important modifier of the association between cognitive performance measured with the McCarthy Scales of Children's Abilities at age 38 months (Stewart et al. 2003). Lederman et al. (2008) found an inverse association between cord blood mercury (mean 7.8 µg Hg/L) and IQ measured at age 48 months (Wechsler Preschool and Primary Scale Intelligence, Revised), after adjustment for fish and seafood consumption during pregnancy and other potential confounders (maternal age, race, education IQ, income, marital status, exposure to tobacco smoke, and material hardship; child sex, gestational age, and age at testing). The effect size was -3.6 IQ point per ln (µg/L), which corresponds to a 2.5-point decrease in IQ per doubling of cord blood mercury.

Latency of brainstem auditory evoked potentials was not associated with increasing maternal hair mercury levels in a prospective study (327 mother-infant pairs) conducted in Japan (Murata et al. 2004b). This observation is notable because increased latency of auditory evoked potentials was observed in the Faroe Islands and Madeira Portugal studies of high fish consumption populations (Grandjean et al. 1997, 1998, 2003; Murata et al. 1999a, 1999b). Maternal hair mercury was higher in the Faroe Islands cohort (median 4.3 µg Hg/g) and Madeira cohort (9.4) compared to the Japanese cohort (mean 2 µg Hg/g). A cross-sectional analysis of data from the KNHANES (853 adolescents) found no association between blood mercury levels in 853 adolescents (mean 2.0 µg Hg/L) or 5,187adults (mean 3.6 µg Hg/L) and speech-frequency or high-frequency hearing loss (Choi and Park 2017).

Several studies have examined association between mercury exposure biomarkers (blood or urinary mercury) and signs of autism spectrum disorder (Golding et al. 2016a, 2016b, 2017, 2018; Hertz-Piccioto et al. 2010; McKean et al. 2015; Ryu et al. 2017; Skogheim et al. 2021; Yau et al. 2014). In general,

these studies found no associations between behaviors indicative of autism spectrum disorder and exposure to mercury. The largest prospective study reported (approximately 3,000 mother infant pairs) found no associations between maternal blood mercury levels (median 1.86 µg Hg/L) and signs of autism (Golding et al. 2016a, 2017, 2018). A smaller prospective study (450 mother-infant pairs) found an association between increasing maternal blood mercury levels (median 3.3 µg Hg/dL) and increasing scores for autistic behaviors on the Social Responsiveness Scales, in male children age 5 years, but not in females (Ryu et al. 2017). Several case-control studies have not found differences in covariate-adjusted blood mercury concentrations between autism cases and controls (Hertz-Piciotto et al. 2010; McKean et al. 2015; Yau et al. 2014). Skogheim et al. (2021) found a nonlinear relationship between maternal blood mercury concentrations and OR for autism spectrum diagnosis, with elevated ORs at maternal blood mercury levels (<1 µg/L) but not at levels from >1 to 5 µg/L. The OR for ADHD diagnosis was negative.

2.16.2 Neurological Effects in Adults

Elemental Mercury—Epidemiological Studies. Studies of neurological function have been conducted in workers in various industries who were exposed to mercury vapor. Studies of neurological outcomes in workers are summarized in Table 2-49. The following populations exposed to elemental mercury were evaluated: chloralkali workers; florescent lamp workers; thermometer production workers; dental workers; workers in other industries; and populations with amalgam fillings. In some studies, work area or breathing zone mercury levels measured in a subset of the study group were reported. The most common biomarker reported was urine mercury (µg Hg/L or µg Hg/g creatinine). In cross-sectional studies, these were based on measurements made at the time of outcome assessment. In retrospective studies, urine mercury estimates were derived from historical industrial hygiene monitoring data and, in some studies, were aggregated into metrics of cumulative exposure (e.g., sum of quarterly average values for all exposure years) or exposure intensity (sum/exposure years). Most of the studies included in this discussion compared outcomes measured in exposed workers to a reference group of workers who were not exposed to elemental mercury. Potential selection bias and confounding were addressed by matching (e.g., age, sex, alcohol and smoking history, duration of exposure-related work) or by exclusion (e.g., head injuries, known neurological disease). However, other numerous potential variables that could have affected performance on tests of cognitive function (e.g., nutrition, exposure to other chemicals) were not evaluated (see discussion of characterization of effects on neurodevelopment). Collectively, these studies provide evidence for associations between exposure to mercury vapor and several categories of neurological effects, including tremor, vision, nerve conduction, and cognitive performance (motor speed and coordination, memory, and integrative function).

Table 2-49. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Neurological Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Chloralkali workers			
Albers et al. 1982 Retrospective cohort of 138 workers; United States	UHg working mean 36-months: normal: 80 µg/L polyneuropathy: 120 µg/L	Motor nerve conduction	↓ UHg
		Sensory nerve conduction	↓ UHg
Bast-Pettersen et al. 2005 Retrospective cohort of 49 former workers and 49 referents; Norway	UHg cumulative work mean: 16.5 µg/g Cr/year UHg mean at testing Workers: 2.93 µg/g Cr Referents: 2.04 µg/g Cr BHg mean at testing Workers: 4.63 µg/L Referents: 3.51 µg/L	Hand tremor	0 (exposed versus referents)
		Digit span test	0 (exposed versus referents)
		Digit symbol test	0 (exposed versus referents)
		Trail making test	0 (exposed versus referents)
		Visual retention test	0 (exposed versus referents)
		Finger tapping test	0 (exposed versus referents)
		NES CPT	0 (exposed versus referents)
Bluhm et al. 1992 Cross-sectional study of 26 workers and referent population (n=27); United States	UHg mean: 100–200 µg/24 hours BHg mean: 50–100 µg/L	Trail making test	↓ UHg ↓ (exposed versus referents)
		Stroup color-word test	↓ UHg ↓ (exposed versus referents)
		Finger tapping test	↓ UHg ↓ (exposed versus referents)
		Grooved pegboard test	↓ UHg ↓ (exposed versus referents)

Table 2-49. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Neurological Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Chang et al. 1995 Retrospective cohort of 26 workers; China	UHg mean at testing Workers: 40.5 µg/24 hours Referents: NR	Visual evoked potential N1-P1 interpeak amplitude	↑ (exposed versus referents)
	UHg mean at testing Workers: 358 µg/g Cr Referents: NR	BAEP latency	↑ (exposed versus referents)
	BHg mean at testing Workers: 28 µg/L Referents: NR		
Ellingsen et al. 2001 Retrospective cohort of 47 former workers and 47 referents; Norway	UHg cumulative work mean: 16.0 µg/g Cr/year	Hand steadiness	0 (exposed versus referents)
		Digit span test	0 (exposed versus referents)
	UHg mean at testing Workers: 10.5 µg/g Cr Referents: 2.3 µg/g Cr	Digit symbol test	↓ (BHg inorganic)
		Trail making test	0 (exposed versus referents)
	BHg inorganic mean at testing Workers: 4.15 µg/L Referents: 1.1 µg/L	Visual retention test	↓ (BHg inorganic)
		Finger tapping test	0 (exposed versus referents)
		NES CPT	0 (exposed versus referents)
Frumkin et al. 2001 Retrospective cohort of 139 former workers and 107 referents; United States	UHg mean at testing Workers: 2.76 µg/g Cr Referents: 2.31 µg/g Cr	Tremor	↑ (exposed versus referents)
		Vibration threshold	↑ (exposed versus referents)
	UHg working mean: 72.1 µg/L	Finger tapping	↓ (exposed versus referents)
	Air mercury average: range: 2,106 µg/m^3	NC composite	↑ (exposed versus referents)
		Motor speed composite	0 (exposed versus referents)
		Motor coordination composite	0 (exposed versus referents)
		Memory composite	0 (exposed versus referents)
		Integrative functions	0 (exposed versus referents)

Table 2-49. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Neurological Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Langolf et al. 1978 Retrospective study of 79 workers and 51 referents; United States	UHg working mean Workers: 240 µg/L Referents: 30 µg/L	Forearm tremor	↑ (UHg)
		Forearm EMG bandwidth	↑ (UHg)
		Finger tapping rate	↓ UHg
		Hand-eye coordination	↓ UHg
Langworth et al. 1992a Retrospective sectional cohort of 89 workers and 75 referents; Sweden	UHg working median Workers: 25.4 µg/g Cr Referents: 1.9 µg/g Cr BHg working median Workers: 11 µg/L Referents: 3.0 µg/L Air mercury mean: 25 µg/m^3	Forearm tremor	0 (exposed versus referents)
		Hand-eye coordination	0 (exposed versus referents)
		Finger tapping	0 (exposed versus referents)
		Simple reaction time	0 (exposed versus referents)
		Symbol digit	0 (exposed versus referents)
		Digit span	0 (exposed versus referents)
		Sternberg memory task	0 (exposed versus referents)
Levine et al. 1982 Retrospective cohort of 18 workers; United States	UHg working mean 12-month average: 290 µg/L 24-month average: 210 µg/L	Motor nerve conduction latency	↑ UHg (24-month average)
		Sensory nerve conduction latency	↑ UHg (12- and 24-month average)
Mathiesen et al. 1999 Retrospective cohort of 75 former workers and 52 referents; Norway	UHg cumulative work mean: 108 µg/L/year UHg mean at testing Workers: 0.36 µg/g Cr Referents: 0.24 µg/g Cr BHg mean at testing Workers: 5.24 µg/L Referents: 5.54 µg/L	Visual retention	↓ UHg (cumulative/year)
		Grooved pegboard test	↓ UHg (months of exposure)
		Trailmaking test	↓ UHg (cumulative/year)
		Digit symbol test	↑ UHg (≥50 µg/g Cr) ↑ BHg (≥10 µg/L UHg (cumulative/year)
Miller et al. 1975 Cross-sectional cohort of 77 workers and 65 referents; United States	UHg group mean range Workers: 129–787 µg/L Referents: 7.11–152 µg/L BHg group mean range Workers: 3.97–17.11 µg/L Referents: 0.90–5.89 µg/L	Forearm tremor	↑ UHg
		Forearm EMG bandwidth	↑ UHg

Table 2-49. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Neurological Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Piikivi et al. 1984 Retrospective cohort of 36 workers and referents; Finland	UHg mean at testing Workers: 58.3 µg/L Referents: NR BHg mean at testing Workers: 20.0 µg/L Referents: NR	Picture similarity test	↓ UHg (TWA >110 µg/L) ↓ UHg (highest >300 µg/L)
		Logical memory	0 UHg (TWA >110 µg/L) ↓ UHg (highest >300 µg/L)
		Santa Ana dexterity test	↓ UHg (TWA <110 µg/L) ↓ UHg (highest <300 µg/L) ↓ (exposed versus referents)
Piikivi and Hanninen 1989 Retrospective cohort of 60 workers and referents; Finland	UHg mean at testing Workers: 17.9 µg/g Cr Referents: 2.1 µg/g Cr BHg mean at testing Workers: 6.78 µg/L Referents: 0.92 µg/L BHg (inorganic) TWA working mean: 5.94 µg/L	Hand-eye coordination	↑ (exposed versus referents)
		Finger tapping	0 (exposed versus referents)
		Memory and learning	0 (exposed versus referents)
		Continuous performance test	0 (exposed versus referents)
Roels et al. 1982 Cross-sectional cohort of 43 chloralkali and mercury battery workers and 47 referents; Belgium	UHg median at testing Workers: 71.0 µg/g Cr Referents: 1.2 µg/g Cr BHg median at testing Workers: 20.6 µg/L Referents: 1.9 µg/L	Hand tremor	↑ UHg (≥50 µg/g Cr) ↑ BHg (≥10 µg/L)
		Hand-eye coordination	↓ UHg (≥50 µg/g Cr) ↓ BHg (≥10 µg/L
Smith et al. 1983 Retrospective cohort of 86 workers; United States	UHg working mean Plants 1 and 2 (n=26) 3 months: 195 µg/L 24 months: 143 µg/L Plants 3 and 4 (n=60) 3 months: 108 µg/L 24 months: 93 µg/L	Short-term memory	↓ UHg
Urban et al. 2003 Cross-sectional cohort of 24 workers and 24 referents; Czech Republic	UHg mean Workers: 20.5 µg/g Cr Referents: 1 µg/L Air mercury 8 hours TWA: 59 µg/m^3	Visual color discrimination	0 UHg ↓ UHg (DMPS-provoked) ↓ (exposed versus referents)

Table 2-49. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Neurological Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Wastensson et al. 2006, 2008 Retrospective cohort of 43 workers and 22 referents; Sweden	UHg cumulative work mean: 266 µg year/g Cr (mean 15 years), which corresponds to an average of 1.7 µg/g Cr UHg median at testing Workers: 5.9 µg/g Cr Referents: 0.7 µg/g Cr	Postural tremor	0 UHg at testing 0 UHg cumulative
		Hand tremor	↓ UHg at testing ↓ UHg cumulative
		Hand-eye coordination	0 UHg at testing 0 UHg cumulative
		Hand-eye coordination	0 UHg at testing 0 UHg cumulative
Florescent lamp workers			
Barboni et al. 2008 Retrospective cohort of 35 former workers and 34 referents; Brazil	UHg working mean: 41.15 µg/g Cr UHg mean at testing Workers: 2.39 µg/g Cr Referents: NR	Visual field loss	↓ (exposed versus referents)
Fawer et al. 1983 Cross-sectional cohort of 26 workers (12 chloralkali, 7 lamp and 7 acetaldehyde) and 25 referents; Belgium	UHg mean Workers: 20.1 µg/g Cr Referent: 6.0 µg/g Cr Air mercury TWA: 26 μgm^3	Tremor	↑ (exposed versus referents)
Milioni et al. 2017 Cross-sectional cohort of 31 workers and 31 referents; Brazil	NR	Recover of pupil contraction response to light	↓ (exposed versus referents)
Ventura et al. 2005 Retrospective cohort of 39 former workers and 21 referents; Brazil	UHg working mean: 41.09 µg/g Cr	Color vision loss	↓ (exposed versus referents)
Verberk et al. 1986 Retrospective cohort of 20 workers; The Netherlands	UHg mean at testing: 35.7 µg/g Cr	Tremor	↑ UHg
Thermometer production workers			
Cavalleri and Gobba 1998 Cross-sectional cohort of 21 workers and 21 referents; Italy	Workers: 114.9 µg/g Cr Referents: NR UHg mean after chelation: 10.0 µg/g Cr	Color discrimination	↓ (exposed versus referents) ↓ UHg

Table 2-49. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Neurological Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Ehrenberg et al. 1991 Cross-sectional cohort of 83 workers and 79 referents; United States	UHg mean: 73 µg/g Cr Air mercury, 80-hour TWA, range: 9.3–75.6 µg/m^3	Abnormal heal-to-toe walk	↑ (exposed versus referents)
Tang and Li 2006 Cross-sectional cohort of 143 workers; China	UHg mean: 30 µg/L Air workplace mean: 27 µg/m^3	Tremor	↑ UHg (≥50 µg/L versus <10 µg/L)
		Neurasthenic symptoms (self-reported)	↑ UHg (≥50 µg/L versus <10 µg/L)
		Emotional changes (self-reported)	↑ UHg (≥50 µg/L versus <10 µg/L)
		Oral or gum inflammation	↑ UHg (≥50 µg/L versus <10 µg/L)
Dental workers			
Anglen et al. 2015 Retrospective cohort of 13,906 dental workers; United States	UHg mean Year 1976: 20.1 µg/L Year 2012: 2.04 µg/L basis for OR: 4.7 µg/L	Tremor	↑ UHg 0 Restorations per week
		Multiple sclerosis	0 UHg 0 Restorations per week
Bittner et al. 1998 Pooled study cohort of 230 dental workers; United States	UHg: 95% <55 µg/L	Hand steadiness	↓ UHg
		Finger tapping	0 UHg
		One-hole test	0 UHg
		Reaction time	0 UHg
		Hand tremor	0 UHg
Canto-Pereira et al. 2005 Cross-sectional cohort of 15 dental workers and 13 referents; Brazil	UHg geomean testing Workers: 1.54 µg/g Cr Referents: 0.66 µg/g Cr	Color contrast sensitivity	↓ (exposed versus referents)
		Color discrimination	↓ (exposed versus referents)
		Color confusion index	0 (exposed versus referents)
Echeverria et al. 1998 Cross-sectional cohort of 49 dental workers (24 dentists, 15 assistants); United States	UHg mean Dentists: 0.89 µg/L Assistants: 1.07 µg/L	Mood symptoms	↑ UHg
		Motor coordination	↓ UHg
		Visual processing performance	↓ UHg
		Verbal processing and attention	0 UHg

Table 2-49. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Neurological Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Echeverria et al. 2005 Cross-sectional cohort of 427 male dentists, 233 female dental assistants; United States	UHg mean Females: 1.98 µg/L Males: 3.32 µg/L	Attention	↓ UHg
		Working memory	↓ UHg
		Visual memory	↓ UHg
		Motor performance	↓ UHg
		Hand steadiness	↓ UHg
Franzblau et al. 2012 Longitudinal cohort of 2,767 dental workers, United States	UHg median 2.58 µg/L	Median NCV	0 UHg
		Ulnar NVC	0 UHg
Heyer et al. 2004 Cross-sectional cohort of 423 dental workers (193 male dentists, 230 female dental assistants); United States	UHg mean 2.32 µg/L	Mood symptoms	↑ UHg
		Neurologic symptoms	↑ UHg
Ngim et al. 1992 Cross-sectional cohort of 98 dental workers and 54 referents; Singapore	Air mercury geomean 8-hour TWA: 13.6 µg/m^3 BHg geometric mean Dentists: 9.8 µg/L Referents: NR	Motor coordination	↓ UHg
		Visual processing performance	↓ UHg
		Working memory	↓ UHg
		Visual-motor performance	↓ UHg
Ritchie et al. 2002 Cross-sectional cohort of 170 dental workers and 179 referents; United Kingdom	UHg median Workers: 0.34 µg/g Cr Referents: 0.10 µg/g Cr Air mercury median range: 5.7–21.2 µg/m^3	Attention	0 UHg
		Reaction time	0 UHg
		Visual memory	0 UHg
		Working memory	0 UHg
Sletvold et al. 2012 Cross-sectional cohort of 91 female dental workers; Norway	UHg median 12.0 µg/L	Motor function	0 UHg
		Short-term memory	0 UHg
		Working memory	0 UHg
		Verbal long-term memory	0 UHg
		Visual long-term memory	↓UHg
		Executive function	0 UHg
		Mental flexibility	0 UHg

Table 2-49. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Neurological Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Wang et al. 2012 Cross-sectional cohort of 513 dental workers (244 dentists and 269 dental assistants and hygienists); United States	UHg geomean 0.65 µg/L HHg median: 0.28 µg/g	Sural nerve conduction latency	↓ UHg ↓ HHg
		Ulnar nerve conduction latency	0 UHg ↓ HHg
Other workers			
Albers et al. 1988 Retrospective cohort of 247 lithium 6 workers and 255 referents; United States	UHg working mean 199.9 µg/L[a]	Tremor	↑ UHg ↑ (exposed versus referents)
Barboni et al. 2009 Cross-sectional cohort of 10 mercury recycling workers and 79 referents (10–20 referents per test); Brazil	UHg mean Workers: 22.3 µg/g Cr Referents: NR	Color discrimination	↓ (exposed versus referents)
		Visual field threshold	↓ (exposed versus referents)
		Visual contrast sensitivity	↓ (exposed versus referents)
Boogaard et al. 1996 Retrospective cohort of 40 natural gas workers and 19 referents; The Netherlands	UHg working median High exposure: 41 µg/L Low exposure: 12 µg/L UHg median at testing High exposure: 17 µg/L Low exposure: 5 µg/L Referents: 2 µg/L UHg median at testing high exposure: 17 µg/L low exposure: 5 µg/L	Tremor	0 UHg 0 (exposed versus referents)
Chapman et al. 1990 Cross-sectional cohort of 18 battery workers and 18 referents; United States	UHg mean at testing Workers: 23.1 µg/L Referents: NR	Tremor	↑ (exposed versus referents)
Harari et al. 2012 Cross-sectional cohort of 200 gold miners or processors, 37 gold merchants, and 72 referents; Ecuador	UHg mean at testing Merchants: 36.9 µg/g Cr Miners: 3.3 µg/g Cr Referents: 1.6 µg/g Cr BHg mean at testing Merchants: 30.1 µg/L Miners: 5.3 µg/L Referents: 5.0 µg/L	Postural tremor	↑ UHg
		Postural sway	↑ UHg
		Hand coordination	0 UHg

Table 2-49. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Neurological Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Iwata et al. 2007 Cross-sectional cohort 27 cinnabar miners and 52 referents; China	UHg geomean at testing Workers: 228 µg/g Cr Referents: 2.59 µg/g Cr	Tremor	0 UHg ↑ (exposed versus referents)
		Postural sway	↑ UHg (transverse sway) 0 (exposed versus referents)
Letz et al. 2000 Retrospective cohort of 104 lithium 6 workers and 101 referents; United States	UHg working median 180 µg/L	Polyneuropathy (tremor, decreased hand grip strength, slowed peripheral nerve conduction)	↑ UHg ↑ (exposed versus referents)
Mercury amalgam fillings			
Factor-Litvak et al. 2003 Cross-sectional cohort of 550 health center employees not exposed occupationally (mean age 40 years); New York	UHg median: 1.3 µg/g Cr Median number of amalgams: 10 Median number of occlusal amalgam surfaces: 6	SRT (verbal memory)	0 UHg 0 number of amalgams 0 number of occlusal amalgams
		BVRT (nonverbal memory)	0 UHg 0 number of amalgams 0 number of occlusal amalgams
		WAIS trail-making	0 UHg 0 number of amalgams 0 number of occlusal amalgams
		WAIS digit symbol	0 UHg 0 number of amalgams 0 number of occlusal amalgams
		Grooved pegboard (fine motor control)	0 UHg 0 number of amalgams 0 number of occlusal amalgams
Hsu et al. 2016 Retrospective cohort of 10,236 people with amalgam restorations matched to referents without amalgam restorations (age >55 years); China	None	Parkinson's Disease at death	↑ (amalgams versus no amalgams)

Table 2-49. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Neurological Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Sun et al. 2015 Retrospective cohort of 31,379 people with amalgam restorations and 176,208 without amalgam restorations (age >65 years); Taiwan	None	Alzheimer's Disease at death	↑ (amalgams versus no amalgams)

[a]Interpretation of neurobehavioral test scores:
BVRT: higher score = higher performance
CPT: longer response time = lower performance
Digit span: higher score = higher performance
Digit symbol test: higher score = higher performance
Finger tapping: higher score = higher performance
Grooved pegboard: longer time = lower performance
Picture similarity test: higher score = higher performance
RVRT: higher score = higher performance
Sant Ana dexterity test: higher score = higher performance
SRT: higher score = higher performance
Steinberg memory test: higher score = higher performance
Stoop color-word test: higher score = higher performance
Trailmaking: longer time = lower performance
Visual retention test: higher score = higher performance

[b]The UHg working mean value was not reported by Albers et al. (1988) but was calculated based on data presented in Letz et al. (2000). There is substantial overlap between subjects in this study and the study by Letz et al. (2000); 89 exposed and 83 referents examined in both studies.

↑ = positive association; ↓ = inverse association; 0 = no association; BAEP = brainstem auditory evoked potential; BHg = blood mercury; BVRT = Benton Visual Retention Test; Cr = creatinine; DMPS = 2,3-dimercapto-1-propane sulfonate; EMG = Electromyography; HHg = hair mercury; NCV = nerve conduction velocity; NES CPT = Neurobehavioral Evaluation Systems Continuous Performance Test;; NR = not reported; SRT = Selective Reminder Test; TWA = time-weighted average; UHg = urine mercury; WAIS = Wechsler Adult Intelligence Scale

Chloralkali workers. Chloralkali workers are exposed to mercury vapor during handling, processing, and storage of elemental mercury used in mercury electrolysis cells in the production of sodium hydroxide. These studies have found associations between exposure to mercury vapor or mercury biomarkers (urine mercury) and tremor, vision, peripheral nerve conduction and sensory evoked potentials, and performance on tests of hand-eye coordination and memory.

Several studies of chloralkali workers have found associations between exposure to mercury vapor and tremor (Chapman et al. 1990; Fawer et al. 1983; Frumkin et al. 2001; Langolf et al. 1978; Miller et al. 1975; Roels et al. 1982). Urine mercury levels (mean or median) in these studies ranged from approximately 20 to 240 µg Hg/g creatinine. The largest of these studies examined 139 former

chloralkali workers and found increased tremor and increased threshold for sensing vibration in workers compared to a referent group matched with workers for sex, age, race, education, and urine mercury levels at time of testing age-matched referents (Frumkin et al. 2001). The mean urinary mercury level during measured at the time of work in the plant was 72 µg Hg/L. Several metrics of cognitive performance were also assessed in this study and were not found to be associated with exposure to mercury. These included tests of motor speed and fine motor and visuomotor coordination, memory, and integrated cognitive function. Several studies that evaluated tremor in chloralkali workers did not find associations with mercury exposure (Bast-Pettersen et al. 2005; Ellingsen et al. 2001; Langworth et al. 1992a; Wastensson et al. 2006, 2008). Urine mercury levels (mean or median) in these studies ranged from approximately 11 to 18 µg Hg/g creatinine.

A clinical study found decreased visual color discrimination in a group of chloralkali workers (n=24) compared to a sex- and age-matched referent group (n=24; Urban et al. 2003). Color discrimination was not associated with urine mercury levels (mean 21 µg Hg/g creatinine; range 0.15–62 µg Hg/g creatinine); however, discrimination decreased in association with urinary mercury excretion provoked with administration of 2,3-dimercapto-1-propane sulfonate (DMPS), a metric of mercury body burden. A clinical study found changes in visual evoked potentials and increased brainstem auditory evoked potentials in a group of chloralkali workers (n=26; mean urine mercury: 358 µg Hg/g creatinine) compared to sex- and age-matched referents (Chang et al. 1995). Increased latency of ulnar nerve conduction was observed in workers (n=18) in association with increasing urine mercury levels (mean 290 µg Hg/L; Levine et al. 1982).

Several studies of chloralkali workers have found associations between exposure to mercury and various measures of cognitive function (Bluhm et al. 1992; Mathiesen et al. 1999; Piikivi et al. 1984 and Smith et al. 1983). These studies found associations between increasing urine mercury and performance on various tests of motor coordination, visual memory, and working memory. Urine mercury levels (mean or median) in these studies ranged from 100 to 140 µg Hg/L. A study of former chloralkali workers (n=49) found no differences between cognitive performance of workers and a referent group (Bast-Pettersen et al. 2005). Mean urine mercury level at testing was 2.9 µg Hg/g creatinine (range 0.3–9.2 µg Hg/g creatinine) and the average over the working period was 16.5 µg Hg/g creatinine per year (range 7–45 µg Hg/g creatinine per year).

Cessation of mercury exposure or chelation therapy to lower the mercury body burden resulted in improvement of outcomes (Bluhm et al. 1992; Langolf et al. 1978). A study of workers (n=26) who were

exposed to mercury vapor while performing construction work in a chloralkali plant found lower performance on trial making and Stroup color word tests, relative to a reference group (Bluhm et al. 1992). The mean urinary mercury excretion rate measured 20–36 days after cessation of exposure was approximately 100–200 µg Hg/day and mean blood mercury level was approximately 50–100 µg Hg/L. Scores on trial making tests improved following treatment with DMSA which accelerated excretion of mercury in urine. A study of chloralkali workers (n=79) found increased tremor and lower performance on tests of hand coordination (Langolf et al. 1978). The mean urine mercury level was 240 µg Hg/L. Follow up of five subjects whose exposures were decreased showed that their neurological outcomes improved after exposures were decreased. Urine mercury levels were 660 µg Hg/L during the high exposure period and 300 µg Hg/L after 6–10 months working in a lower exposure environment.

Mercury battery production workers. Studies of mercury battery production workers are summarized in Table 2-49. Increased prevalence of tremor was observed in workers exposed to mercury vapor in the production of mercury cell batteries (Chapman et al. 1990; Roels et al. 1982). A study of workers (n=43) that included battery production and chloralkali workers, found a higher prevalence (relative to a reference group) of hand tremor in workers who had urine mercury in the range of 50–100 µg Hg/g creatinine and blood mercury in the range of 10–20 µg Hg/L (Roels et al. 1982). Another study (n=15), found a shift in the power spectrum of finger tremor to higher tremor frequencies in battery workers compared to a reference group (Chapman et al. 1990). The mean urine mercury level was 23 µg Hg/L (range <10–121 µg Hg/L). A study of battery production workers (n=8) observed changes in brainstem auditory evoked potential latencies, relative to subjects in a reference group (Discalzi et al. 1993). The mean urine mercury level was 325 µg Hg/g creatinine.

Studies of fluorescent lamp production workers. Studies of fluorescent lamp production workers are summarized in Table 2-49. These studies compared signs and symptoms in workers and reference groups and found higher prevalence of tremor and impaired vision in workers. Increased prevalence of tremor was observed in workers exposed to mercury vapor in the production of mercury fluorescent lamps (Al-Batanony et al. 2013; Fawer et al. 1983; Verberk et al. 1986). In a study of lamp workers (n=25), hand tremor correlated with urine mercury level (mean 36 µg Hg/g creatinine; range 9–53 µg Hg/g creatinine) (Verberk et al. 1986). In a study that evaluated a combined cohort of workers in lamp, chloralkali, and acetaldehyde production (n=26); prevalence of hand tremor was higher in workers exposed to mercury vapor compared to a reference group not exposed to mercury vapor (Fawer et al. 1983). Mean urine mercury in exposed workers was 20 µg Hg/g creatinine (SD 2.1) compared to the reference group

(6.0±1.2 µg Hg/g creatinine). The mean time-weighted average mercury air level of the mercury workers was 26 µg Hg/m^3.

Decreased color discrimination and color vision loss was observed in lamp workers (Barboni et al. 2008; Feitosa-Santana et al. 2010; Ventura et al. 2004, 2005). Studies of former lamp workers (n=30–40) observed, relative to reference groups, lower red-green and blue-yellow discrimination and foveal visual field loss. Mean working urinary levels were 41 µg Hg/g creatinine (SD 1.7) and 2.4 µg Hg/g creatinine at the time of evaluation, approximately 7 years without occupational exposure (Barboni et al. 2008; Ventura et al. 2005). Recovery of pupillary contraction in response to a light flash (a sympathetic nervous system response) was prolonged in former lamp workers (n=31) relative to an age-matched reference group (Milioni et al. 2017). In this same study, mean scores on tests of working memory, spatial memory, and visual memory were lower in the lamp production workers compared to workers in the reference group.

Thermometer production workers. Studies of thermometer production workers are summarized in Table 2-49. Neurological effects have been studied in mercury thermometer production workers (Cavalleri and Gobba 1998; Ehrenberg et al. 1991; Tang and Li 2006). These studies compared signs and symptoms in workers and reference groups and found higher prevalence of tremor, impaired motor coordination, and impaired vision in workers.

The prevalence of neurological symptoms was evaluated in a group of workers (n=122) (Ehrenberg et al. 1991). Prevalence of difficulty in heel-to-toe walk was lower in workers compared to the reference group (relative risk 5.78; 95% CI 1.63, 20.50). Mean urinary mercury level was 73 µg Hg/g creatinine in workers (range 1–344 µg Hg/g creatinine) and 4.2 µg Hg/g creatinine (range: non-detected to 10 µg Hg/g creatinine) on reference workers. Mean 8-hour time-weighted average air mercury levels in the breathing zone ranged from 9.3 to 75.6 µg Hg/m^3.

The prevalence of neurological symptoms was evaluated in a group of workers (n=143) (Tang and Li 2006). Prevalence increased in workers who had urinary mercury levels ≥50 µg Hg/L compared to a group who had urine levels <10 µg Hg/L. The symptoms included tremor and self-reported neurasthenic symptoms (e.g., headache, dizziness, insomnia, memory loss, fatigue, weakness) and emotional changes (mood swings, irritability, nervousness, timidity, loss of confidence). The mean air mercury level measured in workplaces was 27 µg Hg/m^3 (range 11–57 µg Hg/m^3).

Decreased visual color discrimination was observed in a group of workers (n=21) who had a mean urine mercury level of 115 µg Hg/g creatinine (range 34–287 µg Hg/g creatinine) relative to a matched reference group (matched for age, sex, alcohol consumption, and cigarette smoking) with mean urine mercury levels of 1.1 µg Hg/g creatinine (SD 0.13) (Cavalleri and Gobba 1998). Color discrimination was not different from the reference group following implementation of improved industrial hygiene procedures which resulted in mean urinary mercury levels of 10 µg Hg/g creatinine.

Dental practitioners. Several studies of dental practitioners have examined possible associations between exposures to mercury vapor and cognitive function and behavior; studies are summarized in Table 2-49. In these studies, exposures included elemental mercury released from during preparation, installation, or removal of mercury amalgam restorations, as well as exposures to methylmercury and inorganic mercury from other sources (e.g., diet). As a result, biomarkers such as urinary or blood mercury were not specific metrics of exposures to mercury vapor. Few studies reported estimates of exposure concentrations (Decharat et al. 2014; Ngim et al. 1992; Ritchie et al. 2002). Ritchie et al. (2002) measured breathing zone air concentrations in various areas of 180 active dental surgery facilities and reported median time-weighted average concentrations that ranged from 6 to 21 µg Hg/m^3. The median time-weighted average concentration measured in the breathing zones of 124 working dentists was 12 µg Hg/m^3 (range 2–38 µg Hg/m^3) (Decharat et al. 2014). Air mercury vapor concentrations are highly dynamic during some procedures, such as removal drilling of amalgam restorations (Warwick et al. 2019) and, as a result, time-weighted average concentrations may not reflect peak exposures experienced during the procedure.

Most studies of neurological outcomes in dentists have assessed exposure from biomarkers, typically urinary mercury in units of µg Hg/L or µg Hg/g creatinine. The largest study (n=13,905) matched historical records of urinary mercury and health survey data in which subjects self-reported experiencing tremor or diagnosis of multiple sclerosis (Anglen et al. 2015). Urinary mercury levels declined substantially during the survey period from a mean of 20.1 µg Hg/L in 1976 to 2.0 µg Hg/L in 2012. Increasing urinary mercury was associated with an increased OR of tremor per change in cohort mean urine mercury (OR 1.10 per 4.7 µg Hg/L urine; 95% CI 1.00, 1.22) but not with the number of mercury amalgam restorations placed or removed per week. No association was found with diagnosis of multiple sclerosis. Results of several smaller cross-sectional cohort studies that examined cognitive performance in dental practitioners were inconsistent. Some studies have found age-adjusted associations between increasing urinary mercury and decreasing performance on tests of motor coordination, visual processing, and working memory (Bittner et al. 1998; Echeverria et al. 1998, 2005; Ngim et al. 1992), while other studies have found no associations (Ritchie et al. 2002: Sletvold et al. 2012). Changes in self-reported

mood states or neurological symptoms were associated with increasing urinary mercury (Echeverria et al. 1998; Heyer et al. 2004). Results of studies of nerve conduction have also been inconsistent (Franzblau et al. 2012; Wang et al. 2012). Clinical studies have compared neurosensory or cognitive performance in dental practitioners compared to a reference group (Aydin et al. 2003; Canto-Pereira et al. 2005). Decreased visual color discrimination and contrast sensitivity was observed in a group of 15 dentists (median urinary mercury 1.54 µg Hg/g creatinine) compared to an age-matched reference group (0.66 µg Hg/g creatinine) (Canto-Pereira et al. 2005). Decreased performance on tests of logical memory and retention were found in a clinical study of 43 dental practitioners, compared to a reference group (hospital workers) (Aydin et al. 2003).

*Other worker populations. S*tudies of other worker populations are summarized in Table 2-49. Increased tremor was observed in cinnabar miners (n=27), relative to a referent group (Iwata et al. 2007). The median urine mercury level in miners was 228 µg Hg/g creatinine (range 23–4,577 µg Hg/g creatinine). Increased urine mercury was associated with increases in postural sway in workers exposed to mercury vapor during mining (n=200) and processing of gold (n=37) (Harari et al. 2012). The mean urine mercury levels in merchants were 36.9 µg Hg/g creatinine (range 3.2–420 µg Hg/g creatinine) and 3.3 µg Hg/g creatinine (range 0.3–170 µg Hg/g creatinine) in miners. Exposures to mercury vapor occurred during handling, processing, and storage of elemental mercury used in the COLEX process of lithium isotope separation. A study of workers exposed to mercury vapor during production of lithium 6 (n=195) found increased tremor, decreased hand grip strength, and changes in peripheral nerve conduction in association with increased urine mercury (Albers et al. 1988; Letz et al. 2000). The neurological outcomes were prominent when historic peak urine mercury levels were >600 µg Hg/L (Albers et al. 1988). The median quarterly average urine mercury in exposed workers was 180 µg Hg/L (range 64–7,000 µg Hg/L) (Letz et al. 2000). Neurologic outcomes were studied in workers (n=40) in natural gas production (Boogaard et al. 1996). Exposures in gas production occurs typically during maintenance and clean-up operations when mercury (from source materials) that has accumulated on equipment surfaces can vaporize. In a comparison to a reference group, no differences were observed in tests of tremor, hand-eye coordination, or peripheral never conduction velocity (Boogaard et al. 1996). Median urine mercury levels were 41 µg Hg/L (range 7–72 µg Hg/L) in a high-exposure group and 17 µg Hg/L (range 7–53 µg Hg/L) in a low-exposure group. Median air mercury concentration was 67 µg Hg/m^3 (range 10–1,500 µg Hg/m^3). A study of workers in the mercury recycling industry (n=10) found changes to visual field thresholds and contrast sensitivity color discrimination in workers compared to a reference group (Barboni et al. 2009). Mean urine mercury levels at the time of examination was 22 µg Hg/g creatinine (range 9–35 µg Hg/g creatinine). Performance improved after chelation with DMSA.

Mercury released from amalgam dental restorations. Details of studies that examined associations between dental amalgams and neurological effects are summarized in Table 2-49. A cross-sectional study of 530 health center employees who had no known occupational exposure to mercury found no associations between urinary mercury (median 1.3 μg Hg/g creatinine) or number of mercury amalgam restorations and performance on tests of memory or fine motor control (Factor-Litvak et al. 2003). Two large retrospective studies found elevated hazard ratios for diagnosis at death of Parkinson's Disease (hazard ratio 1.58; 95% CI 1.12, 2.23; 20,000 subjects) or Alzheimer's Disease (hazard ratio 1.1; 95% CI 1.01, 1.19; 200,000 subjects) in adults who had mercury amalgam restorations (Hsu et al. 2016; Sun et al. 2015). Results from studies of associations between mercury amalgam restorations and multiple sclerosis have been inconsistent (Aminzadeh and Etminan2007). A case-control study (143 cases, 128 controls) estimated the OR to be 1.05 (95% CL 1.19, 3.53) (Bangsi et al. 1998); however, other studies have found no association between amalgam restorations and multiple sclerosis (Bates et al. 2004; Casetta et al. 2001; McGrother et al. 1999).

Several studies have reported improvement in self-reported signs of psychological disturbances following removal of mercury amalgam restorations; however, because placebo treatments are not possible in these types of studies, the association between the observed outcome changes and exposure to mercury is highly uncertain (Weidenhammer et al. 2010; Zwicker et al. 2014).

Other non-occupational exposures. A clinical study was conducted of families who had resided for up to 2 years in a florescent lamp factory that had been converted to apartments (Fiedler et al. (1999). Average air levels ranged from 5 $\mu g/m^3$ (adult breathing zone) to 888 $\mu g/m^3$ over visible pools of elemental mercury. The study included motor and cognitive testing of 19 adults and 6 children. The median adult urine mercury level was 19.4 μg/g creatinine. The study did not find significant differences in tremor between subjects who had urine mercury ≥19 μg/g creatine, compared to subjects with urine mercury <19 μg/g creatinine (low urine). Hand-eye coordination errors (Neurobehavioral Evaluation System 2) were significantly higher in the higher urine mercury group. Results of other tests were not different between the high and low urine mercury groups (finger tapping, grooved pegboard, trail making, symbol-digit substitution, simple reaction time, continuous performance, verbal learning, and memory). Statistical comparison of test outcomes in children were not reported, and results were characterized as "no clinically significant deficits relative to age-adjusted normative values."

Elemental Mercury—Animal Studies. Two acute inhalation studies evaluated neurological effects in adult animals following acute exposure to metallic mercury vapor. One study observed reduced grip strength in female mice when assessed 4–7 months after a single 4-hour exposure to 0.5 mg Hg/m^3 (Stankovic 2006). Upon necropsy at 7 months, decreased motor axon diameter was observed. The other acute study observed clinical signs of neurotoxicity (mild tremor, lethargy, and unsteady gait) in maternal rats following exposure to 8 mg Hg/m^3 during GDs 6–15 for 2 hours/day (Morgan et al. 2002). These rats were sacrificed moribund on PND 1 based on excessive body weight loss and clinical signs. Similar effects were not observed at ≤4 mg Hg/m^3.

A limited number of intermediate-duration studies found clinical signs of toxicity, impaired learning, and pathological findings in the central nervous system following adult exposure to metallic mercury vapor. Tremors and impaired conditioned response learning (conditioned avoidance and escape response testing) were observed in rats intermittently exposed to 3 Hg/m^3 for 12–42 weeks (Kishi et al. 1978). In another study, exaggerated reflexes, clonus, and tremors were observed in rabbits following intermittent exposure to 4 mg Hg/m^3 for 11–13 weeks (Fukuda 1971). Mild to moderate unspecified pathological brain lesions were observed in rabbits exposed to 0.86 mg Hg/m^3 for 2–12 weeks (7 hours/day, 5 days/week) (Ashe et al. 1953).

The size of the myelin sheath of the dorsal nerve root of the spinal cord was decreased in adult male rats intermittently exposed to 0.48 mg Hg/m^3 for 8 weeks (Schiønning et al. 1998b). Findings were not accompanied by clinical signs of neurotoxicity, obvious microscopic lesions, changes in ganglia volume, changes in number or size of motor neurons, or changes in the ventral nerve root. Therefore, the biological relevance of this finding is unclear, and a NOAEL/LOAEL determination for this study could not be made. In a companion study, male rats similarly exposed to 0.5 mg Hg/m^3 for 8 weeks showed irritability and aggressiveness during the final 2 weeks of exposure (Sørensen et al. 2000). At necropsy, stereological changes in the cerebellum showed a reduction in the number of Purkinje and granular cells and a reduced volume of the granular cell layer. Based on these findings, the study authors concluded that elemental mercury vapor predominantly affects the central nervous system, rather than the peripheral nervous system.

Inorganic Mercury—Animal Studies. Available studies in adult rodents exposed to mercuric chloride indicate that exposure is potentially associated with altered neurobehavior (hyperactivity, impaired coordination, impaired learning and memory), damage to the dorsal route ganglion and cerebellum, and severe clinical signs of neurotoxicity with repeated, high-dose exposure. Neurological effects have also been reported in adult rodents following oral exposure to mercuric sulfide; doses associated with toxicity are much higher for mercuric sulfide compared to mercuric chloride. Available data following inhalation exposure to mercuric oxide are too limited to draw conclusions.

A series of studies evaluated neurobehavior in adult male rats following intermediate-duration exposure to mercuric chloride. Rats exposed to 0.277 mg Hg/kg/day showed reduced total, horizontal, and vertical activity in an open field, impaired motor coordination and balance on both the rotarod and beam walking tests, and impaired learning and memory in the Morris water maze (Teixeira et al. 2014, 2018, 2019). No changes in social behavior were observed in the social recognition test. Alterations in behavior were associated with apoptosis and loss of neurons and astrocytes in the motor cortex and elevated glutamate uptake in the motor cortex and hippocampus (Teixeira et al. 2018, 2019).

No additional studies were available that were designed to evaluate neurobehavior in adult animals following exposure to mercuric chloride. However, severe clinical signs of neurotoxicity were observed in rats following intermediate-duration exposure to doses ≥0.7 mg Hg/kg/day, including hindlimb spread and/or crossing, severe ataxia and abnormal gait, tremor, decreased activity, and partial paralysis (Chang and Hartmann 1972a; Goldman and Blackburn 1979). No clinical signs of toxicity were observed in rats following acute exposure to doses up to 9.24 mg Hg/kg/day (Chang and Hartmann 1972a; Lecavalier et al. 1994). No exposure-related clinical signs were observed in mice following intermediate-duration exposure to doses up to 11 mg Hg/kg/day for 7 weeks (Dieter et al. 1983; Khan et al. 2004).

Ultrastructural changes were noted at in the dorsal root ganglia (vacuole formation, focal cytoplasmic lesions) and cerebellum (vacuolation, degeneration of granule cells) of male rats following acute- or intermediate-duration exposure to mercuric chloride at doses of 0.7 mg Hg/kg/day (Chang and Hartmann 1972a). No changes were observed in anterior horn motoneurons. No exposure-related changes in brain histology were observed in rats exposed to mercuric chloride at acute doses up to 9.24 mg Hg/kg/day (Lecavalier et al. 1994) or intermediate- or chronic-duration doses up to 4 mg Hg/kg/day (Dieter et al. 1992; NTP 1993). No exposure-related changes in brain histology were observed in mice at intermediate-duration doses up to 15 mg Hg/kg/day (Dieter et al. 1983; Khan et al. 2004; NTP 1993) or chronic-duration doses up to 7.4 mg Hg/kg/day (NTP 1993).

A series of studies evaluated neurological function in adult laboratory animals following gavage exposure to mercuric sulfide. In rats, peripheral nerve conduction was altered following a 5- or 14-day exposure to 860 mg Hg/kg/day, specifically suppression and/or incomplete recovery of compound muscle action potentials (CMAPs) after induced tetany (Chuu et al. 2007). No changes in motor equilibrium or nociceptive testing were observed in exposed rats. In mice, increased thresholds for auditory brainstem responses were observed 5 weeks after a 7-day exposure to 860 mg Hg/kg/day, indicative of hearing loss (Chuu et al. 2001a). Thresholds returned to normal by 11 weeks post-exposure. No changes in thresholds were observed at 86 mg Hg/kg/day. In guinea pigs, an abnormal vestibular ocular reflex (VOR) and impaired equilibrium (measured using rotarod test) were observed after acute- or intermediate-duration exposure to mercuric sulfide at ≥86 mg Hg/kg/day (Chuu et al. 2001b). In the acute study, outcomes were persistent 2 weeks after exposure at 860 mg Hg/kg/day and were accompanied by Purkinje cell loss in the cerebellum (recovery and histopathology were not evaluated in the intermediate-duration study).

The effects of inhaled mercuric oxide on the cerebellum of female rats were evaluated in a single study. Following exposure to 1 mg Hg/m^3 for 45 days (9 hours/day), treated rats showed cerebellar gliosis and perineuronal and perivascular vacuolization, reduced cerebellar volume, and decreased number and density of Purkinje cells (Altunkaynak et al. 2019). Purkinje cells from treated animals showed irregular cellular boundaries, eosinophilic cytoplasm, and heterochromatic nuclei.

Organic Mercury—Epidemiological Studies. Outbreaks of severe neurological effects have occurred in association with ingestion of methylmercury in seafood (Minamata disease) and from ingestion of wheat contaminated with a methylmercury fungicide (Iraq outbreak). Studies of associations between exposure to methylmercury and neurological function in adults have also been conducted in populations that consume large amounts of fish or marine mammals (Table 2-50); these populations include communities from the Amazonian River basin, the St. Lawrence River, coastal Japan (whaling communities), and other fish consuming populations. Collectively, these studies provide evidence for associations between exposure to methylmercury and decreasing performance on tests of fine motor coordination and speed, muscle strength, tactile sensation, color vision and visual contrast sensitivity, and memory and learning.

Table 2-50. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurological Effects

Reference, study type, and population	Biomarker	Outcome evaluated[s]	Result
Amazonian River basin studies			
Hoshino et al. 2015 Cross-sectional cohort (n=58, age range 1–47 years); Brazil	HHg median 10.91 µg/g	Tympanometry	0 HHg
		Acoustic reflexes	0 HHg
		Pure tone audiometry	0 HHg
		Transient otoacoustic emissions	0 HHg
Khoury et al. 2015 Cross-sectional cohort (n=108; age range 13–53 years) and 49 referents; Brazil	HHg mean Exposed: 8.8 µg/g Referent: 0.73 µg/g	Tactile sensation threshold	↑ HHg ↑ (exposed versus referents)
		Vibration sensation duration	0 HHg ↓ (exposed versus referents)
		2-point tactile discrimination threshold	0 Hg ↑ (exposed versus referents)
Mergler 2002 (Dolbec et al. 2000, 2001; Lebel et al. 1996, 1998) Cross-sectional cohort (n=233, age >15 years); Brazil	HHg median: 11 µg/g	Fine motor coordination	↓ HHg
		Muscle strength	↓ HHg
		Vision (visual contrast, color vision)	↓ HHg
Yokoo et al. 2003 Cross-sectional cohort (n=129, age rage 17–81 years); Brazil	HHg median 3.7 µg/g	Fine motor speed	↓ HHg
		Memory	↓ HHg
		Learning	↓ HHg
St. Lawrence River studies			
McKeown-Eyssen and Ruedy 1983 Case-control study of 41 cases and 179 controls (age range: adults), Canada	HMeHg mean: Mistassini cases: males: 15.9 µg/g females: 16.7 µg/g Great Whale cases: males: 10.5 µg/g females: 10.1 µg/g	Bilateral coordination, visual field, nystagmus, tremor, sensory loss, or tactile discrimination	↓ HMeHg, males ↓ HMeHg, females

Table 2-50. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurological Effects

Reference, study type, and population	Biomarker	Outcome evaluated[s]	Result
Mergler 2002 Cross-sectional cohort of 63 fish consumers and 63 non-fish-consumers (age range 20–69 years); Canada	BMeHg median Fish consumers: 37.3 µg/L Non-consumers: 29.0 µg/L	Auditory or visual memory	↓ (fish consumers versus non-consumers)
		Cognitive flexibility	↓ (fish consumers versus non-consumers)
		Fine motor coordination	↓ (fish consumers versus non-consumers)
		Reaction time	↓ (fish consumers versus non-consumers)
		Vision (visual color vision)	0 (fish consumers versus non-consumers)
Coastal Japan whaling communities			
Nakamura et al. 2014 Cross-sectional cohort (n=194, age range: 20–85 years); Japan	HHg geometric mean 14.9 µg/g	Sensorineural hearing loss	↑ HHg (>50 µg/g versus <50 µg/g)
		Gait disturbance	↑ HHg (>50 µg/g versus <50 µg/g)
		Muscular weakness	0 HHg
		Tremor	0 HHg
		Rigidity	0 HHg
		Coordinated movements	0 HHg
		Tactile, pain, vibration sensation	0 HHg
Studies of other fish consuming populations			
Carta et al. 2003 Cross-sectional cohort (n=22, median age 52 years) and 22 referents; Italy	Organic BHg median Exposed (n=10): 41.5 µg/L Referent (n=6): 2.6 µg/L	Digit-symbol reaction time	↑ BHg ↑ (exposed versus referents)
		Motor coordination	↓ BHg 0 (exposed versus referents)
		Color word reaction time	↑ BHg ↑ (exposed versus referents)
		Finger tapping speed	0 BHg ↓ (exposed versus referents)

Table 2-50. Results of Epidemiological Studies Evaluating Exposure to Methylmercury and Neurological Effects

Reference, study type, and population	Biomarker	Outcome evaluated[s]	Result
		Digit span	0 BHg 0 (exposed versus referents)
		Tremor	0 BHg 0 (exposed versus referents)

[a]Interpretation of neurobehavioral tests:
Color word reaction time: longer reaction time = lower performance
Digit span: higher score = higher performance
Digit-symbol reaction time: longer reaction time = lower performance
Finger tapping speed: higher speed = higher performance
2-Point tactile discrimination threshold: higher threshold = lower performance
Tactile sensation threshold: higher threshold = lower performance
Vibration sensation duration: lower duration = lower performance

↑ = positive association; ↓ = inverse association; 0 = no association; BHg = blood mercury; BMeHg = blood methylmercury; HHg = hair mercury

Poisoning case studies. A lethal dose of dimethylmercury occurred to a 48-year-old female laboratory chemist following accidental contact of the dorsal surface of a latex gloved hand to "a few drops" of liquid dimethylmercury (Nierenberg et al. 1998; Siegler et al. 1999). Approximately 5 months after the exposure, the patient developed severe neurological symptoms that included deterioration of balance, gait and speech, paresthesia, and disturbances of vision and hearing; the patient died 298 days following the exposure (Nierenberg et al. 1998). Autopsy revealed thinning of the cerebral cortex and atrophy of the cerebellum (Siegler et al. 1999). The applied dose was reconstructed based on measurements of blood mercury made approximately 5 months following the accident and the estimated half-time of 75 days for hair mercury in the subject (Nierenberg et al. 1998). The applied dose was estimated to have been approximately 1,344 mg mercury contained in approximately 0.48 mL of liquid dimethylmercury (density 3.2 g dimethylmercury/mL) (Nierenberg et al. 1998).

Minamata, Japan. Discharges of wastewater from an acetaldehyde production facility into the Shiranui Sea located in the Kumamato Prefecture of Japan resulted in exposure to methylmercury ingested in locally contaminated fish and shellfish (Harada 1995). An outbreak of what became known as Minamata disease occurred in the area. Patients diagnosed with Minamata disease showed a common set of signs which included: severe neuromotor (e.g., tremor, dysarthria, rigidity, ataxia), sensory disturbances (visual and auditory; paresthesia) and, in lethal cases, pathological changes in the cerebral cortex, cerebellar cortex, and dorsal root ganglia of the spinal cord (Ekino et al. 2007; Eto et al. 2002; Harada 1995).

Measurements of mercury in blood and hair were not made until several years following the period of most intense exposure and, therefore, do not provide reliable estimates of exposures that may have contributed to Minamata disease. Hair mercury levels in Minamata disease patients measured 4–5 years following onset of Minamata disease ranged from 2 to 700 µg Hg/g (Harada 1995). In a study of fishermen residents of the Shiranui Sea coastline (n=191) conducted approximately 40 years following onset of Minamata disease, area mean total hair mercury levels ranged from 1.9 to 3.7 µg Hg/g; the percent methylmercury ranged from 70 to 94% (Harada et al. 1998). Follow-ups of Minamata disease patients conducted 40–50 years following onset of disease found evidence for persistence of neurological symptoms (Futatsuka et al. 2005; Uchino et al. 2005). Follow-up studies have also found evidence for higher prevalence of neurological disorders in residents of the Minamata area (Yorifuji et al. 2008, 2009, 2011, 2016). Symptoms observed included paresthesia, ataxia, dysarthria, tremor, and abnormal reflexes (Yorifuji et al. 2008). In a follow-up conducted approximately 15–20 years following onset of Minamata disease, prevalence odds ratios for perioral sensory loss among residents of the Shiranui Sea coast (Minamata and Goshonoura) were associated with increasing hair mercury level (Yorifuji et al. 2009). Hair mercury levels in the study group (n=120) ranged from 0 to 10 µg Hg/g (36% of subjects) to >50 µg Hg/g in 10% of subjects. Prevalence odds ratios were also elevated in Minamata residents (relative to a reference population) for impairment of intelligence and mood and behavior dysfunction (Yorifuji et al. 2011). A subsequent study of a larger population of Minamata residents (n=833), conducted 15–20 years following onset of Minamata disease, found elevated prevalence odds ratios (relative to a reference population) for paresthesia, ataxia, dysarthria, tremor, and abnormal reflexes (Yorifuji et al. 2016).

Iraq. An outbreak of methylmercury poisoning occurred in Iraq in as a result of widespread consumption of wheat that had been treated with a methylmercuric fungicide (Al-Mufti et al. 1976; Bakir et al. 1973; Clarkson et al. 1976). Approximately 6,500 cases of mercury poisoning occurred, with approximately 459 related deaths (Clarkson et al. 1976). Blood mercury levels in poisoning cases measured approximately 65 days after exposure ranged from 10 to 3,000 µg Hg/L (Clarkson et al. 1976). Cases of poisonings occurred across all age ranges. Neurological symptoms included paresthesia, ataxia, visual disturbances, dysarthria, and hearing defects (Bakir et al. 1973). Prevalence of multiple symptoms increased with increasing blood mercury levels (Bakir et al. 1973). Based on measurements of methylmercury in flour used to bake contaminated bread and estimates of bread consumption, methylmercury intake was estimated to have ranged from 80 to 1,000 mg over a 3-month period (Al-Mufti et al. 1976).

Amazonian riverine populations. Studies of methylmercury exposure and neurological outcomes have been conducted in populations residing in Amazon River basins (Dolbec et al. 2000, 2001; Hoshino et al. 2015; Khoury et al. 2015; Lebel et al. 1996, 1998; Mergler 2002; Yokoo et al. 2003). Exposure to methylmercury in these populations derives primarily from methylation of inorganic mercury released to local aquatic ecosystems from alluvial gold mining (Mergler 2002). These studies have found associations between increasing hair mercury and decreasing performance on tests of fine motor coordination and speed, muscle strength, tactile sensation, color vision and visual contrast sensitivity, and memory and learning (Khoury et al. 2015; Mergler 2002; Yokoo et al. 2003). Median hair mercury levels in these studies ranged from 4 to 11 µg Hg/g. One of the largest studies evaluated residents of the Tapjós River basin in Brazil (n=233) and found associations between increasing hair mercury (median 11 µg Hg/g; range <2–150) and decreasing performance on tests of fine motor coordination, muscle strength, color vision, and visual contrast sensitivity (Mergler 2002).

Other high fish or marine mammal consumers. A case-control study of fish and fish-eating mammal consumers (n=41 cases, 179 controls) who resided in Northern Quebec found increased ORs for neurologic symptoms (any of the following: impaired bilateral coordination, visual field, nystagmus, tremor, sensory loss, or tactile discrimination) in association with increasing hair methylmercury levels (McKeown-Eyssen and Ruedy 1983). Adjusted ORs for a 20 µg/g increase in hair methylmercury level were 5.1 (95% CI 1.3, 20.8) in males and 2.9 (95% CI 1.1, 7.3 in females). Mean hair methylmercury levels measured at the time of evaluation were 15.9 and 10.5 µg/g in male cases (from subjects who resided either of two locations) and 16.7 and 10.1 µg/g in female cases. A study of fish consumers (n=63) who resided in the St. Lawrence River basin found poorer performance on tests of auditory or visual memory, cognitive flexibility, and fine motor coordination among fish consumers compared to people who did not consume fish (Mergler 2002; Mergler et al. 1998). The median blood methylmercury levels were 37 µg Hg/L for fish consumers and 27 µg Hg/L for nonconsumers. A study of a whaling community in Japan (n=194) found associations between increasing hair mercury levels (median 19 µg Hg/g, range 1–102 µg Hg/g) and hearing loss and gait disturbances (Nakamura et al. 2014). A study of fish consumers who resided in St Peter Island, Sardinia, Italy (n=22 and 22 referents) found associations between increasing blood organic mercury levels (median 41 µg Hg/L, range 13–85 µg Hg/L) and digit-symbol reaction time and motor coordination (Carta et al. 2003).

Organic Mercury—Animal Studies. Methylmercury is neurotoxic to several species of experimental animals following acute-, intermediate-, and chronic-duration oral exposure. The major neurobehavioral effects that are seen across studies include sensorimotor dysfunction, vision and hearing deficits, and impaired learning and memory, with overt signs of neurotoxicity at higher doses. Methylmercury exposure is associated with degenerative brain changes (particularly in the cerebellum), spinal cord degenerations (particularly the sensory regions), and peripheral nerve degeneration. Effects observed in adult rodents following methylmercury exposure are consistent with findings observed in developing animals; however, effects generally occur at exposure levels higher than those associated with neurodevelopmental effects in animals.

Neurological effects have also been observed in adult macaque monkeys following exposure to methylmercury compounds (Table 2-51). Overt clinical signs of neurotoxicity (clumsiness, impaired fine motor coordination, insensitivity to touch), impaired high-frequency hearing function, and increased reactive gliosis in the brain were observed following intermediate- or chronic-duration exposure to 0.05 Hg/kg/day (Charleston et al. 1994, 1995, 1996; Rice 1989c; Rice and Gilbert 1992). No changes in visual function or operant training were observed at 0.05 mg Hg/kg/day (Rice 1998b; Rice and Hayward 1999). Chronic exposure to 0.08 mg Hg/kg/day resulted in slight tremors and decreased sucking responses, followed by claw-like grasp, gross motor incoordination, and apparent blindness in monkeys (Burbacher and Mottet 1988; Burbacher et al. 1984, 2005). Overt signs of neurotoxicity were not observed in adult monkeys at doses ≤0.04 mg Hg/kg/day (Burbacher and Mottet 1988; Petruccioli and Turillazzi 1991); no other neurological endpoints were evaluated at doses <0.05 mg Hg/kg/day. In adult marmoset monkeys, exposure to 0.5 mg Hg/kg/day for 242 days resulted in clinical signs of neurotoxicity (restlessness, irritability, mild ataxia of the hindlimbs) and cortical findings consistent with anoxic-ischemic encephalopathy observed in Minamata disease, including white matter edema and compression near the calcarine fissure and astrogliosis and microcytic changes in the cortex (Eto et al. 2001).

Table 2-51. Neurological Effects[a] in Primates Following Oral Exposure to Methylmercury Compounds

Species (sex); exposure duration	Overt clinical signs	Learning/ memory	Auditory function	Visual function	Neuro-pathology	Reference (compound)
M. fascicularis (F); 150 days	0 N: 0.04 (NR)[b]	–	–	–	–	Petruccioli and Turillazzi 1991 (MMC)
Marmoset (M); up to 242 days	+ L:0.5 (~10)	–	–	–	+ L:0.5 (~10)	Eto et al. 2001 (MM)

Table 2-51. Neurological Effects[a] in Primates Following Oral Exposure to Methylmercury Compounds

Species (sex); exposure duration	Overt clinical signs	Learning/ memory	Auditory function	Visual function	Neuro-pathology	Reference (compound)
M. fascicularis (F); up to 395 days	+ L: 0.08 (1.56–2.209)	–	–	–	–	Burbacher and Mottet 1988; Burbacher et al. 1984, 2005 (MMH)
M. fascicularis (F); up to 548 days	0 N: 0.05 (1.1–2)	–	–	–	+ L: 0.05 (1.1–2)	Charleston et al. 1994, 1995, 1996; Vahter et al. 1994 (MMH)
M. fascicularis (M, F): up to 2,555 days (from birth)[c]	+ L: 0.05 (0.6–0.9)	0	↓ L: 0.05 (0.6–0.9)	0	–	Rice 1998b, 1989c; Rice and Gilbert 1992; Rice and Hayward 1999 (MMC)

[a]Studies with exposure in post-pubertal animals, including macaque monkey studies that include exposures, beginning during early neonatal periods and continuing through puberty (which occurs at ~5 years).
[b]NOAEL (N) or LOAEL (L) for dose administered in mg Hg/kg/day (blood level in mg Hg/L).
[c]Findings in studies with exposure extending from birth through adulthood may be due to developmental exposure, post-pubertal exposure, or both.

↓ = decreased; 0 = no change; – = not assessed; + = present; F = female; LOAEL = lowest-observed-adverse-effect level; M = male; MM = methylmercury; MMC = methylmercuric chloride; MMH = methylmercury hydroxide; NOAEL = no-observed-adverse-effect level; NR = not reported

Numerous acute- and intermediate-duration studies have reported neurobehavioral and/or neuro-physiological changes in adult rodents following oral exposure to methylmercury, often at or below doses associated with frank neurotoxic signs. Effects observed have including altered motor function, impaired memory, decreased nociception, impaired reflexes, altered sleep patterns, and changes in peripheral and central nervous system electrophysiology (see Table 2-52).

Table 2-52. Neurobehavioral and Neurophysiological Effects in Rodents Following Adult Oral Exposure to Methylmercury Compounds

Species; duration	Motor activity, coordination, strength[a]	Learning and memory[a]	Neuro-physiology[a]	Other[a]	Reference (compound)
Acute					
Rat; 1 day	↓ (L: 20)	↓ (L: 20)	–	–	Post et al. 1973 (MMC)

Table 2-52. Neurobehavioral and Neurophysiological Effects in Rodents Following Adult Oral Exposure to Methylmercury Compounds

Species; duration	Motor activity, coordination, strength[a]	Learning and memory[a]	Neuro-physiology[a]	Other[a]	Reference (compound)
Rat; 2 days	–	–	–	↑ Altered sleep patterns (L: 4)	Arito and Takahashi 1991 (MMC)
Rat; 2 days	↓ (L: 10)	–	↓ PNS (L: 20)	0	Fehling et al. 1975 (MMC)
Rat; 5 or 14 days	↓ (L: 1.9)	–	↓ PNS (L: 1.9)	0 Nociception: 0 (N: 1.9)	Chuu et al. 2007 (MM)
Mouse; 5 days	↓ (L: 0.9)	–	–	–	Bellum et al. 2013 (MMC)
Mouse; 7 days	–	–	↓ Auditory: (L: 0.2)	–	Chuu et al. 2001a (MM)
Mouse; 7 or 14 days	0 (N: 5.6)	–	–	–	Moreira et al. 2012 (MM)
Mouse; 7 or 14 days	0 (N: 4.6)	–	–	–	Kirkpatrick et al. 2015 (MM)
Mouse; 7 or 14 days	↓ (L: 8.7)	–	–	–	Dietrich et al. 2005 (MMC)
Intermediate					
Rat; 26 days	↓ (L: 1.6)	–	–	–	Tamashiro et al. 1986 (MMC)
Rat; 35 days	↓ (L: 0.5)	–	↓ Auditory, visual, SMS, hippocampal (L: 0.5)	↓ Reflexes (L: 0.5) 0 Pre-pulse inhibition (N: 2.0)	Vezér et al. 2005 (MMC)
Rat; 60 days	0 (N: 0.04)	↓ (L: 0.04)	–	0 Anxiety, sociability: (N: 0.04)	Bittencourt et al. 2019 (MMC)
Rat; 60 days	↓ (L: 0.037)	–	–	0 Anxiety (N: 0.037)	Santana et al. 2019 (MM)
Mouse; 21 days	↓ (L: 4.7)	–	–	–	Dietrich et al. 2005 (MMC)
Mouse; 21 days	0 (N: 4.6)	–	–	–	Kirkpatrick et al. 2015 (MM)
Mouse; 21 days	↓ (L: 5.6)	–	–	–	Moreira et al. 2012 (MM)

Table 2-52. Neurobehavioral and Neurophysiological Effects in Rodents Following Adult Oral Exposure to Methylmercury Compounds

Species; duration	Motor activity, coordination, strength[a]	Learning and memory[a]	Neuro-physiology[a]	Other[a]	Reference (compound)
Mouse; 28 days	↓ (L: 4.6)	–	–	–	Kirkpatrick et al. 2015 (MM)
Mouse; 60 days	–	↓ (L: 0.0073)	–	0 Anxiety (N: 0.0073)	Bourdineaud et al. 2011 (MM)
Mouse; 60 days	↓ (L: 0.25)	–	–	–	Berthoud et al. 1976 (MMC)
Mouse; 196 days	↓ (L: 0.89)	–	–	–	MacDonald and Harbison 1977 (MMC)

[a]NOAEL (N) or LOAEL (L) dose in mg Hg/kg/day for endpoint category.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; LOAEL = lowest-observed-adverse-effect level; MM = methylmercury; MMC = methylmercuric chloride; NOAEL = no-observed-adverse-effect level; PNS = peripheral nervous system; SMS = somatosensory

Dose- and duration-dependent clinical signs of neurotoxicity have also been observed in adult rats following oral exposure to methylmercury compounds. Transient effects (lethargy, ataxia) were observed following a single exposure to 20 mg Hg/kg (Post et al. 1973). With repeated acute exposure, mild effects (weakness, hindlimb crossing) were observed at ≥4 mg Hg/kg/day progressing to severe and persistent effects (spasms, ataxia, gait disturbances) at ≥6 mg Hg/kg/day for 8–10 days include (Fuyuta et al. 1978; Miyakawa et al. 1974; Su et al. 1998; Usuki et al. 1998). In intermediate-duration studies, severe clinical signs of neurotoxicity were observed in rats following exposure to ≥1.6 mg Hg/kg/day for 2–4 weeks or ≥0.8 mg Hg/kg/day for 5–6 weeks, including ataxia, tremor, unsteady/uncoordinated gait, partial paralysis, and hindlimb crossing (Chang and Hartmann 1972a; Gandhi et al. 2013; Larsen and Brændgaard 1995; Schiønning et al. 1998a; Sitarek and Gralewicz 2009; Tamashiro et al. 1986; Tonk et al. 2010). No clinical signs of toxicity were observed in rats following chronic exposure to doses up to 0.18 mg Hg/kg/day (Verschuuren et al. 1976).

Overt signs of neurotoxicity (e.g., ataxia, muscular incoordination, intention tremors, partial paralysis) were observed in mice exposed to intermediate doses ≥0.89 mg Hg/kg/day (MacDonald and Harbison 1977; Mitsumori et al. 1981) and in male, but not female, mice chronically exposed to 0.686 mg Hg/kg/day (Mitsumori et al. 1990). However, another study did not report clinical signs of neurotoxicity in mice following intermediate- or chronic-duration exposure to doses up to 0.724 mg Hg/kg/day (Hirano

et al. 1986). Severe clinical signs of neurotoxicity (e.g., ataxia, impaired gait, tremors, convulsions) were observed in cats following intermediate-duration exposure to ≥0.012 mg Hg/kg/day (Chang et al. 1974; Charbonneau et al. 1976; Khera et al. 1974) or chronic-duration exposure to ≥0.074 mg Hg/kg/day (Charbonneau et al. 1976). In rabbits, ataxia and intermittent convulsions were observed following intermediate-duration exposure to ≥0.49 mg Hg/kg/day (Koller et al. 1977).

Following acute exposure to methylmercury compounds, the most sensitive effects were observed in mice, including impaired hearing at ≥0.2 mg Hg/kg/day (Chuu et al. 2001a) and decreased motor activity and impaired motor coordination at 0.9 mg Hg/kg/day (Bellum et al. 2013). Additional details on neurobehavioral testing and dose-response information for sensitive effects observed in mice following acute-duration oral exposure can be found in Table 2-53. For hearing impairment findings in mice following acute-duration exposure, degree and persistence of hearing impairment were dose-dependent when measured immediately following a 7-day exposure and 5 and 11 weeks post-exposure (Chuu et al. 2001a). No other mouse studies evaluated auditory function. Available data indicate that age and strain may influence exposure-related changes in motor activity and coordination. In C57BL/6 mice, no exposure-related changes in motor activity were observed following exposure to 5.6 mg Hg/kg/day for 7 or 14 days starting at 3 months of age (Moreira et al. 2012); however, when exposure started at 16–20 months of age (aged mice), five daily doses of 0.9 mg Hg/kg/day resulted in decreased motor activity, altered gait, and impaired coordination/balance on the vertical pole test (Bellum et al. 2013). In 2-month-old Swiss mice, dose- and duration-dependent decreases in motor activity and coordination were observed following exposure to 4.7 or 8.7 mg Hg/kg/day for 7 or 14 days (Dietrich et al. 2005).

Table 2-53. Dose-Response Data for Sensitive Neurobehavioral Effects in Mice following Acute Oral Exposure to Methylmercury

Reference, study duration	Assay/ outcome measured	Dose (mg Hg/kg/day)	Result (% change compared to control)
Auditory function			
Chuu et al. 2001a 7 days	Hearing threshold	0.2	End of exposure: 0 5 weeks post-exposure: ↑ (180)[a] 11 weeks post-exposure: 0
		1.9	End of exposure: ↑ (200)[a] 5 weeks post-exposure: ↑ (520)[a] 11 weeks post-exposure: ↑ (300)[a]
		9.3	End of exposure: ↑ (710)[a] Post-exposure: ND[b]

Table 2-53. Dose-Response Data for Sensitive Neurobehavioral Effects in Mice following Acute Oral Exposure to Methylmercury

Reference, study duration	Assay/ outcome measured	Dose (mg Hg/kg/day)	Result (% change compared to control)
	ABR absolute latency	0.2	End of exposure: Wave V: ↑ (10)[c] 5 weeks post-exposure: Wave V: ↑ (9)[c] 11 week post-exposure: 0
		1.9	End of exposure: Wave V: ↑ (23)[c] 5 weeks post-exposure: Wave IV: ↑ (14)[c] Wave V: ↑ (15)[c] 11 weeks post-exposure: Wave IV: ↑ (11)[c] Wave V: ↑ (16)[c]
	ABR interwave latency (Waves I–V)	0.2	End of exposure: ↑ (19)[c] 5 weeks post-exposure: 0 11 weeks post-exposure: 0
		1.9	End of exposure: ↑ (41)[c] 5 weeks post-exposure: ↑ (18)[c] 11 weeks post-exposure: ↑ (21)[c]
Motor activity and coordination			
Bellum et al. 2013 5 days; exposure began at 16–20 months; all tests were conducted 6 days post-exposure	Motor activity in open field (30 minutes)	0.9	First 5 minutes: ↓ (25)[a] Total 30 minutes: 0
	Gait analysis	0.9	Angle of foot placement: ↓ (50)[a] Stride length: 0 Base length: 0
	Vertical pole test	0.9	% animals that didn't fall at 90°: ↓ (45)[c] % animals falling between 45 and 90°: ↑ (39)[c]
	Rotarod	0.9	0
Kirkpatrick et al. 2015, 7 or 14 days	Rotarod	4.6	Latency to fall: 0
Dietrich et al. 2005, 7 or 14 days; exposure began at 2 months	Motor activity in open field (20 minutes)	4.7	7 days: 0 14 days: ↓ (30)[a]
		8.7	7 days: ↓ (25)[a] 14 days: ↓ (45)[a]

Table 2-53. Dose-Response Data for Sensitive Neurobehavioral Effects in Mice following Acute Oral Exposure to Methylmercury

Reference, study duration	Assay/ outcome measured	Dose (mg Hg/kg/day)	Result (% change compared to control)
	Beam walking (10 mm circle beam)	4.7	7 days: 0 14 days: ↑ (150)[a]
		8.7	Latency to cross beam: 7 days: 0 14 days: ↑ (500)[a]
Moreira et al. 2012, 7 or 14 days; exposure began at 3 months	Motor activity in open field (5 minutes)	5.6	0

[a]Estimated from graphically presented data.
[b]All animals died prior to 5-week examination.
[c]Calculated from quantitative data.

↑ = increased; ↓ = decreased; ABR = auditory brainstem response; ND = no data

In intermediate-duration studies, mice were again more sensitive than rats, with impaired memory in the Y-maze observed at ≥0.0073 mg Hg/kg/day as the most sensitive effect following intermediate-duration exposure (Bourdineaud et al. 2011). In the Y-maze, the rate of spontaneous alteration was significantly decreased by 14% following exposure to 0.0073 mg Hg/kg/day for 2 months, compared to controls, suggesting that the animals had difficulty remembering which arm was entered last. No other mouse study evaluated memory following intermediate-duration exposure, but impaired social and spatial memory in the Morris water maze were also observed in rats exposed to 0.04 mg Hg/kg/day for 60 days (Bittencourt et al. 2019).

Data on neurobehavior following chronic exposure is limited to a single study in cats, rats, and mice. The most sensitive finding was decreased nociception in cats exposed to dietary levels of 0.046 mg Hg/kg/day for 2 years; additional effects observed at 0.074 mg Hg/kg/day included muscle weakness, impaired balance and coordination (during beam walking), and impaired reflexes (righting, hopping, placing, optical, patellar) (Charbonneau et al. 1976). No adverse neurobehavioral effects were observed in cats at chronic doses up to 0.02 mg Hg/kg/day. In the rat study, no changes in motor activity were observed following exposure to dietary doses up to 0.18 mg Hg/kg/day for 2 years (Verschuuren et al. 1976). In the mouse study, lifetime exposure to methylmercury (including gestation and lactation via dam) resulted in impaired spatial learning in the delayed alternation task and altered gait (increased hindlimb splay) at 5,

15, and/or 26 months of age at drinking water doses ≥0.2 mg Hg/kg/day (lowest dose tested); impaired operant training was observed at 0.6 mg Hg/kg/day (Weiss et al. 2005).

Histopathological changes in the brain have been reported in rats and mice following oral exposure to methylmercury; similar to neurodevelopmental studies, lesions were primarily in regions involved in motor and movement control. Ultrastructural changes were noted in the rat cerebellum (vacuolation, degeneration of granule cells) following acute- or intermediate-duration exposure to doses ≥0.8 mg Hg/kg/day (Chang and Hartmann 1972a).

In acute-duration rat studies, degeneration of cortical and cerebellar neurons was observed in rats exposed to 8 mg Hg/kg/day for 10 days (Su et al. 1998). Other studies observed no histopathological damage in the brain at doses up to 20 mg/kg/day for 1 or 2 days or 7 mg Hg/kg/day for 10 days (Fehling et al. 1975; Miyakawa et al. 1974; Post et al. 1973).

In intermediate-duration rat studies, no exposure-related histopathological changes were observed at doses up to 9.72 mg Hg/kg/day for up to 35 days (Larsen and Brændgaard 1995; Sakamoto et al. 2017; Schiønning et al. 1998a), but reduced neuronal and astrocyte cell number and/or density were observed in the motor cortex and hippocampus of rats exposed to ≥0.037 mg Hg/kg/day for 60 days (Bittencourt et al. 2019; Santana et al. 2019). In mice, histopathological brain lesions were observed following intermediate-duration exposures ≥0.89 mg Hg/kg/day, including neuronal degeneration and microgliocytosis in subcortical regions (e.g., the putamen and corpus striatum, and to a lesser extent, the thalamus, hypothalamus, and amygdala) and degenerative changes in Purkinje cells and loss of granular cells in the cerebellum (Berthoud et al. 1976; MacDonald and Harbison 1977).

No histopathological changes were observed in the mouse brain following intermediate- or chronic-duration exposure to doses up to 0.724 mg Hg/kg/day (Hirano et al. 1986; Mitsumori et al. 1990). No histopathological brain lesions were observed in rats at chronic doses up to 0.18 mg Hg/kg/day (Verschuuren et al. 1976).

Several studies have reported damage and degeneration of sensory regions of the spinal cord in rats (e.g., dorsal nerve root and ganglia, posterior column) following oral exposure to methylmercury at acute doses of 20 mg Hg/kg/day (Fehling et al. 1975) and intermediate-duration doses ≥1.4 mg Hg/kg/day (Larsen and Brændgaard 1995; Sakamoto et al. 2017; Schiønning et al. 1998a; Yip and Chang 1981). Ultrastructural changes were also noted at in the dorsal root ganglia (vacuole formation, focal cytoplasmic

lesions) of rats following acute or intermediate-duration exposure to doses ≥0.8 mg Hg/kg/day (Chang and Hartmann 1972a; Yip and Chang 1981). No changes were observed in anterior horn motor neurons in these studies. However, degeneration of the large motor neurons in spinal cord and myelinated fibers of spinal anterior roots was observed in rats exposed to 8 mg Hg/kg/day for 10 days (Su et al. 1998). No exposure-related histopathological changes in the spinal cord were observed in rats following chronic exposure to 0.18 mg Hg/kg/day (Verschuuren et al. 1976) or in mice at intermediate- or chronic-duration doses up to 9.5 or 0.724 mg Hg/kg/day, respectively (Hirano et al. 1986; MacDonald and Harbison 1977; Mitsumori et al. 1990).

A few studies have reported damage to peripheral nerves in rats and mice exposed to methylmercury. Degeneration of peripheral nerves was also observed in rats following a 2-day exposure to 20 mg Hg/kg/day (Fehling et al. 1975) or a 10-day exposure to 7 mg Hg/kg/day (Miyakawa et al. 1974). No histopathological changes in peripheral nerves were observed in rats following chronic exposure to doses up to 0.18 mg Hg/kg/day (Verschuuren et al. 1976). In mice, no histopathological changes in peripheral nerves were observed at intermediate-duration doses up to 0.724 mg Hg/kg/day for 26 weeks (Hirano et al. 1986). In chronic studies, one study observed degeneration and fibrosis of the sciatic nerve in female mice at 0.627 mg Hg/kg/day, but not in males at doses up to 0.724 mg Hg/kg/day (Hirano et al. 1986). A second study observed peripheral nerve damage in males at 0.686 mg Hg/kg/day, but not females at doses up to 0.601 mg Hg/kg/day (Mitsumori et al. 1990).

Neuropathological data are limited for other laboratory animal species. Degeneration and/or necrosis of cerebellar granule and Purkinje cells and cortical neurons were observed in cats following intermediate-duration exposure to ≥0.012 mg Hg/kg/day (Chang et al. 1974; Khera et al. 1974). Degeneration of the cerebral cortex, cerebellum, and dorsal root ganglia was also observed in cats following intermediate- or chronic-duration exposure to 0.176 or 0.074 mg Hg/kg/day, respectively (Charbonneau et al. 1976). In rabbits, cerebellar degeneration was observed following intermediate-duration exposure to doses ≥1.0 mg Hg/kg/day (Koller et al. 1977).

Predominant Mercury Form Unknown (General Populations). A cross-sectional study of adults in Korea (n=172; age range 20–65 years) found decreasing finger tapping speed in association with increasing urine mercury levels (median 1.2 µg/g creatinine; range 0–33 µg/g creatinine) (Kim et al. 2013a).

Mechanisms of Action. General mechanisms of toxicity of mercury (reviewed in Section 2.21) are likely involved in adverse neurodevelopmental and neurological effects of mercury. Mercury is distributed to the fetus and has been measured in fetal tissues (see Section 3.1.2, Distribution), providing a toxicokinetic mechanism for direct exposure of the placental tissues and fetus. Transfer of methylmercury across the placenta may be facilitated by amino acid or organic anion transporters that recognize CH_3Hg^{2+}-thiol conjugates of amino acids (Bridges and Zalups 2017). Amino acid transporters also participate in transfer of CH_3Hg^{2+}-S-cysteine conjugate across the blood brain barrier (Bridges and Zalups 2017).

A variety of toxicodynamic mechanisms contributing to neurological effects of methylmercury have been proposed. These include alteration or disruption of regulation of intracellular calcium homeostasis, the cytoskeleton, mitochondrial function, oxidative stress, neurotransmitter release, and DNA methylation (Aaseth et al. 2020; Cardenas et al. 2016, 2017a; Culbreth and Aschner 2016; Johansson et al. 2007; Patel and Reynolds 2013; dos Santos et al. 2016). Several specific mechanisms for neurological effects have been proposed, including tau hyperphosphorylation in the cerebral cortex, which is associated with neurodegenerative diseases (Fujimura et al. 2009); disruption of neurite membrane structure and growth rate, potentially leading to neurodegeneration (Leong et al. 2001); inhibition of Na^+,K^+-ATPase and decreased update of norepinephrine and dopamine in brain tissue (Rajanna and Hobson 1985); and accumulation of amyloid beta protein, which is associated with Alzheimer's disease, through increased production of amyloid precursor protein and reduction of neprilysin, a protease (Song and Choi 2013).

The vulnerability of the nervous system to mercury vapor is related to its pronounced distribution to the brain following inhalation. This is attributed, in part, to the high solubility of Hg^0 in lipid, its affinity for proteins such as hemoglobin, and its extracellular and intracellular oxidation, which can favor absorption from the lung and delivery to the brain (Hursh 1985; Magos 1967; Magos et al. 1978; U.S. Atomic Energy Commission 1961).

2.17 REPRODUCTIVE

Overview. The database for reproductive effects associated with exposure to mercury includes epidemiological studies and studies in laboratory animals. Epidemiological studies are available for workers exposed to elemental mercury, populations with high fish diets, and general populations. Few studies meeting inclusion criteria were identified for workers and populations with high fish diets, whereas the database for general populations was more robust (see inclusion criteria, Section 2.1). Few studies examined the same reproductive endpoints, and those that did often reported conflicting results.

The available epidemiological studies do not provide convincing evidence that the reproductive system is a sensitive target of mercury exposure in males or females.

Studies evaluating reproductive function in animals (mating, fertility, pregnancy, and live birth indices) are available for inhalation exposure to elemental mercury or oral exposure to mercuric chloride or methylmercury. Overall, oral studies indicate dose-dependent decreases in fertility in female monkeys exposed to methylmercury, in male rodents exposed to mercuric chloride and methylmercury, and in female rodents exposed to mercuric chloride. Data are inconsistent and/or inadequate to determine fertility effects in male monkeys and female rodents exposed to methylmercury. Supporting studies suggest that alterations in sperm parameters and/or estrous cyclicity may contribute to observed decreases in fertility. Evidence from inhalation studies are too limited to draw conclusions.

The following summarizes results of epidemiological and animal studies on reproductive outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - It is not possible to determine if there are associations between elemental mercury exposure and adverse reproductive outcomes in males or females; few studies have been conducted, with most reporting no effects.
    - Studies in males show no effects on testosterone levels or increased risk of spontaneous abortion in their partners.
    - One study in females reported increased spontaneous abortion. This finding has not been corroborated.
  - *Animal studies*
    - Few studies investigated effects on reproductive function; data are insufficient to draw conclusions.
- ***Inorganic mercury salts***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to inorganic mercury salts and reproductive effects were identified.
  - *Animal studies*
    - Reproductive studies consistently reported dose-related impairments in fertility in male and female rodents following oral exposure.
    - Oral studies showed multiphasic changes in testosterone levels with respect to dose and duration, with initial decreases, followed by increases, followed by return to

baseline/control levels. Few studies investigated effects of other male or female reproductive hormones. Data are insufficient to draw conclusions about effects on reproductive hormones other than testosterone.

- Two oral studies have shown dose-related decreases in sperm motility and/or number in male rats.
- Evidence for histopathological lesions in testes is inconsistent in acute- and intermediate-duration oral studies, and reports are generally qualitative; no histopathological lesions were identified in male reproductive tissue following chronic oral exposure.
- No histopathological lesions were identified in female reproductive tissue following acute-, intermediate-, or chronic-duration oral exposure.
- Few studies investigated effects of inhalation exposure on reproductive function; data are insufficient to draw conclusions.

- ***Organic mercury***
  - *Epidemiology studies*
    - Few epidemiology studies in populations with high fish diets have evaluated reproductive endpoints. Available data are not adequate to determine if methylmercury from high fish diets is associated with adverse reproductive effects.
    - In males, there were no adverse effects on sperm quality or serum levels of reproductive hormones; however, only one study was identified.
    - In females, results of two studies reported conflicting results for duration of gestation.
  - Animal studies
    - Reproductive studies consistently reported dose-related impairments in fertility in male rats and female monkeys following oral exposure; male monkeys were not assessed for fertility but showed alterations in sperm parameters.
    - Alterations in sperm parameters were observed in male rats following acute- or intermediate-duration exposure, but there is no clear evidence of increased magnitude of effect with dose or duration.
    - Evidence for exposure-related impairments in female rodent fertility following oral exposure is inconsistent.
    - Evidence for histopathological lesions in male reproductive organs in rodents is inconsistent; no histopathological lesions were identified in male reproductive organs in monkeys following intermediate-duration exposure.
    - No histopathological lesions were identified in female reproductive organs following intermediate- or chronic-duration oral exposure.

- ***Predominant mercury form unknown (general populations)***
    - No adverse effects of mercury exposure on sperm quality or serum levels of reproductive hormones were observed in males. Mercury exposure in general populations does not appear to adversely affect the male reproductive system.
    - Most epidemiological studies assessing reproductive effects in females did not examine the same endpoints; therefore, data are inadequate to corroborate findings, or to draw conclusions as to whether mercury exposure is adverse to female reproductive function from studies of general populations. A few studies examined preterm birth as an outcome, but results were not consistent.

Confounding Factors. Numerous factors may add uncertainty in the interpretation of studies examining associations between mercury and reproductive effects, including overall health, body weight, nutrition, and SES. Exposures to other substances, including recreational drugs, alcohol, therapeutic agents, industrial chemicals, insecticides, and pesticides, also may affect fertility (Foster and Gray 2008). Failure to account for these factors may attenuate or strengthen the apparent associations between mercury exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Elemental Mercury—Epidemiological Studies. The effects of occupational exposure to elemental mercury have not been well-studied. Studies, summarized in Table 2-54, have been conducted in small populations (n≤147) of males and females exposed at chloralkali plants and dental offices. Small population sizes limit the power to detect effects. All studies quantified elemental mercury exposure using UHg, with or without adjustment for urine creatinine.

Table 2-54. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Reproductive Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Males			
Barregard et al. 1994a Cross-sectional; 41 male chloralkali workers and 41 matched controls (Sweden)	UHg mean Workers: 27 µg/g Cr Controls: 3.3 µg/g Cr	Testosterone	0 (UHg, workers versus controls)
		Free testosterone	0 (UHg, workers versus controls)
		prolactin	0 (workers versus controls)

Table 2-54. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Reproductive Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Cordier et al. 1991 Cross-sectional; 152 male chloralkali workers (France)	UHg quartiles Q1: 0 (reference) Q2: 1–19 µg/L Q3: 20–49 µg/L Q4: ≥50 µg/L	Spontaneous abortion	Q4: 0 (UHg)
Erfurth et al. 1990 Cross-sectional; 9 male dentist 11 controls and 11 chloralkali workers and 10 controls (Sweden)	UHg mean, dentists Dentists: 2.3 µg/g Cr Controls: 0.71 µg/g Cr UHg mean, workers Workers: 46 µg/g Cr Controls: 1.1 µg/g Cr	Testosterone	0 (UHg, workers or dentists versus respective controls)
Females			
El-Badry et al. 2018 Prospective; 64 pregnant dental workers and 60 pregnant controls (Egypt)	UHg mean, workers 1st trimester: 42.2 µg/g Cr 2nd trimester: 41.8 µg/g Cr 3rd trimester: 42.8 µg/g Cr UHg mean, control: 1st trimester: 6.2 µg/g Cr 2nd trimester: 6.3 µg/g Cr 3rd trimester: 7.1 µg/g Cr	Spontaneous abortion	↑ (UHg, relative to control)
		Pre-eclampsia	↑ (UHg, relative to control)
Males and females			
Frumkin et al. 2001 Retrospective cohort; 147 chloralkali workers (137 males and 10 females) and 132 controls (117 males and 15 females) (Brunswick, Georgia)	UHg mean Workers: 2.76 µg/g Cr Controls: 2.31 µg/g Cr	Spontaneous abortion	0 (UHg)
		Preterm birth	0 (UHg)

↑ = positive association or increased compared to controls; 0 = no association or no increase compared to controls; Cr = creatinine; Q = quartile; UHg = urine mercury

Studies in male workers did not identify effects on reproductive hormones including testosterone and prolactin (Barregard et al. 1994a; Erfurth et al. 1990). In addition, exposure of males was not associated with risk of spontaneous abortion in their partners (Cordier et al. 1991). In females, a prospective study of dental workers found an increased risk of spontaneous abortion and pre-eclampsia, relative to controls (El-Badry et al. 2018). However, no increases in spontaneous abortion or preterm birth were observed in partners of males or in female chloralkali workers compared to controls. Given the small number of studies, data are not adequate to determine if elemental mercury adversely affects reproductive function in males or females.

Elemental Mercury—Animal Studies. The effects of exposure to elemental mercury have not been well-studied in animals. A single study found significant testicular damage in male rats exposed to 1 mg/m^3 for 6 weeks (7 days/week, 9 hours/day), including seminiferous tubule atrophy; damage to spermatogenic cells; decreased volume of the testicles; decreased diameter and volume of the seminiferous tubules; and decreased Sertoli cells, spermatogonia, spermatocytes, and spermatids (Altunkaynak et al. 2015). In a series of experiments in female rats, Davis et al. (2001) found estrous cycle abnormalities following nose-only exposure to mercury vapor at concentrations ≥2 mg Hg/m^3 for 6–11 days (2 hours/day), including a concentration-related increase in the number of females with prolonged estrous cycles (≥5 days) and evidence of immature corpora lutea during estrus and metestrus phases. Significant alterations in reproductive hormone levels (decreased estradiol, increased progesterone) were observed at 4 mg Hg/m^3. However, no evidence of impaired fertility was observed when females were exposed to concentrations up to 2 mg Hg/$m^3$for 8 days (2 hours/day) prior to mating to unexposed males; fertility was not assessed at 4 mg Hg/m^3 (Davis et al. 2001).

Inorganic Mercury Salts—Animal Studies. Studies in laboratory animals have evaluated effects of inorganic mercuric mercury (e.g., mercuric chloride) on reproductive function following intermediate-duration inhalation exposure and intermediate- and chronic-duration oral exposure. Additional data regarding reproductive endpoints (e.g., histology, organ weights, hormone levels, sperm parameters) are available from acute-, intermediate-, and chronic-duration oral studies. Available inhalation data are too limited to draw conclusions; however, results from oral studies indicate that exposure to mercuric chloride can impair male and female fertility in rodents.

The effects of inhaled mercuric oxide on the female rat reproductive system were evaluated in a single study. Following continuous exposure to 0.9 mg Hg/m^3 for 45 days, treated rats showed reduced ovary volume, decreased number of ovarian follicles, and various histopathological changes in the ovaries, including thickened tunica albuginea, increased fibrils within connective tissue, congested capillaries and blood vessels, thinned walls of large and dilated veins, fibrin deposits in veins, edema and maldeveloped follicles in the stroma, and irregular oocyte borders within follicles (Altunkaynak et al. 2016).

Reproductive capacity was reduced in a dose- and duration-related manner in generational studies in rats and mice following oral exposure to mercuric chloride (see Table 2-55). In rats, exposure to both males and females in a 2-generation study resulted in dose-related decreases in fertility index, live birth index, implantation efficiency, and number of live pups/litter in the F0 generation at all tested doses (≥0.37 Hg/kg/day in males; ≥0.55 Hg/kg/day in females); no significant impairments were observed in the

F1 generation at doses up to 1.31 mg Hg/kg/day in males and 1.98 mg Hg/kg/day in females (Atkinson et al. 2011). In mice, premating exposure to mercuric chloride in a 1-generation study in males and females (40 and 16 days, respectively) resulted in a decreased fertility index at ≥0.18 mg Hg/kg/day and a decreased live birth index at 0.74 mg Hg/kg/day. Collectively, these studies indicate that mercuric chloride can impair rodent reproductive function; however, it is unclear if impaired fertility observed in generational studies was attributable to reproductive effects in males, females, or both. Findings from single-sex studies suggest that oral mercuric chloride exposure can alter reproductive function in both male and female rodents (see Tables 2-56 and 2-57, respectively). Studies in male rats indicate dose-related impairments in reproductive function, including increased time to impregnate and decreased fertility at 1.5 mg Hg/kg/day, decreased viable embryos at ≥3 mg Hg/kg/day, and decreased mating index at 6 mg Hg/kg/day (Boujbiha et al. 2009, 2011; Heath et al. 2012). In females, decreased number of implantations and increased resorptions were observed in rats exposed to 1.5 mg Hg/kg/day prior to mating (Heath et al. 2012), and decreased live pups per litter was observed in mice exposed to 0.4 mg Hg/kg/day prior to mating through lactation (Huang et al. 2011). No evidence of impaired fertility was observed in male or female rats were exposed to ≤0.7 mg Hg/kg/day when mated to untreated animals (Heath et al. 2012; Szász et al. 2002).

Table 2-55. Reproductive Function in Rodents Orally Exposed to Mercuric Chloride when Both Sexes are Exposed

Species; duration	Dose (mg Hg/kg/day)	FI[a,b]	LBI[a,c]	IE[a,d]	Live pups/ litter[a]	Reference (study type)
Rat; 80 days	0.46[e]	F0: ↓ (32) F1: 0	F0: ↓ (12) F1: 0	F0: ↓ (38) F1: 0	F0: ↓ (38) F1: 0	Atkinson et al. 2001 (2-generation)
Rat; 80 days	0.93[e]	F0: ↓ (58) F1: 0	F0: ↓ (10) F1: ↓ (6)	F0: ↓ (49) F1: ↓ (34)	F0: ↓ (49) F1: 0	Atkinson et al. 2001 (2-generation)
Rat; 80 days	1.65[e]	F0 ↓ (83) F1: –	F0 ↓ (22) F1: –	F0 ↓ (56) F1: –	F0 ↓ (56) F1: –	Atkinson et al. 2001 (2-generation)
Mouse; 61–79 days	0.18	↓ (30)	0	0	0	Khan et al. 2004 (1-generation)
Mouse; 61–79 days	0.37	↓ (30)	0	0	0	Khan et al. 2004 (1-generation)

Table 2-55. Reproductive Function in Rodents Orally Exposed to Mercuric Chloride when Both Sexes are Exposed

Species; duration	Dose (mg Hg/kg/day)	FI[a,b]	LBI[a,c]	IE[a,d]	Live pups/ litter[a]	Reference (study type)
Mouse; 61–79 days	0.74	↓ (30)	↓ (81)	0	0	Khan et al. 2004 (1-generation)

[a]Numbers in ( ) are percent change compared to control, calculated from quantitative data.
[b]Fertility index = number of dams delivering/number of dams cohabited.
[c]Live birth index = number of live pups/total number of pups.
[d]Implantation efficiency = number of pups born/number of implants.
[e]Doses are the midpoint of estimated male and female doses for the F0 generation. Estimated F0 male doses were 0.37, 0.74, and 1.31 mg Hg/kg/day, respectively, and estimated F0 female doses were 0.55, 1.11, and 1.98 mg Hg/kg/day, respectively.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; FI = fertility index; IE = implantation efficiency; LBI = live birth index

Table 2-56. Reproductive Function in Male Rodents Orally Exposed to Mercuric Chloride Prior to Mating to Unexposed Females

Species; duration	Dose (mg Hg/kg/day)	MI[a,b]	Time-to-pregnant[a]	FI[a,c]	Live pups/ litter[a]	Reference
Rat; 60 days	0.7	–	0	0	–	Heath et al. 2012
Rat; 60 days	1.5	–	↑ (53[c])	↓ (30)	–	Heath et al. 2012
Rat; 90 days	3	0	–	–	↓ (36)	Boujbiha et al. 2009, 2011
Rat; 90 days	6	↓ (50)	–	–	↓ (76)	Boujbiha et al. 2009, 2011

[a]Numbers in ( ) are percent change compared to control, calculated from quantitative data.
[b]Mating index = number of confirmed matings/number of pairs cohabited.
[c]Fertility index = number of dams delivering/number of dams cohabited.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; FI = fertility index; MI = mating index

Table 2-57. Reproductive Function in Female Rodents Orally Exposed to Mercuric Chloride Prior to Mating to Unexposed Males

Species duration	Dose (mg Hg/kg/day)	FI[a]	Live pups/ litter	Number of implants	Number of resorptions	Reference
Rat; 60 days	0.7	–	–	0	0	Heath et al. 2012
Rat; 60 days	1.5	–	–	↓ (15[b])	↑ (1,900[b])	Heath et al. 2012
Rat; 70–77 days	0.6	0	0	–	–	Szász et al. 2002
Mouse; 70 days	0.4	–	↓ (14[c])	–	–	Huang et al. 2011

[a]Fertility index = number of dams delivering/number of dams cohabited.
[b]Percent change compared to control, calculated from quantitative data.
[c]Percent change compared to control, estimated from graphically presented data.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; FI = fertility index

A 3-generation study in male and female rats with continuous breeding reported a decrease in the number of F3 litters and litter size (Lukacinova et al. 2012); however, reporting of the study design and results were inadequate for independent review and analysis of the results. Therefore, this study was not included in Table 2-55 or the LSE tables.

Alterations in sperm parameters and male reproductive hormones have also been reported following oral exposure to mercuric chloride (see Table 2-58). Dose-related decreases in sperm number and mobility have been reported in rats following oral exposure to mercuric chloride at drinking water doses ≥3 Hg/kg/day for 3–90 days or gavage doses ≥0.7 Hg/kg/day for 60 days (Boujbiha et al. 2009, 2011; Heath et al. 2012); findings were generally duration-dependent, although there is some variation in the effect of exposure duration. In rats, alterations in serum testosterone levels show a multiphasic response with respect to dose and duration. Significant decreases were observed after exposure to 3 mg Hg/kg/day for 3–15 days, 6 mg Hg/kg/day for 3 days, or 0.7 or 1.5 mg Hg/kg/day for 30 days; significant increases were observed after exposure to 3 mg Hg/kg/day for 30 or 60 days or 6 mg Hg/kg/day for 7 days; and no significant changes were observed after exposure to 3 mg Hg/kg/day for 90 days, 6 mg Hg/kg/day for 15–90 days, or 0.7 or 1.5 mg Hg/kg/day for 60 days (Boujbiha et al. 2009, 2011; Heath et al. 2012; Ramalingam et al. 2003). Similarly, testicular testosterone was significantly elevated following exposure to 0.7 or 1.5 mg Hg/kg/day for 60 days (Heath et al. 2012), but significantly decreased following exposure to ≥3 mg Hg/kg/day for 90 days (Boujbiha et al. 2009, 2011). Data on other male reproductive hormones is limited. Significant decreases in serum luteinizing hormone (LH) were observed in male rats

following exposure to 0.7 mg Hg/kg/day for 30 days; serum prolactin and follicle stimulating hormone (FSH) were also decreased at 1.5 mg Hg/kg/day (Ramalingam et al. 2003). Both serum and testicular estradiol (E2) levels were significantly decreased in male rats after exposure to ≥3 mg/kg/day for 90 days (Boujbiha et al. 2009, 2011). Interpretation of observed serum hormone changes at higher doses is complicated based on known renal toxicity in animals (acute exposures ≥7.4 mg Hg/kg/day, intermediate-duration exposures ≥0.923 mg Hg/kg/day; see Section 2.11, Renal) because impaired renal function can alter testosterone production in humans and animals (e.g., Iglesias et al. 2012; Nakada and Adachi 1999) and the kidney participates in the metabolism and excretion of steroids (Schiffer et al. 2019).

Table 2-58. Sperm Parameters and Male Reproductive Hormones in Male Rodents Orally Exposed to Mercuric Chloride

Species; duration	Dose (mg Hg/kg/day)	Sperm No.	Sperm mobility	Serum T	Other hormone levels	Reference
Rat; 3 days	3	↓ (10[a])	↓ (10[a])	↓ (13[a])	–	Boujbiha et al. 2009
Rat; 3 days	6	↓ (35[a])	↓ (30[a])	↓ (22[a])	–	Boujbiha et al. 2009
Rat; 7 days	3	↓ (24[a])	↓ (30[a])	↓ (40[a])	–	Boujbiha et al. 2009
Rat; 7 days	6	↓ (44[a])	↓ (38[a])	↑ (52[a])	–	Boujbiha et al. 2009
Rat; 15 days	3	↓ (27[a])	↓ (31[a])	↓ (52[a])	–	Boujbiha et al. 2009
Rat; 15 days	6	↓ (33[a])	↓ (34[a])	0	–	Boujbiha et al. 2009
Rat; 30 days	0.7	–	–	↓ (35[a])	FSH: 0 LH: ↓ (47[a]) PRL: 0	Ramalingam et al. 2003
Rat; 30 days	1.5	–	–	↓ (63[a])	FSH: ↓ (15[a]) LH: ↓ (65[a]) PRL: ↓ (33[a])	Ramalingam et al. 2003
Rat; 30 days	3	↓ (16[a])	0	↑ (93[a])	–	Boujbiha et al. 2009, 2011
Rat; 30 days	6	↓ (29[a])	0	0	–	Boujbiha et al. 2009, 2011
Rat; 60 days	0.7	↓ (10[b])	–	0	TT: ↓ (30[b])	Heath et al. 2012
Rat; 60 days	1.5	↓ (10[b])	–	0	TT: ↓ (30[b])	Heath et al. 2012
Rat; 60 days	3	↓ (9[a])	↓ (17[a])	↑ (103[a])	–	Boujbiha et al. 2009, 2011

Table 2-58. Sperm Parameters and Male Reproductive Hormones in Male Rodents Orally Exposed to Mercuric Chloride

Species; duration	Dose (mg Hg/kg/day)	Sperm No.	Sperm mobility	Serum T	Other hormone levels	Reference
Rat; 60 days	6	↓ (21[a])	↓ (34[a])	0	–	Boujbiha et al. 2009, 2011
Rat 90 days	3	↓ (31[a])	↓ (16[a])	0	TT: ↑ (23[a]) E2: ↓ (19[a]) TE2: ↓ (15[a])	Boujbiha et al. 2009, 2011
Rat; 90 days	6	↓ (38[a])	↓ (23[a])	0	TT: ↑ (35[a]) E2: ↓ (37[a]) TE2: ↓ (26[a])	Boujbiha et al. 2009, 2011

[a]Percent change compared to control, calculated from quantitative data.
[b]Percent change compared to control, estimated from graphically reported data.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; E2 = serum estradiol; FSH = serum follicle stimulating hormone; LH = serum luteinizing hormone; PRL = serum prolactin; T = testosterone; TE2 = testicular estradiol; TT = testicular testosterone

Evidence for histopathological damage to male reproductive organs is inconsistent in rats and mice following oral exposure to mercuric chloride. Boujbiha et al. (2009, 2011) reported changes in the histoarchitecture of the testes and seminiferous tubules in Wistar rats following drinking water exposure to mercuric chloride at doses of 3 or 6 mg Hg/kg/day for 3–90 days; the study authors reported that findings were "prominent" at the higher dose, but do not provide incidence data or additional dose- or time-specific details. Changes included interstitial effusion, increased space between seminiferous tubules, enlarged tubule lumen, degenerative and detachment of lining cells, reduced number of round spermatids, and an absence of mature spermatozoa in 48–70% of tubules. The only dose-specific quantitative data reported were increased degree of testicular edema (3.18 and 13.42% of tissue weight) and a 14 and 27% reduction in thickness of the germinative layer of the seminiferous tubules at 3 and 6 mg Hg/kg/day, respectively, after exposure for 90 days. In contrast, no exposure-related lesions were observed in male reproductive organs in F344 rats following intermediate- or chronic-duration gavage doses up to 4 mg Hg/kg/day (NTP 1993), in C57Bl/6 mice at intermediate-duration gavage doses up to 0.74 mg Hg/kg/day (Khan et al. 2004; NTP 1993), or in B6C3F1 mice at intermediate- or chronic-duration gavage doses up to 15 or 7.4 mg Hg/kg/day, respectively (NTP 1993).

Two additional studies in rodents qualitatively reported histopathological changes in the testes following acute- or intermediate-duration exposure to low doses of mercuric chloride; however, these studies were not included in the LSE tables due to reporting deficiencies that precluded independent evaluation of the

data. Penna et al. (2009) reported time- and dose-related increases in testicular histopathology in male Sprague-Dawley rats exposed to mercuric chloride via drinking water for up to 90 days, with "mild" lesions in ≤10% of seminiferous tubules in <50% of animals (n=5) after exposure to 0.0133 mg Hg/kg/day for 30 days or 0.0011 mg Hg/kg/day for 60 days, and "moderate" lesions in 20–50% of seminiferous tubules in >50% of animals after exposure to ≥0.0059 mg Hg/kg/day for 60 days or ≥0.0011 mg Hg/kg/day for 90 days. Histopathological findings for control animals were not explicitly reported. Nagar and Bhattacharya (2001) reported various histopathological changes in the testes (detached tunica albuginea, hypertrophied and/or vacuolized spermatogenic and interstitial cells, luminal dilation) following gavage exposure to 0.006 mg Hg/kg/day (as mercuric chloride) for 7–21 days; incidence data were not reported, but effects reportedly became more pronounced with longer exposure duration (Nagar and Bhattacharya 2001). Control testes were "normal." Decreased diameter of seminiferous tubules, germ cells (spermatogonia, spermatocytes, spermatids, and/or sperm), Sertoli cells, and interstitial cells were also observed. The study authors also reported elevated testosterone; however, no measures of variance or statistics were reported.

A series of oral dosing studies in Wistar rats showed dose- and time-related 12–24% increases in relative testes weight following exposure to doses of 3 or 6 mg Hg/kg/day (as mercuric chloride) for 30, 60, or 90 days; no changes were observed in testes weight in rats similarly exposed for 3, 7, or 15 days (Boujbiha et al. 2009, 2011). In other studies, no exposure-related changes in testes weight were observed in Sprague-Dawley rats at intermediate-duration doses up to 1.31 mg Hg/kg/day (Atkinson et al. 2001) or F344 rats at intermediate- or chronic-duration doses up to 4 mg Hg/kg/day (NTP 1993). Significant, dose-related 15–20% decreases in seminal vesicle weight were reported in F0 male Sprague-Dawley rats exposed to ≥0.74 mg Hg/kg/day in a 2-generation study; no changes were observed in F1 males at doses up to 1.31 mg Hg/kg/day (Atkinson et al. 2001). No exposure-related changes were noted in epididymides or prostate weight in Sprague-Dawley rats exposed to intermediate-duration doses up to 1.31 mg Hg/kg/day (Atkinson et al. 2001). In mice, no exposure-related changes were noted in testes weight at intermediate-duration doses up to 15 mg Hg/kg/day (Khan et al. 2004; NTP 1993). Khan et al. (2004) also reported a lack of exposure-related changes in seminal vesicles, epididymides, and prostate weight in mice at intermediate-duration doses up to 0.74 mg Hg/kg/day.

Studies in female laboratory animals orally exposed to mercuric chloride provide no evidence of alterations to reproductive organs and minimal evidence of alterations in reproductive hormones. Histopathological lesions in female reproductive organs have not been reported following gavage exposure to mercuric chloride at acute-duration doses up to 9.24 mg Hg/kg/day in rats (Lecavalier et al.

1994), intermediate-duration doses up to 4 mg Hg/kg/day in rats or 15 mg Hg/kg/day in mice (Khan et al. 2004; NTP 1993), or chronic-duration doses up to 4 mg Hg/kg/day in rats or 7.4 mg Hg/kg/day in mice (NTP 1993). No changes in ovary or uterus weight were observed in F0 or F1 rats exposed to gavage doses up to 1.98 mg Hg/kg/day in a 2-generation study (Atkinson et al. 2001), and no changes in ovary weight were observed in mice exposed to gavage doses up to 0.74 mg Hg/kg/day for 79 days during premating, gestation, and lactation (Khan et al. 2004). Female reproductive hormone data are limited to a 60-day gavage study reporting an 18% decrease in serum progesterone and a 19% increase in pituitary LH levels at 1.5 mg Hg/kg/day, compared to control; these hormones were not altered at 0.7 mg Hg/kg/day and pituitary FSH was not altered at doses up to 1.5 mg Hg/kg/day (Heath et al. 2009).

One study reported reduced maternal care (increased latency to retrieve a pup removed from the nest) in dams exposed to mercuric chloride on GDs 1–21 at drinking water concentrations ≥6.1 mg Hg/kg/day (Chehimi et al. 2012). This may be secondary to altered pup behavior (e.g., decreased pup vocalizations), because foster dams also showed reduced maternal care; however, pup vocalizations were not measured.

Organic Mercury—Epidemiological Studies. Few epidemiological studies on male and female reproductive effects have been conducted in populations with high fish diets, with one study in males and two studies in females. Studies are summarized in Table 2-59. A study of male Inuit adults from Greenland examined comprehensive endpoints to evaluate male reproductive function (Mocevic et al. 2013). This study did not find adverse associations between BHg and sperm quality or serum levels of male reproductive hormones. The increase in serum levels of inhibin B, which reflects high Sertoli cell activity and high sperm counts, is not considered to be adverse. The single outcome evaluated for female reproductive function was duration of gestation, with studies reporting conflicting results (Dallaire et al. 2013; Murcia et al. 2016). A prospective study in Quebec Inuit mother-infant pairs reported an inverse association between umbilical cord BHg and the duration of gestation (Dallaire et al. 2013). In contrast, a cohort study of mother-infant pairs with high maternal fish consumption did not find an association (Murcia et al. 2016). Several factors may have contributed to these different observations: (1) differences may be due to differences in the types of fish consumed and corresponding intakes of methylmercury; (2) differences may exist in genetic predispositions between study populations; (3) mean cord BHg was higher in the Dallaire et al. (2013) study compared to the Murcia et al. (2016) study (21.3 versus 8.2 µg/L), although the Murcia study did not find an association between cord BHg and duration of gestation for the highest cord BHg tertile (≥15.0 µg/L); (4) sample size in the Murcia study was approximately 7 times larger than in the Dallaire et al. (2013) study; and (5) the Dallaire et al. (2013) study considered additional confounding factors (exposure to PCBs and fatty acids from fish). Given

these conflicting data, it is unclear if methylmercury exposure from high fish diets is associated with decreased gestational length.

Table 2-59. Epidemiological Studies Evaluating Associations between Mercury and Reproductive Effects in Populations with High Fish Diets

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Males			
Mocevic et al. 2013 Cross-sectional; 194 male Inuits from Greenland	BHg median: 9.2 µg/L	Semen volume	0 (BHg)
		Sperm concentration	0 (BHg)
		Total sperm count	0 (BHg)
		Sperm motility	0 (BHg)
		Normal sperm morphology	0 (BHg)
		LH	0 (BHg)
		FSH	0 (BHg)
		Testosterone	0 (BHg)
		Free androgen index	0 (BHg)
		Inhibin B[a]	↑ (BHg)
Females			
Dallaire et al. 2013 Prospective longitudinal; 248 mother-infant pairs; Inuit (Arctic Quebec) (adjustments included PCBs and DHA acid from fish and seafood intake)	Cord BHg mean: 21.3 µg/L	Duration of gestation	↓ (BHg)
Murcia et al. 2016 Cohort; 1,756 mother-infant pairs with high maternal fish consumption (Spain)	Cord BHg Gmean: 8.2 µg/L Tertiles T1: 5.0–<8.5 µg/L T2: 8.5–<15.0 µg/L T3: ≥15.0 µg/L	Duration of gestation	0 (BHg, T3)

[a]Increased serum levels of inhibin B, which reflects high Sertoli cell activity and high sperm counts, is not considered to be adverse.

↑ = positive association; ↓ = inverse association; 0 = no association; BHg = blood mercury; DHA = docosahexaenoic acid; FSH = follicle-stimulating hormone; Gmean = geometric mean LH = luteinizing hormone; PCBs = poly-chlorinated biphenyls; SGA = small for gestational age; T = tertile

Organic Mercury—Animal Studies. Studies in laboratory animals have evaluated effects of methylmercury compounds on reproductive function following acute-, intermediate-, and chronic-duration oral exposure. Additional data regarding reproductive endpoints (e.g., histology, organ weights,

hormone levels, sperm parameters) are available from acute-, intermediate-, and chronic-duration oral studies. Available oral data suggest that organic mercury can impair male and female fertility in monkeys and male fertility in rats. Data in male mice are too limited to draw conclusions. Available data in rodents do not provide consistent evidence of impaired female rodent fertility following oral exposure to organic mercury.

Studies in male rats found that acute- or intermediate-duration gavage exposure to methylmercury prior to mating with untreated females resulted in dose- and duration-dependent decreases in reproductive performance; no evidence of impaired fertility was observed in male mice following acute-duration gavage exposure (see Table 2-60). In Wistar rats, decreased male fertility was observed after acute-duration exposure to 5 mg Hg/kg/day or intermediate-duration exposure to 1 mg Hg/kg/day (Khera 1973). Additionally, the number of viable embryos per litter (embryos/litter) was significantly decreased after acute-duration exposure to 5 mg Hg/kg/day or intermediate-duration exposure to ≥0.05 mg Hg/kg/day (Khera 1973). In male Brown Norway rats dosed 22 times over an 11-week period prior to mating, fertility rates were 36, 22, 11, and 0% at 0, 0.0008, 0.008, and 0.08 mg Hg/kg/day, respectively (Friedmann et al. 1998). No viable fetuses were observed in the single litter produced at 0.008 mg Hg/kg/day. In mice, no exposure-related changes in fertility indices or viable embryos/litter were observed following acute-duration exposure to doses up to 5 mg Hg/kg/day prior to mating (Khera 1973).

Table 2-60. Reproductive Function in Male Rodents Orally Exposed to Methylmercuric Chloride via Gavage Prior to Mating to Unexposed Females

Species; duration	Dose (mg Hg/kg/day)	FI[a]	Live fetuses/ embryos per litter	Reference
Rat; 7 days	1	0	0	Khera 1973
Rat; 7 days	2.5	0	0	Khera 1973
Rat; 7 days	5	↓ (8–15[b])	↓ (12–13[b])	Khera 1973
Rat; 77 days[c]	0.0008	0	0	Friedmann et al. 1998
Rat; 77 days[c]	0.008	0	↓ (100[b])	Friedmann et al. 1998
Rat; 77 days	0.08	↓ (36[b])	NA	Friedmann et al. 1998
Rat; 95–125 days	0.1	0	0	Khera 1973
Rat; 95–125 days	0.5	0	↓ (30[d])	Khera 1973

Table 2-60. Reproductive Function in Male Rodents Orally Exposed to Methylmercuric Chloride via Gavage Prior to Mating to Unexposed Females

Species; duration	Dose (mg Hg/kg/day)	FI[a]	Live fetuses/ embryos per litter	Reference
Rat; 95–125 days	1	↓ (>60[d])	↓ (70[d])	Khera 1973
Mouse; 7 days	1	0	0	Khera 1973
Mouse; 7 days	2.5	0	0	Khera 1973
Mouse; 7 days	5	0	0	Khera 1973

[a]Fertility index = number of dams confirmed pregnant/number of dams with successful matings.
[b]Percent change compared to control, calculated from quantitative data.
[c]Rats only dosed 2 times/week.
[d]Percent change compared to control, estimated from graphically reported data.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; FI = fertility index

There is no evidence for impaired ability to become pregnant in female monkeys or mice orally exposed to methylmercury prior to mating untreated males: however, there is evidence for dose-related decreases in the ability for exposed monkeys to bring a pregnancy to term and decreased live pups/litter in mice exposed via gavage (see Table 2-61). In monkeys, no exposure-related changes in fertility, menstrual cyclicity, or gestation length were observed following exposure to methylmercury in apple juice over one or two breeding cycles at doses up to 0.08 mg Hg/kg/day; however, a 50–54% decrease in the number of viable pregnancies occurred following exposure to ≥0.06 mg Hg/kg/day (Burbacher and Mottet 1988; Burbacher et al. 1984, 2005). In rats, no changes in female fertility, live birth index, or number of live pups/litter were observed following intermediate-duration exposure to methylmercury at drinking water doses up to 0.6 mg Hg/kg/day (Elsner 1991; Newland and Reile 1999; Newland and Rasmussen 2000; Newland et al. 2004; Szász et al. 2002) or dietary doses up to 0.25 mg Hg/kg/day over 2 generations (Khera and Tabacova 1973). There were also no exposure-related changes in the number of implantations, resorptions, or corpora lutea in a 2-generation study of female rats (Khera and Tabacova 1973). In mice, the number of live pups/litter were significantly decreased by 16% following exposure to methylmercury at a dose of 0.4 mg Hg/kg/day via gavage before mating and through gestation and lactation (Huang et al. 2011); however, no exposure-related changes in the number of live pups/litter were observed in mice similarly exposed to methylmercury at drinking water doses up to 0.6 mg Hg/kg/day (Weiss et al. 2005) or dietary doses up to 0.98 mg Hg/kg/day (Thuvander et al. 1996). Studies in mice did not evaluate any additional reproductive function parameters.

Table 2-61. Reproductive Function in Female Laboratory Animals Orally Exposed to Methylmercury Compounds

Species; duration	Dose (mg Hg/kg/day)	Viable pregnancies/LBI[a,b]	Live pups/ litter[a]	Reference (compound)
Exposure prior to mating with unexposed males and through gestation and lactation				
Monkey; 395 days	0.04	0	–	Burbacher et al. 1984 (MMH)
Monkey; 395 days	0.08	↓ (50)	–	Burbacher et al. 1984 (MMH)
Monkey; 1,456 days	0.04	0	–	Burbacher and Mottet 1988; Burbacher et al. 2005 (MMH)
Monkey; 1,456 days	0.06	↓ (54)	–	Burbacher and Mottet 1988; Burbacher et al. 2005 (MMH)
Monkey; 1,456 days	0.08	↓ (54)	–	Burbacher and Mottet 1988; Burbacher et al. 2005 (MMH)
Rat; 60 days	0.19	–	0	Elsner 1991 (MMC)
Rat; 60 days	0.74	–	0	Elsner 1991 (MMC)
Rat; 70–77 days	0.6	–	0	Szasz et al. 2002 (MMC)
Rat; 70–91 days	0.045–0.6	0	0	Newland and Reile 1999; Newland and Rasmussen 2000; Newland et al. 2004 (MMC)
Rat; 122 days	0.002–0.25	0	0	Khera and Tabacova 1973 (MMC)
Mouse; 70 days	0.2	–	0	Weiss et al. 2005 (MM)
Mouse; 70 days	0.4	–	↓ (16)	Huang et al. 2011 (MMC)
Mouse; 70 days	0.6	–	0	Weiss et al. 2005 (MM)
Mouse; 105–112 days	0.098–0.98	–	0	Thuvander et al. 1996 (MMC)
Exposure throughout gestation and lactation only (GD 1–PND 21)				
Rat; 42 days	0.05–0.23	0	0	Fujimura et al. 2012 (MM)
Rat; 42 days	0.5	↓ (100)	↓ (100)	Fujimura et al. 2012 (MM)
Rat; 42 days	0.7	0	0	Chang et al. 2015 (MM)
Mouse; 42 days	0.9–1.3	–	0	Goulet et al. 2003 (MMH)

Table 2-61. Reproductive Function in Female Laboratory Animals Orally Exposed to Methylmercury Compounds

Species; duration	Dose (mg Hg/kg/day)	Viable pregnancies/LBI[a,b]	Live pups/ litter[a]	Reference (compound)
Mouse; 42 days	1.7	–	↓ (18)	Goulet et al. 2003 (MMH)

[a]Numbers in ( ) are percent change compared to control, calculated from quantitative data.
[b]Viable pregnancies (monkeys) or Live birth index (rodents = number of live pups/number of pups).

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; GD = gestation day; LBI = live birth index; MM = methylmercury; MMC = methylmercuric chloride; MMH = methylmercury hydroxide; PND = postnatal day

Evidence for reproductive effects in rodents following exposure to methylmercury throughout gestation and lactation (GD 1 to PND 21) is mixed (see Table 2-61). In one gestational/lactational rat study, no viable litters were produced at a drinking water dose of 0.5 mg Hg/kg/day; no changes in live birth index or litter size were observed at drinking water doses ≤0.23 mg Hg/kg/day (Fujimura et al. 2012). However, in a second gestational/lactation study in rats, no exposure-related changes were observed in live birth index or litter size at drinking water doses up to 0.7 mg Hg/kg/day (Chang et al. 2015). In mice, exposure to methylmercury at a drinking water dose of 1.7 mg Hg/kg/day resulted in an 18% decrease in the number of live pups/litter (Goulet et al. 2003).

Alterations in sperm parameters have been reported in monkeys, rats, and mice following oral exposure to methylmercury (see Table 2-62). In monkeys, morphological examination of semen smears indicated an increased incidence of tail defects (primarily bent and kinked tails) following intermediate-duration exposure to methylmercury in apple juice at doses ≥0.046 mg Hg/kg/day; at 0.065 mg Hg/kg/day, additional sperm effects included a decrease in the mean percentage of motile spermatozoa and the mean sperm speed (Mohamed et al. 1987). No changes in the sperm count in monkey semen were observed at doses up to 0.065 mg Hg/kg/day.

In rats, decreased sperm number (in the cauda epididymides) and/or decreased sperm mobility were observed following acute-duration exposure to doses ≥0.5 mg Hg/kg/day (Fossato da Silva et al. 2011; Chen et al. 2019) or intermediate-duration exposure to 0.08 mg Hg/kg/day (Friedmann et al. 1998). Acute-duration findings do not appear to be strongly dose-related; however, effects persisted and worsened post-exposure following higher exposure levels (9 mg Hg/kg/day) (Chen et al. 2019). Fossato da Silva et al. (2011) also reported an increase in the proportion of sperm with head abnormalities following acute-duration gavage exposure to 0.5 mg Hg/kg/day, but not at higher doses (≥0.93 mg

Hg/kg/day). In mice, decreased spermatogenesis was qualitatively reported in the testes of mice exposed to methylmercury at a dietary dose of 0.724 mg Hg/kg/day for 2 years (Hirano et al. 1986).

Table 2-62. Sperm Parameters in Male Laboratory Animals Orally Exposed to Methylmercury Compounds

Species; duration	Dose (mg Hg/kg/day)	Number	Mobility	Percent immobile	Speed	Percent abnormal	Reference
Monkey; 140 days	0.046	0	0	–	0	↑ (17[a])	Mohamed et al. 1987 (MM)
Monkey; 140 days	0.065	0	0	–	↓ (33[a])	↑ (16[a])	Mohamed et al. 1987 (MM)
Rat; 5 days	9	↓ (17–45[b,c])	–	↑ (11–32[b,c])	–	–	Chen et al. 2019 (MMC)
Rat; 14 days	0.5	↓ (17[b])	↓ (50[a])	↑ (30[a])	–	↑ (350[b])	Fossato da Silva et al. 2011 (MM)
Rat; 14 days	0.93	↓ (18[b])	↓ (43[a])	↑ (20[a])	–	0	Fossato da Silva et al. 2011 (MM)
Rat; 14 days	2.8	↓ (16[b])	↓ (36[a])	0	–	0	Fossato da Silva et al. 2011 (MM)
Rat; 56 days	3.2	0	–	–	–	–	Moussa et al. 2010 (M)
Rat; 133 days[d]	0.0008–0.008	0	–	–	–	–	Friedmann et al. 1998 (MMC)
Rat; 133 days[d]	0.08	↓ (17[a])	–	–	–	–	Friedmann et al. 1998 (MMC)
Mouse; 728 days	0.03–0.15	0	–	–	–	–	Hirano et al. 1986 (MMC)
Mouse; 728 days	0.724	↓ (NR[e])	–	–	–	–	Hirano et al. 1986 (MMC)

[a]Percent change compared to control, estimated from graphically reported data.
[b]Percent change compared to control, calculated from quantitative data.
[c]Alterations in sperm parameters observed 19–26 days after initial exposure.
[d]Rats only dosed 2 times/week.
[e]"Decreased spermatogenesis" reported in the testes; no quantitative data reported.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; MM = methylmercury; MMC = methylmercuric chloride; NR = not reported

No exposure-related changes in serum testosterone levels or Leydig cell testosterone secretion were observed in monkeys following intermediate-duration exposure to methylmercury in apple juice at doses up to 0.065 mg Hg/kg/day (Mohamed et al. 1987). In rats, a limited number of studies reported dose- and

duration-related decreases in serum testosterone following acute- or intermediate-duration exposures to methylmercury. Acute-duration gavage exposure to 2.8 mg Hg/kg/day resulted in a 65% decrease in serum testosterone (Fossato da Silva et al. 2011) and intermediate-duration drinking water exposure to 3.2 mg Hg/kg/day resulted in a 98% decrease in serum testosterone (Moussa et al. 2010). No exposure-related changes were observed for serum testosterone following gavage exposure to methylmercury at acute-duration doses up to 0.93 mg Hg/kg/day (Fossato da Silva et al. 2011) or intermediate-duration doses up to 0.08 mg Hg/kg/day (Friedmann et al. 1998). Decreased testicular (interstitial) testosterone levels were also reported following intermediate-duration exposure to methylmercury at a drinking water dose of 3.2 mg Hg/kg/day (-74%) (Moussa et al. 2010) or a gavage dose of 0.08 mg Hg/kg/day (-44%) (Friedmann et al. 1998). No changes in serum FSH or LH were reported in rats following acute-duration gavage exposure to methylmercury at doses up to 2.8 mg Hg/kg/day (Fossato da Silva et al. 2011).

No exposure-related changes in testicular histology were observed in monkeys following intermediate-duration exposure to methylmercury in apple juice at doses up to 0.065 mg Hg/kg/day (Mohamed et al. 1987). In rats, the only reported damage to the testes was reported 26 days after the start of a 5-day exposure to 9 mg Hg/kg/day via gavage as methylmercury (Chen et al. 2019). Treatment-related findings included significant disruption of the germinal epithelium of the seminiferous tubules and few spermatozoa; these findings were not evident 12 or 19 days after the start of exposure. In other rat studies, no histopathological changes in the testes were observed following oral exposure to methylmercury at acute-duration doses up to 2.8 mg Hg/kg/day (Fossato da Silva et al. 2011), intermediate-duration doses up to 3.2 mg Hg/kg/day (Moussa et al. 2010), or chronic-duration exposure to doses up to 0.16 mg Hg/kg/day (Verschuuren et al. 1976). In B6C3F1 mice, chronic-duration exposure to methylmercury at a dietary dose of 0.686 mg Hg/kg/day resulted in increased incidence of tubular atrophy of the testes; this increase was not observed at doses up to 0.139 mg Hg/kg/day (Mitsumori et al. 1990). However, no exposure-related testicular lesions were observed in ICR mice similarly exposed to intermediate- or chronic-duration dietary doses up to 0.724 mg Hg/kg/day (Hirano et al. 1986).

A single study in rats reported numerous histopathological lesions in the prostate following 14-day gavage exposure to methylmercury (Fossato da Silva et al. 2012). Alterations in prostate histology included increased incidence of inflammatory foci in 6/10 at 0.5 mg Hg/kg/day, periacinar connective tissue causing epithelial folds at 0.93 mg Hg/kg/day, and apparent thinning of the glandular epithelium, dilation of glandular acini, and higher nuclear-to-cytoplasmic ratio at 2.8 mg Hg/kg/day. Stereological measurements showed 40 and 34% increases in the epithelial component of the prostate at 0.5 and 0.93 mg Hg/kg/day, respectively; 46 and 56% decreases in the stromal component at 0.93 and 2.8 mg

Hg/kg/day, respectively; and a 25% increase in the size of the lumen at 2.8 mg Hg/kg/day. In other studies, no evidence of pathological lesions in the prostate were observed following dietary exposure to methylmercury for up to 2 years at doses up to 0.16 mg Hg/kg/day in rats (Verschuuren et al. 1976) or 0.724 mg Hg/kg/day in mice (Hirano et al. 1986; Mitsumori et al. 1990).

There is no consistent evidence for alterations in male reproductive organ weights in rats following exposure to methylmercury. One study reported a significant 8% decrease in absolute testes weight following exposure to methylmercury at a gavage dose of 0.08 mg; relative testes weight was not reported, but no body weight effects were noted in the study (Friedmann et al. 1998). However, other studies reported no exposure-related changes in testes weight at acute-duration doses up to 2.8 mg Hg/kg/day (Fossato da Silva et al. 2011), intermediate-duration doses up to 3.2 mg Hg/kg/day (Moussa et al. 2010), or chronic-duration doses up to 0.16 mg Hg/kg/day (Verschuuren et al. 1976). A significant 28% decrease in relative seminal vesicle weight was reported in rats following acute-duration gavage exposure to 2.8 mg Hg/kg/day, but not ≤0.93 mg Hg/kg/day (Fossato da Silva et al. 2011); no other available studies evaluated seminal vesicle weight. No dose-related changes in prostate weight were observed at acute-duration doses up to 2.8 mg Hg/kg/day (Fossato da Silva et al. 2012) or chronic-duration doses up to 0.16 mg Hg/kg/day (Verschuuren et al. 1976), and no dose-related changes in epididymides weights were observed at acute-duration doses up to 2.8 mg Hg/kg/day (Fossato da Silva et al. 2011) or intermediate-duration doses up to 0.08 mg Hg/kg/day (Friedmann et al. 1998).

Studies in female laboratory animals provide no evidence of alterations to reproductive organ weight and/or histology following dietary exposure to methylmercury for up to 2 years at doses up to 0.18 mg Hg/kg/day in rats (Verschuuren et al. 1976) or 0.627 mg Hg/kg/day in mice (Hirano et al. 1986; Mitsumori et al. 1990).

Predominant Mercury Form Unknown (General Populations). Studies evaluating reproductive effects of mercury in general populations are summarized in Table 2-63. Studies of male reproductive effects used cross-sectional designs and evaluated sperm quality and serum reproductive hormones. Most studies had small study populations (n=30–394) and were conducted in male partners of infertile couples for which other causes for decreased fertility may have been effect modifiers. The most common biomarker was BHg. In males, a large range for mean or median BHg was reported (1.1–14.3 µg/L). In women, several study designs were used to evaluate reproductive effects, including several prospective studies. Reproductive effects were primarily assessed by measurement of serum levels of reproductive hormones and incidence of preterm birth, with some studies evaluating effects of ovarian stimulation in sub- or

infertile women. Studies evaluating reproductive effects in females were generally larger (30–≥18,000). The most common biomarkers were BHg or HHg, with a range of BHg of 1.0–5.3 µg/L. In addition, a few studies evaluated reproductive success in couples.

Table 2-63. Overview of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Reproductive Effects in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Male reproductive effects			
Choy et al. 2002 Cross-sectional; 111 subfertile men (Hong Kong)	BHg mean: 8.3 µg/L	Sperm concentration	0 (BHg)
		% motile sperm	0 (BHg)
Leung et al. 2001 Cross-sectional; 51 male partners of infertile couples (Hong Kong)	BHg median Low Hg: 6.32 µg/L High Hg: 14.3 µg/L	Sperm concentration	0 (BHg, low versus high BHg)
		Normal sperm morphology	0 (BHg, low versus high BHg)
		Sperm velocity	0 (BHg, low versus high BHg)
		FSH	0 (BHg, low versus high BHg)
		LH	0 (BHg, low versus high BHg)
		Testosterone	0 (BHg, low versus high BHg)
		Prolactin	0 (BHg, low versus high BHg)
Meeker et al. 2008 Cross-sectional; 219 men (Michigan)	BHg median: 1.10 µg/L	Sperm concentration	0 (BHg)
		Sperm motility	0 (BHg)
		Sperm morphology	0 (BHg)
Mendiola et al. 2011 Case-control; 30 infertile men and 31 controls (Spain)	BHg mean Cases: 5.8 µg/L Control: 6.2 µg/L	FSH	0 (BHg)
		LH	0 (BHg)
		Testosterone	0 (BHg)
		Sperm concentration	0 (BHg)
		Sperm motility	0 (BHg)
		Sperm morphology	0 (BHg)
Minguez-Alarcon et al. 2018 Cross-sectional; 129 men enrolled in a study for infertile couples (Massachusetts)	HHg median: 0.72 µg/g Quartiles Q1: 0.03–0.37 µg/g Q2: 0.38–0.67 µg/g Q3: 0.70–1.25 µg/g Q4: 1.26–8.01 µg/g	Semen volume	0 (HHg, Q1 versus Q4) 0 (HHg, continuous)
		Sperm concentration	0 (HHg, Q1 versus Q4) ↑ (HHg, continuous)

Table 2-63. Overview of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Reproductive Effects in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Total sperm count	0 (HHg, Q1 versus Q4) ↑ (HHg, continuous)
		Sperm motility	0 (HHg, Q1 versus Q4) ↑ (HHg, continuous)
		Normal sperm morphology	0 (HHg, Q1 versus Q4) 0 (HHg, continuous)
Sukhn et al. 2018 Cross-sectional; 116 male partners of infertile couples (Lebanon)	BHg quartiles Q1: ≤4.35 µg/L Q2: 4.36–11.05 µg/L Q3: 11.06–21.47 µg/L Q4: ≥21.48 µg/L	Semen volume	0 (BHg, Q4)
		Sperm concentration	0 (BHg, Q4)
		Sperm count	0 (BHg, Q4)
		Sperm motility	0 (BHg, Q4)
		Sperm motility	0 (BHg, Q4)
		Sperm viability	0 (BHg, Q4)
		Sperm morphology	0 (BHg, Q4)
Zeng et al. 2013 Cross-sectional; 118 men from an infertility clinic (China)	UHg median: 1.98 µg/L Cr	Testosterone	0 (UHg)
Zeng et al. 2015 Cross-sectional; 394 men from an infertility clinic (China)	UHg median: 1.21 µg/L Cr	Sperm concentration	0 (UHg)
		Sperm count	0 (UHg)
		Sperm motility	0 (UHg)
		Sperm morphology	0 (UHg)
Female reproductive effects			
Arakawa et al. 2006 Retrospective; 198 women (Japan)	HHg Gmean: 2.01 µg/g	TTP	0 (HHg)
Dickerson et al. 2011 Prospective; 30 subfertile women undergoing IVF (United Kingdom)	HHg mean: 0.89 µg/g	Oocyte yield after ovarian stimulation	↓ (HHg)
		Follicle number after ovarian stimulation	↓ (HHg)
		IVF fertilization rate	0 (HHg)
Garcia-Fortea et al. 2018 Prospective; 194 subfertile women undergoing IVF (Spain)	HHg mean: 1.145 µg/g	Probability of mature oocytes	↓ (HHg)

Table 2-63. Overview of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Reproductive Effects in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Jackson et al. 2008 Cross-sectional; 1,425 premenopausal women (NHANES)	BHg mean: 1.00 µg/L	Endometriosis	0 (BHg)
		Uterine fibroids	0 (BHg)
Jackson et al. 2011; Pollack et al. 2011 Cross-sectional; 252 premenopausal women (Buffalo, New York)	BHg median: 1.10 µg/L	Menstrual cycle length	0 (BHg)
		FSH	0 (BHg)
		LH	0 (BHg)
		Estradiol	0 (BHg)
		Progesterone	0 (BHg)
Maeda et al. 2019 Case-control; 98 infertile women and 43 controls (Japan)	BHg mean Infertile: 5.3 µg/L Control: 5.0 µg/L	Infertility	↑ (BHg)
		DHRA-S	0 (BHg)
		Testosterone	0 (BHg)
		Estradiol	0 (BHg)
		Prolactin	0 (BHg)
Tsuji et al. 2018 Cohort; 18,847 pregnant women (Japan)	BHg quartiles Q1: ≤2.57 µg/L Q2: 2.58–3.65 µg/L Q3: 3.66–5.16 µg/L Q4: ≥5.17 µg/L	Preterm birth	0 (BHg, Q4)
Wells et al. 2016 Cross-sectional; 271 mother-infant pairs (Baltimore, Maryland)	Cord BMeHg Gmean: 0.94 µg/L	Gestational age	0 (BMeHg)
Xue et al. 2007 Prospective, 1,024 pregnant women (Michigan)	Maternal HHg median: 0.23 µg/g ≥90th percentile: 0.55–2.50 µg/g	Preterm birth (<35 weeks)	↑ (HHg, ≥90th percentile)
Yildirim et al. 2019 Case-control; 30 preterm delivery women and 20 term delivery women (Turkey)	Maternal BHg mean Preterm: 2.60 µg/L Term: 2.41 µg/L	Preterm birth	0 (BHg)
Wright et al. 2015 Prospective; 205 subfertile women undergoing IVF (Massachusetts)	HHg median: 0.62 µg/g	Oocyte yield after ovarian stimulation	0 (HHg)
		IVF fertilization rate	0 (HHg)
		Successful implantation	0 (HHg)
		Live birth	0 (HHg)

Table 2-63. Overview of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Reproductive Effects in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Reproductive effects in couples			
Buck Louis et al. 2012 Prospective; 401 couples (United States)	BHg Gmean Males: 1.81 µg/L Females: 1.40 µg/L	Fecundity	0 (BHg, males) 0 (BHg, females) 0 (BHg, couple)
Buck Louis et al. 2017 Cohort; 344 couples (United States)	BHg (median) Men: 1.18 µg/L Women: 0.98 µg/L	Pregnancy loss	0 (BHg, men and women)
Cole et al. 2006 Cross-sectional; 41 couples (Canada)	BHg quartiles, women Q1: 0.4–0.6 µg/L Q2: 0.7–1.0 µg/L Q3: 1.1–1.2 µg/L Q4: 1.3–3.6 µg/L BHg 1uartiles, men Q1: 0–0.6 µg/L Q2: 0.7–1.0 µg/L Q3: 1.1–1.8 µg/L Q4: 1.9–4.8 µg/L	TTP	↑ (BHg, women Q4) 0 (BHg, men Q4)

↑ = positive association; ↓ = inverse association; 0 = no association; BHg = blood mercury; Cr = creatinine; DHRA-S = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; Gmean = geometric mean; HHg = hair mercury; IVF = *in vitro* fertilization; LH = luteinizing hormone; NHANES = National Health and Nutrition Examination Survey; Q = quartile; TTP = time to pregnancy; UHg = urine mercury

Male reproductive effects. Several studies on male reproductive function have been conducted in general populations. Study populations include men with no known pre-existing reproductive system abnormalities (Meeker et al. 2008), sub- or infertile males (Choy et al. 2002; Mendiola et al. 2011; Zeng et al. 2013, 2015), and male partners of infertile couples (Leung et al. 2001; Minguez-Alarcon et al. 2018; Sukhn et al. 2018). Results of all studies show no inverse associations between mercury and sperm quality or serum levels of reproductive hormones in males. The only association that was observed was positive associations between HHg and sperm concentration, total sperm count, and sperm motility in male partners of infertile couples; these effects are not adverse. Based on these findings, mercury exposure in general populations did not appear to adversely affect the male reproductive system in the populations studied.

Female reproductive effects. Epidemiological studies on female reproductive function have been conducted in different subpopulations: women with no known fertility issues (Arakawa et al. 2006;

Jackson et al. 2008, 2011; Pollack et al. 2011); sub- or infertile women (Dickerson et al. 2011; Garcia-Fortea et al. 2018; Maeda et al. 2019; Wright et al. 2015); and pregnant women (Tsuji et al. 2018; Wells et al. 2016; Yildirim et al. 2019). Cross-sectional and retrospective studies in women with no known fertility issues examined numerous outcome measures to assess reproductive function. Results showed no associations between BHg and menstrual cycle length or serum levels of reproductive hormones (Jackson et al. 2011; Pollack et al. 2011), HHg and time to pregnancy (Arakawa et al. 2006), or BHg and endometriosis or uterine fibroids (Jackson et al. 2008). These findings have not been corroborated.

In sub- or infertile women, a case-control study reported a positive association between BHg and infertility, but no associations were observed between BHg and reproductive hormones (Maeda et al. 2019). Three prospective studies evaluated associations between mercury and ovarian response to stimulation in sub- or infertile women, with studies reporting conflicting results (Dickerson et al. 2011; Garcia-Fortea et al. 2018; Wright et al. 2015). Inverse associations were observed between HHg and oocyte yield, follicle number and probability of mature oocytes (Dickerson et al. 2011; Garcia-Fortea et al. 2018), whereas Wright et al. (2015) did not find an association between HHg and oocyte yield. No associations were observed for *in vitro* fertilization (IVF) rate or successful implantation (Garcia-Fortea et al. 2018; Wright et al. 2015).

Studies in pregnant women examining associations between mercury and preterm birth (<35 weeks of gestation) or gestational age report conflicting results. A prospective study in a U.S. population observed a positive association for HHg and preterm birth (Xue et al. 2007). However, no associations were observed between BHg and preterm birth in a very large cohort study of Japanese women (Tsuji et al. 2018) or in a small case-control study in women from Turkey (Yildirim et al. 2019). Gestational age also was not associated with blood methylmercury (Wells et al. 2016). Taken together, epidemiological studies on females provide conflicting results, with no clear evidence of adverse reproductive effects.

Reproductive effects in couples. Studies evaluating reproductive effects in couples show no associations between fecundity or pregnancy loss (Buck Louis et al. 2012, 2017), although an association was observed for time to pregnancy based on BHg in women, but not in men. Data are inadequate to determine if exposure to mercury adversely affects reproductive success.

Mechanisms of Action. General mechanisms of toxicity of mercury, including oxidative stress and inflammation are likely involved in the toxicity to male and female reproductive systems (see Section 2.21). Several mechanisms may be involved in the toxicity of mercury compounds to the

reproductive system (Ferguson and Chin 2017; Lu et al. 2018; Schuurs 1999; Tan et al. 2009; Wirth and Mijal 2010). Proposed mechanisms include the following: (1) altered hormonal regulation of the hypothalamic-pituitary-gonadal axis; (2) disruption of steroidogenesis; (3) enzyme inhibition; (4) inhibition of DNA, RNA, and protein synthesis; (5) decreased mitochondrial energy production and alterations of microtubule assembly in sperm tails; (6) altered estrogen production resulting in decreased numbers, size, and quality of ova; (7) agonist activity at estrogen receptors; (8) genetic polymorphisms; and (9) DNA methylation in sperm. In addition, mercury has been shown to accumulate in the hypothalamic-pituitary-gonadal axis.

2.18 DEVELOPMENTAL

A large body of literature addresses the potential for mercury exposure to produce neurological effects following exposure during early development. Similarly, several animal studies address the potential for mercury exposure to produce immunological effects following exposure during early development. Studies that have evaluated neurodevelopmental outcomes in humans and animal models are discussed in Section 2.16 (Neurological) and studies that have evaluated altered immune system development in animal models are discussed in Section 2.15 (Immunological) to facilitate comparison with effects observed following adult exposure. This section discusses developmental effects of mercury other than neurodevelopmental and immunodevelopmental effects. The term “developmental” used in the discussion that follows refers to effects other than neurodevelopmental and immunodevelopmental.

Overview. Data on developmental effects of mercury are available from epidemiology studies and studies in animals. Epidemiological studies have assessed effects in workers exposed to elemental mercury, populations with high fish diets, and general populations. These studies examined possible associations between mercury exposure and anthropometric measures in newborns (e.g., birth weight and size) and postnatal growth in children. The studies reported conflicting results, with no strong evidence of associations between mercury exposure and *in utero* or postnatal growth.

Studies evaluating developmental toxicity in animals are available for inhalation exposure to elemental mercury or oral exposure to mercuric chloride, mercuric acetate, or methylmercury. Overall, oral studies indicate dose- and duration-dependent developmental toxicity (increased offspring mortality, increased malformations and variations, decreased body weight) in rodents exposed to methylmercury, predominantly at maternally toxic doses. Oral studies with exposure to inorganic mercury salts are limited but suggest potential decreases in postnatal growth and survival following exposure to mercuric

chloride, primarily at maternally toxic doses. Evidence from inhalation studies are too limited to draw conclusions.

The following summarizes results of epidemiological and animal studies on developmental outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - Few studies have evaluated effects of exposure to elemental mercury and developmental outcomes.
    - One study reported an increased risk of small for gestational age (SGA) infants in dental workers versus controls; this outcome was not evaluated in other studies.
    - No associations were observed between exposure and anthropometric measures in neonates, neonatal mortality, or congenital malformations.
    - Available data are not sufficient to determine if exposure to elemental mercury is associated with adverse developmental outcomes.
  - *Animal studies*
    - Few studies investigated effects on developmental toxicity; one study reported developmental toxicity in rats (increased resorptions, decreased birth weight) following exposure to maternally toxic exposure levels.
- ***Inorganic mercury salts***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to inorganic mercury salts and developmental effects were identified.
  - *Animal studies*
    - Developmental endpoints evaluated in available studies are primarily limited to survival and growth parameters.
    - Decreased postnatal growth and survival have been reported in two multigenerational studies at doses associated with maternal toxicity; a few additional studies have reported decreased body weight in offspring following gestational exposure.
    - Available data are not sufficient to determine if exposure is associated with adverse developmental outcomes at oral exposures below those associated with maternal toxicity.
- ***Organic mercury***
  - *Epidemiology studies*
    - In the Minamata population, congenital defects were observed in infants.

- Results of studies evaluating birth size and postnatal growth in populations with high maternal fish diets were inconsistent, with most results reporting no associations.
- Available studies do not provide evidence of adverse effects on *in utero* or postnatal growth.

- *Animal studies*
  - Developmental studies consistently reported dose- and duration-dependent decreases in offspring survival and increases in malformations and variations in rats and mice. Common malformations observed in both rats and mice at high doses include cleft palate, skeletal malformations (ribs, sternebrae), and hydronephrosis.
  - Developmental studies in mice consistently reported dose- and duration-dependent decreases in offspring body weight; findings in rat were less consistent.
  - The majority of effects were noted at maternally toxic doses, but some effects were observed below doses associated with maternal toxicity.

- ***Predominant mercury form unknown (general populations)***
  - Evidence for effects on mercury exposure on birth size in general populations is inconclusive, with studies reporting inconsistent results. Most studies did not observe associations between mercury biomarkers and birth size.
  - Few studies have evaluated effects of mercury exposure on postnatal growth in general populations. The study results were inconsistent and do not provide clear evidence that mercury exposure in general populations is associated with decreased postnatal growth.

Confounding Factors. Numerous complicating factors may add uncertainty in the interpretation of studies examining associations between mercury exposure and developmental effects if not homogenously distributed in the study population. These factors include nutrition during pregnancy, prenatal care, adequate nutrition during infancy and childhood, socio-economic factors, intercurrent diseases, alcohol consumption, smoking status, and potential exposure to other chemicals. Failure to account for these factors may attenuate or strengthen the apparent associations between mercury exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Elemental Mercury—Epidemiological Studies. Few studies have evaluated effects of occupational exposure and developmental effects; studies are summarized in Table 2-64. Developmental outcomes evaluated were birth size, congenital malformations, and mortality. Two prospective studies examined small populations of females exposed through dental work or amalgam fillings (Bedir Findik et al. 2016; El-Badry et al. 2018) and one retrospective study evaluated neonates of male and female chloralkali

workers (Frumkin et al. 2001). The only adverse effect observed was an increased risk (risk ratio 6.2; 95% CI 2.3, 16.4) of SGA infants in dental workers versus controls (El-Badry et al. 2018). SGA was not evaluated in the other studies. No other adverse associations between biomarkers (cord BHg or UHg) were observed for anthropometric measures, congenital malformations, or neonatal mortality. Data are not adequate to determine if exposure to elemental mercury is associated with adverse developmental outcomes.

Table 2-64. Results of Epidemiological Studies Evaluating Exposure to Elemental Mercury (Hg^0) and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Bedir Findik et al. 2016 Prospective case-control; 28 pregnant women with amalgam fillings and 32 pregnant women with no amalgam fillings (Turkey)	BHg mean, cord Amalgam: 0.5 µg/L No amalgam: 0.3 µg/L BHg mean, maternal Amalgam: 0.50 µg/L No amalgam: 0.27 µg/L	Weight	0 (BHg amalgam versus no amalgam)
		Length	0 (BHg, amalgam versus no amalgam)
		Head circumference	0 (BHg, amalgam versus no amalgam)
		Gender	0 (BHg, amalgam versus no amalgam)
		Neonatal mortality	0 (BHg, amalgam versus no amalgam)
El-Badry et al. 2018 Prospective; 64 pregnant dental workers and 60 pregnant controls (Egypt)	UHg mean, workers 1st trimester: 42.2 µg/g Cr 2nd trimester: 41.8 µg/g Cr 3rd trimester: 42.8 µg/g Cr UHg mean, control: 1st trimester: 6.2 µg/g Cr 2nd trimester: 6.3 µg/g Cr 3rd trimester: 7.1 µg/g Cr	SGA	↑ (UHg, workers versus controls)
		Congenital malformations	0 (UHg, workers versus controls)
Frumkin et al. 2001 Retrospective cohort; 147 chloralkali workers and 132 controls (Brunswick, Georgia)	UHg mean Workers: 2.76 µg/g Cr Controls: 2.31 µg/g Cr	Birth weight	0 (UHg)
		Fetal malformation	0 (UHg)

↑ = positive association or increased compared to controls; 0 = no association; BHg = blood mercury; Cr = creatinine; SGA = small for gestational age; UHg = urine mercury

Elemental Mercury—Animal Studies. The developmental effects of exposure to elemental mercury have not been well-studied in animals. An increase in the number of resorptions, decreased litter size, and decreased pup weight on PND 1 was observed in rats following inhalation exposure to 8 mg Hg/m^3 for 2 hours/day on GDs 6–15; maternal toxicity (body weight loss) was observed in this group (Morgan et al. 2002). These effects were not observed in groups similarly exposed to ≤4 mg Hg/m^3 on GDs 6–15 or

≤8 mg Hg/m^3 on GD 6 or GDs 6–10 (Morgan et al. 2002). In other acute-duration inhalation studies, no exposure-related changes in litter size or birth weight were observed in rats following exposure to 1.8 mg Hg/m^3 for 1 or 3 hours/day on GDs 11–14 plus GDs 17–20 or 1–5 hours/per day on GDs 14–19 (Danielsson et al. 1993; Fredriksson et al. 1996). No changes in postnatal growth were observed in rats following direct postnatal inhalation exposure to 0.05 mg Hg/m^3 for 1 or 4 hours/day on PNDs 11–17 (Fredriksson et al. 1992). In mice, no changes in PND 10 body weight were observed following gestational exposure to 0.03 mg Hg/m^3 for 6 hours/day on GDs 0–18 (Yoshida et al. 2011). In squirrel monkeys, no exposure-related differences in birth weight, weight gain, or body weight through 4 years of age were observed in offspring following exposure to 0.5 or 1 mg Hg/m^3 for 4 or 7 hours/day, 5 days/week during the last two-thirds of gestation (Newland et al. 1996).

No exposure-related changes in emergence of developmental landmarks (e.g., pinna unfolding, tooth eruption) or reflex ontogeny (e.g., surface righting, negative geotaxis) were observed in rats following acute-duration gestational inhalation exposure to 1.8 mg Hg/m^3 for 1–5 hours per day (Danielsson et al. 1993; Fredriksson et al. 1996).

Inorganic Mercury Salts—Animal Studies. A limited number of developmental endpoints have been evaluated in laboratory animals exposed to mercuric chloride in multigenerational, gestational, gestational plus lactational, and early postnatal exposure studies. Most available studies were focused on neurological or immune development, which are discussed in Section 2.16 (Neurological) or Section 2.15 (Immunological), respectively, with limited information on systemic developmental toxicity (e.g., body weight). No comprehensive developmental toxicity evaluations were available (e.g., examinations for skeletal or visceral malformations); therefore, oral data are too limited to draw conclusions. However, some studies indicate that growth and survival of offspring may be impacted following developmental exposure to mercuric chloride, generally at oral doses associated with maternal toxicity in rodents.

Reduced postnatal survival has been reported in rats following developmental exposure to mercuric chloride at high oral doses. In a 2-generation gavage study in rats, neonatal survival to PND 4 decreased by 59% in F1 offspring at 1.98 mg Hg/kg/day and 19% in F2 offspring at 1.11 mg Hg/kg/day (F1 dams were not mated at 1.98 mg Hg/kg/day due to low F1 birth and survival rates); maternal toxicity (decreased body weight, decreased survival) were observed in F0 dams at ≥1.11 mg Hg/kg/day (Atkinson et al. 2001). In a gestation-only study, pup mortality was increased by 16% following maternal drinking water exposure to 9.6 mg Hg/kg/day on GDs 1–21; no maternal toxicity was observed (Chehimi et al. 2012). In mice, no exposure-related changes in postnatal survival were observed following exposure to gavage

doses up to 0.74 mg Hg/kg/day in a 1-generation study (Khan et al. 2004) or drinking water exposure to 1.5 mg Hg/kg/day on GDs 0–21 (Pilones et al. 2009).

No gross malformations were seen in rat offspring following gestational exposure to gavage doses up to 1.6 mg Hg/kg/day on GDs 5–15 (Papp et al. 2005). No changes in reflex ontogeny were observed in rat offspring following drinking water exposure to doses up to 3.8 mg Hg/kg/day from GD 0 to PND 21 (Oliveira et al. 2016). No other identified studies specifically evaluated malformations or reflex ontogeny following developmental exposure to mercuric chloride.

Body weight effects in rat offspring have been reported following gestational and/or postnatal exposure to mercuric chloride; findings were often associated with maternal toxicity. In a 2-generation gavage study, birth weight was decreased by 30% in F1 offspring at 1.98 mg Hg/kg/day and dose-related decreases in body weight were observed at all doses by PND 21 (20, 30, and 35% reductions at 0.55, 1.11, and 1.98 mg Hg/kg/day, respectively); F0 dam body weights were decreased at ≥1.11 mg Hg/kg/day (Atkinson et al. 2001). No exposure-related decreases were observed in F2 offspring at doses up to 1.11 mg Hg/kg/day (no F2 litters at 1.98 mg Hg/kg/day). A non-specified "slight" decrease in birth weight was reported in female rat pups following gestational exposure to gavage doses ≥0.8 mg Hg/kg/day on GDs 5–15; no exposure-related changes were observed in male birth weight and no exposure-related changes were observed in body weights of either sex at 12 weeks of age at gestational doses up to 1.6 mg Hg/kg/day (Papp et al. 2005). Similarly, no body weight effects at 12 weeks of age were observed in similarly treated rats with continued postnatal exposure on PNDs 2–28 (via dam) or PNDs 2–28 (via dam) plus direct exposure on PNDs 29–84 (Papp et al. 2005). In a drinking water study, no changes in fetal body weight on GD 20 were observed in rats following exposure doses up to 0.0301 mg Hg/kg/day on GDs 0–20 (Oliveira et al. 2012). However, maternal exposure to higher drinking water doses of 6.1 or 9.6 mg Hg/kg/day on GDs 1–21 resulted in offspring body weight decreases of approximately 10–15 and 20–30%, respectively, through PND 17 (Chehimi et al. 2012).

Developmental body weight data in mice exposed to mercuric chloride are limited and inconsistent. In ICR mice, a 6% decrease in birth weights and a 12% decrease in PND 70 body weights were observed in offspring following gavage exposure to 0.4 mg Hg/kg/day during gestation plus lactation (GD 0 to PND 21); body weight decreases were slightly more (15%) if direct exposure continued postweaning through PND 70 (Huang et al. 2011). No changes were observed in birth weights of SfvF1 or FvSF1 (autoimmune-susceptible) mice following drinking water exposure to 2.7 mg Hg/kg/day from GD 8 to PND 21 (Zhang et al. 2013). In a gestation-only study, no changes in birth weight were noted in DBF1

mouse offspring following drinking water exposure to 1.5 mg Hg/kg/day on GDs 0–21 (Pilones et al. 2009).

One study evaluated developmental toxicity in hamster offspring on GD 12 or 14 following a single maternal exposure to oral mercuric acetate on GD 8 (Gale 1974). The number of resorptions was increased in a dose-related manner at doses ≥22.1 mg Hg/kg/day, with 99% resorption at 63 mg Hg/kg/day. Additionally, the percentage of "malformed" embryos was increased at ≥15.8 mg Hg/kg/day, and the crown-rump length was decreased at ≥5 mg Hg/kg/day. Maternal toxicity (weight loss, diarrhea, tremor, somnolence, liver and kidney damage) was qualitatively reported; however, the dose(s) associated with effects were not reported.

Organic Mercury—Epidemiological Studies. Epidemiological studies on developmental effects in the Minamata population were not identified. However, congenital malformations have been reported in infants of mothers eating fish diets with very high mercury levels (Harada 1995; Rice et al. 2014). Malformations include polydactyly, syndactyly, craniofacial malformations, microcornea, undescended testicles, enlarged colon, and protrusion of the coccyx.

Studies investigating effects of mercury exposure on developmental outcomes in populations with high fish diets are summarized in Table 2-65. Studies include populations from the Faroe Islands and Seychelles Islands, an Inuit population, and other populations selected for high maternal fish consumption. Most studies evaluated populations with <300 participants, although a few studies evaluated larger populations (1,756–2,152 participants). Several studies used prospective designs and one study was a pooled analysis of prospective studies (Timmerman et al. 2017). Outcomes evaluated included anthropometric measures at birth (weight, length, head circumference), sex ratio, and postnatal growth. Most studies assessed mercury exposure using maternal and/or umbilical cord BHg.

Table 2-65. Epidemiological Studies Evaluating Associations between Mercury and Developmental Effects in Populations with High Maternal Fish Diets

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Faroe Islands			
Grandjean et al. 2001 Cohort; 182 pregnant women (Faroe Islands)	Cord BHg tertiles T1: <14 µg/L T2: 14 -33 µg/L T3: >33 µg/L	Birth weight	0 (BHg, T3)

Table 2-65. Epidemiological Studies Evaluating Associations between Mercury and Developmental Effects in Populations with High Maternal Fish Diets

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Grandjean et al. 2003 Prospective birth cohort; 171 children evaluated at 18 months and 154 evaluated at 42 months (Faroe Islands)	Cord BHg mean: 20.4 µg/L	Postnatal weight	↓ (BHg, 18 months) 0 (BHg, 42 months)
		Postnatal height	0 (BHg, 18 months) 0 (BHg, 42 months
Timmerman et al. 2017 Pooled data from 3 prospective birth cohorts; 2,152 mother-child pairs (Faroe Islands)	Maternal HHg median Cohort 1: 4.49 µg/g Cohort 3: 2.20 µg/g Cohort 5: 0.71 µg/g	Sex ratio (male:female)	↑ (HHg, combined cohorts) 0 (HHg, cohort 1) 0 (HHg, cohort 3) ↑ (HHg, cohort 5)
Seychelles Islands			
van Wijngaarden et al. 2014 Prospective birth cohort; 230 mother-infant pairs (Seychelles Islands)	Maternal HHg mean: 5.9 µg/g	Birth weight	0 (HHg)
Inuit populations			
Dallaire et al. 2013 Prospective longitudinal; 248 mother-infant pairs; Inuit (Arctic Quebec) (adjusted for DHA fatty acids from fish)	Cord BHg mean: 21.3 µg/L	Birth weight	0 (BHg)
		Birth length	0 (BHg)
		Head circumference	0 (BHg)
Other populations			
Murcia et al. 2016 Cohort; 1,756 mother-infant pairs with high maternal fish consumption (Spain)	Cord BHg Gmean: 8.2 µg/L Tertiles T1: 5.0–<8.5 µg/L T2: 8.5–<15.0 µg/L T3: ≥15.0 µg/L	Birth weight	0 (BHg, T3)
		Birth length	0 (BHg, T3)
		Head circumference	↓ (BHg, T3)
Tang et al. 2016 Cross-sectional; 103 mother-infant pairs with high maternal fish consumption (China)	Cord BHg median: 21.94 µg/L	Birth weight	0 (BHg)
		Birth length	0 (BHg)
		Head circumference	0 (BHg)

Table 2-65. Epidemiological Studies Evaluating Associations between Mercury and Developmental Effects in Populations with High Maternal Fish Diets

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Tatsuta et al. 2017 Prospective cohort; 289 mother-infant pairs (252 male newborns and 237 female newborns) with high maternal fish consumption (Japan)	Cord BHg mean: 10.1 µg/L	Birth weight	↑ (BHg, males) 0 (BHg, females) 0 (BHg, males and females)

[a]The toxicological significance of a positive association between HHg and male:female sex ratio is not established.

↑ = positive association, indicating an increase in the measured parameter; ↓ = inverse association, indicating a decrease in the measured parameter; 0 = no association; BHg = blood mercury; DHA = docosahexaenoic acid; Gmean = geometric mean; HHg = hair mercury; T = tertile

Results of studies evaluating anthropometric measures in populations with high maternal fish diets do not provide evidence of adverse effects. No inverse associations were observed between exposure and birth weight and/or birth length (Dallaire et al. 2013; Grandjean et al. 2001; Murcia et al. 2016; Tang et al. 2016; Tatsuta et al. 2017; van Wijngaarden et al. 2014). One study observed a small decrease in head circumference (β -0.052 cm; 95% CI 0.109, 0.005) per doubling of total BHg in a cohort of mother-infant pairs from Spain (Murcia et al. 2016). One prospective study of a Faroe Islands birth cohort evaluated postnatal growth in children from birth to 18 and 42 months of age (Grandjean et al. 2003). Results showed an inverse association between umbilical cord BHg and postnatal weight at 18 months, with a 0.8 kg (95% CI -1.56, -0.04) decrease per 10-fold increase in umbilical cord BHg. However, no association was observed at 42 months, and no associations were observed for postnatal height at 18 or 42 months. One study, a large pooled analysis of data from three prospective birth cohorts in the Faroe Islands, found a positive association between maternal HHg and male:female sex ratio (Timmerman et al. 2017). Examination of individual cohorts showed that this association only occurred in the cohort with the lowest HHg. The clinical significance of this finding is uncertain.

Organic Mercury—Animal Studies. Decreased offspring survival and increased malformations and variations are associated with developmental exposure to methylmercury compounds in rats and mice in a dose- and duration-dependent manner. Offspring body weight decreases in mice are also dose- and duration-dependent, while body weight findings in rats are less consistent. While the majority of effects are noted at maternally toxic doses, some effects were observed below doses associated with maternal toxicity, indicating that the developing organism may be susceptible to methylmercury toxicity.

Several studies have reported increased fetal death/resorption, decreased litter size, and/or decreased neonatal survival in rats following gestational exposure to methylmercury, predominantly at doses associated with maternal toxicity (see Table 2-66). Increased fetal death and decreased live litter size were observed in rats in a dose- and duration-dependent manner following gestational exposure to a single dose ≥8 mg Hg/kg/day, repeat acute-duration doses ≥6 mg Hg/kg/day, or an intermediate-duration dose of 1.9 mg Hg/kg/day; these findings were associated with maternal toxicity (decreased body weight, clinical signs of toxicity) (Fuyuta et al. 1978; Gandhi et al. 2013; Lee and Han 1995). Decreased postnatal survival to weaning was observed following gestational exposure to 7 mg Hg/kg/day on GD 8 or 15, with increased mortality following exposure on GD 15, compared to GD 8; no maternal toxicity was noted (Carratu et al. 2006). No change in postnatal survival was observed in rats exposed to 6.4 mg Hg/kg/day on GD 15 (Cagiano et al. 1990), 1.9 mg Hg/kg/day on GDs 6–9 (Fredriksson et al. 1996), or doses up to 0.9 mg Hg/kg/day on GDs 5–21 (Gandhi et al. 2013).

Table 2-66. Pre- and Postnatal Survival in Rats Following Gestation-Only Exposure to Methylmercury Compounds

Duration; dose (mg Hg/kg/day)	Dead/ resorbed[a]	Live litter size[a]	Postnatal survival[a]	Reference (compound)
1 day, GD 15 Dose: 6.4	–	–	0 PND 21	Cagiano et al. 1990 (MMC)
1 day, GD 8 Dose: 7	–	0	↓ PND 21 (8)	Carratu et al. 2006 (MM)
1 day, GD 15 Dose: 7	–	0	↓ PND 21 (16)	Carratu et al. 2006 (MM)
1 day GD 7 Dose: 8[b]	↑ (17)	↓ (19)	–	Lee and Han 1995 (MMC)
1 day, GD 7 Dose: 16[b]	↑ (19)	↓ (41)	–	Lee and Han 1995 (MMC)
1 day, GD 7 Dose: 24[b]	↑ (41)	↓ (91)	–	Lee and Han 1995 (MMC)
4 day, GDs 6–9 Dose: 0.02–0.4	–	0	–	Stoltenburg-Didinger and Markwort 1990 (MMC)
4 days, GDs 6–9 Dose: 1.9	–	–	0	Fredriksson et al. 1996 (MM)
4 days, GDs 6–9 Dose: 4	–	0	–	Stoltenburg-Didinger and Markwort 1990 (MMC)

Table 2-66. Pre- and Postnatal Survival in Rats Following Gestation-Only Exposure to Methylmercury Compounds

Duration; dose (mg Hg/kg/day)	Dead/ resorbed[a]	Live litter size[a]	Postnatal survival[a]	Reference (compound)
8 days, GDs 7–14 Dose: 2[b] or 4[b]	0	0	–	Fuyuta et al. 1978 (MMC)
8 days, GDs 7–14 Dose: 6[b]	↑ (38)	↓ (45)	–	Fuyuta et al. 1978 (MMC)
9 days, GDs 6–14 Dose: 0.024–4.6[b]	0	0	–	Nolen et al. 1972 (MMC)
17 days, GDs 5–21 Dose: 0.5–0.9	0	0	0	Gandhi et al. 2013 (MM)
17 days, GDs 5–21 Dose: 1.9[b]	↑ (100)	↓ (100)	NA	Gandhi et al. 2013 (MM)

[a]Numbers in ( ) are percent change compared to control, calculated from quantitative data.
[b]Dose associated with maternal toxicity (e.g., decreased body weight, clinical signs).

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; GD = gestation day; MM = methylmercury; MMC = methylmercuric chloride; NA = not applicable; PND = postnatal day

In gestation plus lactation studies in rats, one study reported an unspecified increase in the number of stillbirths and decreased postnatal survival following gavage exposure to methylmercury at 1.6 mg Hg/kg/day from GD 6 to PND 6, a dose associated with maternal toxicity (Tonk et al. 2010). Exposure to methylmercury at gavage doses up to 1.2 mg Hg/kg/day or drinking water doses up to 1.9 mg Hg/kg/day during gestation and lactation did not result in exposure-related changes in live litter size or postnatal survival (Albores-Garcia et al. 2016; Cheng et al. 2015; Fujimura et al. 2012; Giménez-Llort et al. 2001; Rossi et al. 1997; Sitarek and Gralewicz 2009; Tonk et al. 2010). Additionally, no exposure-related changes in live litter size or postnatal survival were observed in 1- or 2-generational studies in rats at doses up to 0.9 mg Hg/kg/day (Beyrouty et al. 2006; Elsner 1991; Khera and Tabacova 1973; Newland and Reile 1999; Szasz et al. 2002).

In mice, increased fetal death/resorption, decreased litter size, and/or decreased neonatal survival have also been observed following gestation or gestation plus lactation exposure to methylmercury at doses below those associated with maternal toxicity (see Table 2-67). Increased fetal death was observed in mice following repeat acute-duration exposures ≥4.8 mg Hg/kg/day and following an intermediate-duration dose of 5 mg Hg/kg/day; in both studies, fetal effects were observed (Fuyuta et al. 1978; Khera and Tabacova 1973). No changes in fetal death/resorption were observed in mice following single gestational methylmercury exposure to doses up to 20 mg Hg/kg/day (Fuyuta et al. 1979; Belles et al. 2002; Yasuda et al. 1985).

Decreased postnatal survival to PND 56 was observed following gestational exposure to 16 mg Hg/kg/day on GD 13, 14, 15, 16, or 17, with the highest mortality after exposure on GD 15 or 16 (Inouye et al. 1985). Decreased postnatal survival to PND 35 was also observed in mice exposed to 5 mg Hg/kg/day on GDs 7–9 or 12–14, but not 3 mg Hg/kg/day; mortality was comparable for both exposure paradigms (Dore et al. 2001). No change in postnatal survival was observed in mice exposed to doses up to 1 mg Hg/kg/day on GDs 6–17 (Khera and Tabacova 1973). No exposure-related changes in postnatal survival were observed in the 1-generation studies (Huang et al. 2011; Thuvander et al. 1996; Weiss et al. 2005).

There is inconsistent evidence for decreased live litter size following single exposures to methylmercury during gestation. No changes were observed in litter sizes following repeated gestational exposure to methylmercury at doses below those associated with 100% fetal death (12-day exposure to 5 mg Hg/kg/day; Khera and Tabacova 1973). In a mouse study with gestational plus lactational exposure, live litter size and postnatal survival were both decreased at 1.7 mg Hg/kg/day, but not at doses ≤1.3 mg Hg/kg/day (Goulet et al. 2003). A 1-generation study in mice reported decreased live litter size following exposure to 0.02 mg Hg/kg/day (Huang et al. 2011); however, no change in live litter size was reported in two other 1-generation studies at doses up to 6 mg Hg/kg/day (Thuvander et al. 1996; Weiss et al. 2005).

Table 2-67. Pre- and Postnatal Survival in Mice Following Gestation-Only or Gestation plus Lactation Exposure to Methylmercury Compounds

Duration; dose (mg Hg/kg/day)	Dead/resorbed[a]	Live litter size[a]	Neonatal survival[a]	Reference (compound)
1 day, GD 8 Dose: 1–2	–	0	–	Hughes and Annau 1976 (MMH)
1 day, GD 8 Dose: 3[b]	–	↓ (35)	–	Hughes and Annau 1976 (MMH)
1 day, GD 8 Dose: 5[b]	–	↓ (40)	–	Hughes and Annau 1976 (MMH)
1 day, GD 10 Dose: 8	0	↓ (13)	–	Fuyuta et al. 1979 (MMC)
1 day, GD 10 Dose: 9.99	0	–	–	Belles et al. 2002 (MMC)
1 day, GD 8 Dose: 10	–	↓ (73)	–	Hughes and Annau 1976 (MMH)
1 day, GD 10 Dose: 12–16	0	0	–	Fuyuta et al. 1979 (MMC)
1 day, GD 13, 14, 15, 16, or 17 Dose: 16[b]	–	0	PND 56: ↓ (67–94%)	Inouye et al. 1985 (MMC)

Table 2-67. Pre- and Postnatal Survival in Mice Following Gestation-Only or Gestation plus Lactation Exposure to Methylmercury Compounds

Duration; dose (mg Hg/kg/day)	Dead/resorbed[a]	Live litter size[a]	Neonatal survival[a]	Reference (compound)
1 day, GD 10 or 12 Dose: 10–20	0	0	–	Yasuda et al. 1985 (MMC)
1 day, GD 10 Dose: 20[c]	0	↓ (15)	–	Fuyuta et al. 1979 (MMC)
3 days, GDs 7–9 or 12–14 Dose: 3	–	0	0	Dore et al. 2001 (MMC)
3 days, GDs 7–9 Dose: 5[b]	–	0	PND 35: ↓ (28)	Dore et al. 2001 (MMC)
3 days, GDs 12–14 Dose: 5[b]	—	0	PND 35: ↓ (26)	Dore et al. 2001 (MMC)
8 days, GDs 6–13 Dose: 2–4	0	0	—	Fuyuta et al. 1978 (MMC)
8 days, GDs 6–13 Dose: 4.8	↑ (25)	0	—	Fuyuta et al. 1978 (MMC)
8 days, GDs 6–13 Dose: 6[c]	↑ (89)	0	—	Fuyuta et al. 1978 (MMC)
12 days, GDs 6–17 Dose: 0.0001–1	0	0	0	Khera and Tabacova 1973 (MMC)
12 days, GDs 6–17 Dose: 5	↑ (100)	NA	NA	Khera and Tabacova 1973 (MMC)
41 days, GD 2–PND 21 Dose: 0.9–1.3	–	0	0	Goulet et al. 2003 (MMC)
41 days, GD 2–PND 21 Dose: 1.7[b]	–	↓ (18)	↓ (14)	Goulet et al. 2003 (MMC)
63–70 days, premating through PND 13 Dose: 0.2–6	–	0	0	Weiss et al. 2005 (MMC)
112 days, premating through PND 15 Dose: 0.098–0.98	–	0	0	Thuvander et al. 1996 (MMC)
119 days, premating through PND 70 Dose: 0.02	–	↓ (16)	0	Huang et al. 2011 (MM)

[a]Numbers in ( ) are percent change compared to control, calculated from quantitative data.
[b]Maternal health not reported.
[c]Dose associated with maternal toxicity (e.g., decreased body weight, clinical signs).

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; GD = gestation day; MM = methylmercury; MMC = methylmercuric chloride; MMH = methylmercury hydroxide; NA = not applicable; PND = postnatal day

A single study in guinea pigs reported 100% fetal death in 20, 50, 67, 50, and 20% of dams following exposure to 11.5 mg Hg/kg/day once on GD 21, 28, 35, 42, or 49, respectively, compared to 0% of control dams (Inouye and Kajiwara 1988). Exposed dams showed clinical signs of toxicity.

Dose- and duration-related increases in malformations and variations have been observed in rats and mice following gestational exposure to methylmercury compounds; some findings were observed at doses below those associated with maternal toxicity and/or offspring lethality (see Tables 2-68 and 2-69, respectively). In rats, total gross malformations, including cleft palate and generalized edema were observed after repeated oral exposures to doses ≥4 mg Hg/kg/day during gestation (Fuyuta et al. 1978; Nolen et al. 1972). Cleft palate was also observed in mice following repeated oral exposures to doses ≥4 mg Hg/kg/day during gestation (Fuyuta et al. 1978) or single gestational exposures ≥9.99 mg Hg/kg/day (Belles et al. 2002; Fuyuta et al. 1979; Yasuda et al. 1985). Observed skeletal malformations and variations in rats included spinal curvature, sternal absence or defects, wavy ribs, absent or bilobed vertebral centra, and delayed ossification at single doses ≥8 mg Hg/kg/day and repeat doses ≥0.024 mg Hg/kg/day (Abd El-Aziz et al. 2012; Fuyuta et al. 1978; Lee and Han 1995; Nolen et al. 1972). Similar effects (delayed ossification, sternal and vertebral defects) were observed in mice following single doses ≥8 mg Hg/kg/day and repeat doses ≥2 mg Hg/kg/day (Belles et al. 2002; Fuyuta et al. 1978, 1979; Yasuda et al. 1985). Visceral malformations in rats included hydrocephaly following exposure to ≥4 mg Hg/kg/day on GDs 7–14 (Fuyuta et al. 1978) and defects in the urinary system (bladder defects, hydronephrosis, and/or hydroureter) following exposure to ≥0.024 mg Hg/kg/day on GDs 6–14 (Nolen et al. 1972). Hydronephrosis and/or dilatation of the renal pelvis were observed in mice following single doses ≥16 mg Hg/kg/day; hydronephrosis was also observed following repeat doses of 4.8 mg Hg/kg/day (Belles et al. 2002; Fuyuta et al. 1978, 1979; Yasuda et al. 1985).

Table 2-68. Malformations and Variations in Rats Following Gestation-Only Exposure to Methylmercury Compounds

Duration; dose (mg Hg/kg/day)	Gross malformations	Skeletal malformation/ variation	Visceral malformation/ variation	Reference (compound)
1 day (GD 7) Dose: 8[a,b]	0	Decreased ossification centers ↓ (9–12[c]) Spinal curvature ↑ (NR)	0	Lee and Han 1995 (MMC)

Table 2-68. Malformations and Variations in Rats Following Gestation-Only Exposure to Methylmercury Compounds

Duration; dose (mg Hg/kg/day)	Gross malformations	Skeletal malformation/ variation	Visceral malformation/ variation	Reference (compound)
1 day (GD 7) Dose: 16[a,b]	0	Decreased ossification centers ↓ (25–63[c]) Spinal curvature ↑ (NR)	0	Lee and Han 1995 (MMC)
1 day (GD 7) Dose: 24[a,b]	0	Decreased ossification centers ↓ (55–100[c]) Spinal curvature ↑ (NR)	0	Lee and Han 1995 (MMC)
8 days (GDs 7–14) Dose: 2[a]	0	0	0	Fuyuta et al. 1978 (MMC)
8 (GDs 7–14) Dose: 4[a]	Total malformations ↑ (7[d])	Wavy ribs ↑ (7[d])	Hydrocephaly ↑ (6[d])	Fuyuta et al. 1978 (MMC)
8 days (GDs 7–14) Dose: 6[a,b]	Total malformations ↑ (80[d]) Cleft palate ↑ (18[d]) General edema ↑ (79[d])	Wavy ribs ↑ (27[d]) Sternal defects/ absence ↑ (20–61[d]) Absence or bilobed vertebral centra ↑ (6–13[d])	Hydrocephaly ↑ (67[d])	Fuyuta et al. 1978 (MMC)
9 days (GDs 6–14) Dose: 0.024	0	Missing 5th sternebra ↑ (7[c]) Incomplete calcification ↑ (15[c])	Bladder defect ↑ (8[c])	Nolen et al. 1972 (MMC)
9 days (GDs 6–14) Dose: 0.23	0	Missing 5th sternebra ↑ (8[c])	Bladder defect ↑ (16[c]) Hydronephrosis ↑ (11[c])	Nolen et al. 1972 (MMC)
9 days (GDs 6–14) Dose: 4.6[a]	Total malformations ↑ (61[c])	Missing 5th sternebra ↑ (22[c])	Bladder defect ↑ (54[c]) Hydronephrosis ↑ (36[c]) Hydroureter ↑ (9[c])	Nolen et al. 1972 (MMC)
21 days (GDs 0–20) Dose: 0.9	–	Delayed ossification ↑ (12[d])	–	Abd El-Aziz et al. 2012 (MMC)

Table 2-68. Malformations and Variations in Rats Following Gestation-Only Exposure to Methylmercury Compounds

Duration; dose (mg Hg/kg/day)	Gross malformations	Skeletal malformation/ variation	Visceral malformation/ variation	Reference (compound)
21 days (GDs 0–20) Dose: 1.8[e]	–	Delayed ossification ↑ (18[d])	–	Abd El-Aziz et al. 2012 (MMC)

[a]Dose associated with maternal toxicity (e.g., decreased body weight, clinical signs).
[b]Dose associated with increased fetal/neonatal death.
[c]Percent change compared to control, calculated from quantitative data.
[d]Percent difference in fetal incidence, compared to control.
[e]Maternal health not reported.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; GD = gestation day; MMC = methylmercuric chloride; NA = not applicable; PND = postnatal day; W = drinking water

Table 2-69. Malformations and Variations in Mice Following Gestation-Only Exposure to Methylmercury Compounds

Duration; dose (mg Hg/kg/day)	Gross malformations[a]	Skeletal malformation/ variation[a]	Visceral malformation/ variation[a]	Reference (compound)
1 day, GD 10 Dose: 8	0	Incomplete fusion sternebrae ↑ (5)	0	Fuyuta et al. 1979 (MMC)
1 day, GD 10 Dose: 9.99	Cleft palate ↑ (61)	Delayed ossification ↑ (69)	0	Belles et al. 2002 (MMC)
1 day, GD 10 or 12 Dose: 10–12	0	0	–	Yasuda et al. 1985 (MMC)
1 day, GD 10 Dose: 12	Total malformations ↑ (29) Cleft palate ↑ (28)	Incomplete fusion sternebrae ↑ (65)	0	Fuyuta et al. 1979 (MMC)
1 day, GD 10 Dose: 16	Total malformations ↑ (61) Cleft palate ↑ (59)	Incomplete fusion sternebrae ↑ (74)	Hydronephrosis ↑ (19)	Fuyuta et al. 1979 (MMC)
1 day, GD 13, 14, 15, 16, or 17 Dose: 16[b]	0	–	–	Inouye et al. 1985 (MMC)
1 day, GD 10 or 12 Dose: 16	Cleft palate GD 10: ↑ (70) GD 12: (81)	0	Dilatation of renal pelvis GD 10: ↑ (22) GD 12: (25)	Yasuda et al. 1985 (MMC)

Table 2-69. Malformations and Variations in Mice Following Gestation-Only Exposure to Methylmercury Compounds

Duration; dose (mg Hg/kg/day)	Gross malformations[a]	Skeletal malformation/ variation[a]	Visceral malformation/ variation[a]	Reference (compound)
1 day, GD 10 or 12 Dose: 20	Cleft palate GD 10: ↑ (99.9) GD 12: (98)	0	Dilatation of renal pelvis GD 10: ↑ (41) GD 12: (36)	Yasuda et al. 1985 (MMC)
1 day, GD 10 Dose: 20[c]	Total malformations ↑ (97) Cleft palate ↑ (100)	Incomplete fusion sternebrae ↑ (88)	Hydronephrosis ↑ (24)	Fuyuta et al. 1979 (MMC)
8 days, GDs 6–13 Dose: 2	Total malformations ↑ (11)	Delayed ossification ↑ (36) Absent sternebra ↑ (18)	0	Fuyuta et al. 1978 (MMC)
8 days, GDs 6–13 Dose: 4	Total malformations ↑ (76) Cleft palate ↑ (57)	Fused thoracic vertebra ↑ (63) Delayed ossification ↑ (72) Absent sternebra ↑ (80)	0	Fuyuta et al. 1978 (MMC)
8 days, GDs 6–13 Dose: 4.8[a]	Total malformations ↑ (98) Cleft palate ↑ (98)	Fused thoracic vertebra ↑ (61) Delayed ossification ↑ (80) Absent sternebra ↑ (91)	Hydronephrosis ↑ (24)	Fuyuta et al. 1978 (MMC)
8 days, GDs 6–13 Dose: 6[b,c]	Total malformations[d] ↑ (100) Cleft palate[d] ↑ (100)	0[d]	0[d]	Fuyuta et al. 1978 (MMC)

[a]Numbers in ( ) are percent difference in fetal incidence, compared to control.
[b]Dose associated with increased fetal/neonatal death.
[c]Dose associated with maternal toxicity (e.g., decreased body weight, clinical signs).
[d]Based on a single live fetus.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; GD = gestation day; MMC = methylmercuric chloride; NA = not applicable; PND = postnatal day

In a 2-generation study in rats, delayed eye opening, suborbital edema, and corneal opacity were observed in offspring following exposure to 0.25 mg Hg/kg/day, but not ≤0.05 mg Hg/kg/day. Delays in developmental landmark acquisitions were not observed at gestation-only doses up to 1.9 mg Hg/kg/day

(Fredriksson et al. 1996; Gandhi et al. 2013) or at doses up to 0.6 mg Hg/kg/day in a 1-generation study in rats (Newland and Reile 1999). Decreased pup vocalization was reported in rat offspring in a 1-generation study at doses ≥0.19 mg Hg/kg/day (Elsner 1991). No other available study examined this endpoint.

No changes in postnatal body weight were observed in monkey offspring following exposure to methylmercury in a 1-generation study (premating through gestation) at a dose of 0.04 mg Hg/kg/day (Burbacher et al. 1984).

Body weight effects in rats following developmental exposure to methylmercury are inconsistent; observed effects were often associated with maternal toxicity (see Table 2-70). Rat fetal body weight and length on GD 20 were decreased in a dose-related manner following gestational exposure to methylmercury at doses ≥8 and 16 mg Hg/kg/day, respectively, on GD 7 (Lee and Han 1995). However, findings from repeat-dose gestational exposure studies in rats do not show consistent dose- or duration-dependent effects for fetal/birth weight (see Table 2-70). Postnatal body weight on PND 21 was decreased following exposure to 7 mg Hg/kg/day on GD 15, but not on GD 8 (Carratu et al. 2006), and no change in postnatal weight was observed in another study following exposure to 6.4 mg Hg/kg/day on GD 15 (Cagiano et al. 1990). No exposure-related changes in postnatal weight were observed following repeated gestation-only exposures up to 1.9 mg Hg/kg/day (Abd El-Aziz et al. 2012; Fredriksson et al. 1996). When exposure continued during lactation, dose-related decreases were observed in postnatal weight during lactation at doses ≥0.8 mg Hg/kg/day (Sitarek and Gralewicz 2009; Tonk et al. 2010).

Table 2-70. Body Weight and Length Effects in Rats Following Gestation or Gestation Plus Lactation Exposure to Methylmercury Compounds

Duration; dose (mg Hg/kg/day)	Fetal/birth weight	Fetal length	Postnatal birth weight	Reference (compound)
1 day, GD 15 Dose: 6.4	0	–	0	Cagiano et al. 1990 (MMC)
1 day, GD 8 Dose: 7[a]	0	–	0	Carratu et al. 2006 (MM)
1 day, GD 15 Dose: 7[a]	0	–	PND 21: ↓ (18)[b]	Carratu et al. 2006 (MM)
1 day, GD 7 Dose: 8[a,c]	GD 20: ↓ (12)[b]	0	–	Lee and Han 1995 (MMC)
1 day, GD 7 Dose: 16[a,c]	GD 20: ↓ (24)[b]	GD 20: ↓ (22)[b]	–	Lee and Han 1995 (MMC)

Table 2-70. Body Weight and Length Effects in Rats Following Gestation or Gestation Plus Lactation Exposure to Methylmercury Compounds

Duration; dose (mg Hg/kg/day)	Fetal/birth weight	Fetal length	Postnatal birth weight	Reference (compound)
1 day, GD 7 Dose: 24[a,c]	GD 20: ↓ (49)[b]	GD 20: ↓ (37)[b]	–	Lee and Han 1995 (MMC)
4 days, GDs 6–9 Dose: 1.9	0	–	0	Fredriksson et al. 1996 (MM)
8 days, GDs 7–14 Dose: 2[c]	0	–	–	Fuyuta et al. 1978 (MMC)
8 days, GDs 7–14 Dose: 4[c]	M: ↓ (9)[b] F: ↓ (8)[b]	–	–	Fuyuta et al. 1978 (MMC)
8 days, GDs 7–14 Dose: 6[a,c]	0	–	–	Fuyuta et al. 1978 (MMC)
9 days, GDs 6–14 Dose: 0.024–4.6[c]	0	–	–	Nolen et al. 1972 (MMC)
17 days, GDs 5–21 Dose: 0.5	PND 1: ↓ (12)[b]	–	0	Gandhi et al. 2013 (MM)
17 days, GDs 5–21 Dose: 0.9	PND 1: ↓ (14)[b]	–	0	Gandhi et al. 2013 (MM)
21 days, GDs 0–20 Dose: 0.9	0	0	–	Abd El-Aziz et al. 2012 (MMC)
21 days, GDs 0–20 Dose: 1.8[d]	GD 20: ↓ (14)[b]	GD 20: ↓ (14)[b]	–	Abd El-Aziz et al. 2012 (MMC)
22 days, GD 7–PND 7 Dose: 0.5	0	–	0	Giménez-Llort et al. 2001; Rossi et al. 1997 (MMH)
26 days, GD 6–PND 10 Dose: 0.08–0.6	–	–	0	Tonk et al. 2010 (MMC)
26 days, GD 6–PND 10 Dose: 0.8	–	–	PND 10: M: ↓ (7)[e] F: 0	Tonk et al. 2010 (MMC)
26 days, GD 6–PND 10 Dose: 1.2	–	–	PND 10: M: ↓ (9)[e] F: 0	Tonk et al. 2010 (MMC)
26 days, GD 6–PND 10 Dose: 1.6[a,c]	–	–	PND 10: M: ↓ (10)[e] F: ↓ (15)[e]	Tonk et al. 2010 (MMC)
36 days, GD 7–PND 21 Dose: 0.5	0	–	0	Sitarek and Gralewicz 2009 (MMC)
36 days, GD 7–-PND 21 Dose: 1.9[c]	0	–	PND 21: ↓ (23)[e]	Sitarek and Gralewicz 2009 (MMC)
38 days, GD 5–PND 21 Dose: 0.2–0.4	0	–	0	Albores-Garcia et al. 2016 (MMC)

Table 2-70. Body Weight and Length Effects in Rats Following Gestation or Gestation Plus Lactation Exposure to Methylmercury Compounds

Duration; dose (mg Hg/kg/day)	Fetal/birth weight	Fetal length	Postnatal birth weight	Reference (compound)
42 days, GD 1–PND 21 Dose: 0.05–0.23	0	–	0	Cheng et al. 2015; Fujimura et al. 2012 (MM)

[a]Dose associated with increased fetal/neonatal death.
[b]Percent change compared to control, calculated from quantitative data.
[c]Dose associated with maternal toxicity (e.g., decreased body weight, clinical signs).
[d]Maternal health not reported.
[e]Percent change compared to control, estimated from graphically reported data.

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; F = female; GD = gestation day; M = male; MM = methylmercury; MMC = methylmercuric chloride; MMH = methylmercury hydroxide; NA = not applicable; PND = postnatal day

Findings regarding alterations in birth and postnatal weight following methylmercury exposure in 1-generation rat studies are inconsistent. One study reported an 11% decrease in birth weight at a drinking water dose of 0.3 mg Hg/kg/day (Szasz et al. 2002), but no changes in birth weight were observed in other studies at drinking water doses up to 0.74 mg Hg/kg/day or gavage doses up to 0.9 mg Hg/kg/day (Beyrouty et al. 2006: Elsner 1991; Newland and Reile 1999). No decreases in offspring postnatal body weight were observed at drinking water doses up to 0.74 mg Hg/kg/day (Elsner 1991; Newland and Reile 1999; Szasz et al. 2002). One study reported a >20% increase in body weight at postnatal week 6 in offspring following F0 drinking water exposure to doses ≥0.0006 mg Hg/kg/day; this finding was no longer observed at postnatal week 12 (Wild et al. 1997). The adversity of this transient increase in offspring body weight is unclear; therefore, it is not included in the LSE tables or Table 2-71. In gavage and dietary studies, 6–12% decreases in postnatal body weight were observed at 0.9 and 0.37 mg Hg/kg/day, respectively (Beyrouty et al. 2006; Ilback et al. 1991). No changes in birth or postnatal weight were observed in a 2-generation study in rats at dietary doses up to 0.25 mg Hg/kg/day (Khera and Tabacova 1973).

Observed decreases in late gestation or birth weight in mice were generally dose- and duration-dependent following gestational exposure to methylmercury and occurred below maternally toxic doses (see Table 2-71). Decreased weights were consistently observed following single exposures to ≥9.99 mg Hg/kg/day or repeat exposures ≥4 mg Hg/kg/day (Belles et al. 2002; Fuyuta et al. 1979; Hughes and Annau 1976), although one study did not report body weight effects on GD 18 following exposure until doses ≥16 mg Hg/kg/day were administered on GD 10 or 12 (Yasuda et al. 1985). Decreased postnatal weight or decreased weight gain was reported during lactation following single gestational exposures to

doses ≥5 mg Hg/kg/day (Hughes and Annau 1976; Inouye et al. 1985). No changes in postnatal weight were observed following repeated exposure to methylmercury during gestation at doses up to 1 mg Hg/kg/day (Khera and Tabacova 1973; Yoshida et al. 2011).

Table 2-71. Body Weight Effects in Mice Following Gestation-Only Exposure to Methylmercury Compounds

Duration; dose (mg Hg/kg/day)	Fetal/birth weight[a]	Postnatal body weight[a]	Reference (compound)
1 day, GD 8 Dose: 1–2	0	0	Hughes and Annau 1976 (MMH)
1 day, GD 8 Dose: 3[b,c]	0	PND 21: ↓ (13)[c]	Hughes and Annau 1976 (MMH)
1 day, GD 8 Dose: 5[b,c]	0	PND 21: ↓ (17)	Hughes and Annau 1976 (MMH)
1 day, GD 10 Dose: 8[c]	0	–	Fuyuta et al. 1979 (MMC)
1 day, GD 10 Dose: 9.99	GD 18: ↓ (17)	–	Belles et al. 2002 (MMC)
1 day, GD 10 or 12 Dose: 10–12	0	–	Yasuda et al. 1985 (MMC)
1 day, GD 8 Dose: 10	PND 1: ↓ (6)	PND 21: ↓ (16)	Hughes and Annau 1976 (MMH)
1 day, GD 10 Dose: 12	GD 18: ↓ (M) (9) ↓ (F) (11)	–	Fuyuta et al. 1979 (MMC)
1 day, GD 10 Dose: 16	GD 18: ↓ (M) (9) ↓ (F) (11)	–	Fuyuta et al. 1979 (MMC)
1 day, GD 10 or 12 Dose: 16	GD 18: ↓ (10–16)	–	Yasuda et al. 1985 (MMC)
1 day, GD 13, 14, 15, 16, or 17 Dose: 16[b,c]	–	PND 14: ↓ (NR)	Inouye et al. 1985 (MMC)
1 day, GD 10 Dose: 20[c,d]	GD 18: ↓ (M) (16) ↓ (F) (19)	–	Fuyuta et al. 1979 (MMC)
1 day, GD 10 or 12 Dose: 20	GD 18: ↓ (21–27)	–	Yasuda et al. 1985 (MMC)
8 days, GDs 6–13 Dose: 2	0	–	Fuyuta et al. 1978 (MMC)
8 days, GDs 6–13 Dose: 4	GD 18: ↓ (M) (18) ↓ (F) (20)	–	Fuyuta et al. 1978 (MMC)
8 days, GDs 6–13 Dose: 4.8[c]	GD 18: ↓ (M) (21) 0 (F)	–	Fuyuta et al. 1978 (MMC)

Table 2-71. Body Weight Effects in Mice Following Gestation-Only Exposure to Methylmercury Compounds

Duration; dose (mg Hg/kg/day)	Fetal/birth weight[a]	Postnatal body weight[a]	Reference (compound)
12 days, GDs 6–17 Dose: 0.0001–1	0	0	Khera and Tabacova 1973 (MMC)
19 days, GDs 0–18 Dose: 0.9	–	0	Yoshida et al. 2011 (MM)

[a]Numbers in ( ) are percent change compared to control, calculated from quantitative data.
[b]Maternal health not reported.
[c]Dose associated with increased fetal/neonatal death.
[d]Dose associated with maternal toxicity (e.g., decreased body weight, clinical signs).

↑ = increased; ↓ = decreased; 0 = no change; – = not assessed; GD = gestation day; F = female; M = male; MM = methylmercury; MMC = methylmercuric chloride; MMH = methylmercury hydroxide; NA = not applicable; NR = not reported; PND = postnatal day

A single study in guinea pigs reported 12, 23, and 30% decreases in GD 3 fetal body weight following methylmercury exposure at 11.5 mg Hg/kg/day once on GD 35, 42, or 49, respectively, compared to controls (Inouye and Kajiwara 1988). No effects on fetal body weight were observed in fetuses following similar exposures on GD 21 or 28. Exposed dams showed clinical signs of toxicity.

A few studies reported body weight effects in laboratory animals following postnatal-only exposure to methylmercury. In monkeys, an approximate 13% decrease in body weight was observed at PND 45 following exposure to 0.5 mg Hg/kg/day from PND 0 to 29 (Willes et al. 1978); no body weight effects were observed in monkeys exposed to 0.05 mg Hg/kg/day for the first 4 years of life (Rice and Gilbert 1982). Inconsistent findings were observed in rats, with a 7% decrease in body weight at PND 15 following exposure to 0.37 mg Hg/kg/day on PNDs 1–15 (Ilback et al. 1991) and by an unspecified amount at PND 33 following exposure to 4 mg Hg/kg/day on PNDs 1–30, but not doses up to 2 mg Hg/kg/day (Sakamoto et al. 2004). No changes in postnatal weight were observed in rats exposed to 0.6 mg Hg/kg/day on PNDs 14–23 (Coluccia et al. 2007). No effects on postnatal weight were observed in mice following acute or intermediate-duration postnatal exposure to doses up to 3.7 or 4.7 mg Hg/kg/day, respectively (Bellum et al. 2007; Fischer et al. 2008; Franco et al. 2006; Huang et al. 2011).

Predominant Mercury Form Unknown (General Populations). Several studies have evaluated relationships between mercury exposure and neonatal anthropometric measures and postnatal growth. The main outcomes assessed in newborns were birth weight, height, and head circumference; for postnatal growth, main outcomes were weight and height for age. Study designs include prospective and cross-sectional studies. Several different biomarkers were used to assess exposure, with BHg as the most common biomarker.

Studies evaluating effects of *in utero* exposure on anthropometric measures in newborns are summarized in Table 2-72. Evidence for effects of mercury exposure on birth size in general populations is inconclusive, with studies reporting inconsistent results. Several prospective (Ding et al. 2013; Guo et al. 2013; Lee et al. 2010; Taylor et al. 2016) and cross-sectional (Al-Saleh et al. 2014; Chang et al. 2015; Govarts et al. 2016) studies did not observe associations between mercury biomarkers and birth weight, birth length, head circumference, and/or SGA. A few studies reported inverse associations between biomarkers and birth size, including birth weight in a pooled analysis of two prospective birth cohorts (Kim et al. 2017) and in a prospective study (Vigeh et al. 2018), and birth weight and height in a prospective study (Ou et al. 2015). A prospective study of mother-child pairs assessed associations between maternal BHg and BMI in children from 1 month through 8 years of age (Papadopoulou et al. 2021). No associations were observed between maternal BHg in the top 10th percentile and BMI in girls ages 1 month through 3 years. However, inverse associations were observed between maternal BHg in the top 10th percentile and BMI in girls at ages 4, 5, 6, 7, and 8 years of age; no associations were observed for boys or boys and girls combined at any assessment age. A cross-sectional study found an inverse association between mercury exposure and ponderal index, but no associations between birth weight, height, and head circumference (Wells et al. 2016). Taken together, these studies do not provide conclusive evidence that birth size is adversely affected by mercury exposure in general populations.

Table 2-72. Overview of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Anthropometric Measures in Newborns in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Al-Saleh et al. 2014 Cross-sectional; 1,578 pregnant women (Saudi Arabia)	BHg (mean) Maternal: 3.005 µg/L Cord: 3.354 µg/L	Birth weight	0 (maternal and cord BHg)
		Birth length	0 (maternal and cord BHg)
		SGA	0 (maternal and cord BHg)
		Head circumference	0 (maternal and cord BHg)

Table 2-72. Overview of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Anthropometric Measures in Newborns in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Chang et al. 2015 Cross-sectional; 252 infants (Korea)	BHg mean: 0.94 µg/L HHg: 0.22 µg/g Body weight and postnatal growth	Z-score birth weight	0 (BHg, HHg)
		Z-score weight for age	0 (BHg, HHg)
		Z-score height for age	0 (BHg, HHg)
		Weight percentiles difference between body weight and weight at time of study	0 (BHg) ↓ (HHg)
Ding et al. 2013 Prospective birth cohort; 258 mother-infant pairs (China)	BHg Gmean Cord: 1.46 µg/L Maternal: 0.84 µg/L	Birth weight	0 (maternal and cord BHg)
		Birth length	0 (maternal and cord BHg)
		Head circumference	0 (maternal and cord BHg)
Gao et al. 2018 Cross-sectional; 14,202 children ages 0–6 years (China)	BHg mean: 1.39 µg/L	Weight	0 (BHg)
		Z-height	0 (BHg)
		Height	0 (BHg)
		Z-weight	0 (BHg)
		BMI	↑ (BHg)
		Z-BMI	↑ (BHg)
Govarts et al. 2016 Cohort; 248 mother-child pairs (Belgium)	HMeHg Gmean: 0.255 µg/g	Birth weight	0 (HMeHg)
Guo et al. 2013 Prospective cohort; 213 mother-infant pairs (China)	Gmean Cord BHg: 1.54 µg/L Maternal HHg: 0.497 µg/kg Fetal HHg: 0.234 µg/g	Birth weight	0 (BHg, HHg)
		Birth length	0 (BHg, HHg)
		Head circumference	0 (BHg, HHg)
Kim et al. 2011 Prospective; 921 mother-infant pairs (South Korea)	BHg Gmean Maternal: 3.1 µg/L Cord: 5.2 µg/L	Infant weight at 12 months	0 (BHg, maternal) 0 (BHg, cord)
		Infant weight at 24 months	↓ (BHg, maternal) ↓ (BHg, cord) infants' attained weight from birth to 24 months of age were decreased 0.19% or 0.36% when mercury exposure was doubled in maternal blood at pregnancy or cord blood, respectively

Table 2-72. Overview of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Anthropometric Measures in Newborns in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Kim et al. 2017 Pooled analysis (2 prospective birth cohorts); 1,147 mother-infant pairs (Taiwan and Korea)	BHg median Cord: 5.75 µg/L Maternal: 3.27 µg/L BHg 25th percentile Cord: 4.18 µg/L Maternal: 2.29 µg/L	Birth weight	0 (BHg, median) ↓ (BHg, >25th percentile)
Lee et al. 2010 Prospective cohort; 417 mother-infant pairs (South Korea)	BHg Gmean Maternal: 3.30 µg/L Cord: 5.53 µg/L	Birth weight	0 (maternal and cord BHg)
Ou et al. 2015 Prospective; 50 mother-infant pairs (China)	Total BHg mean Cord: 2.93 µg/L Maternal: 2.36 µg/L BMeHg mean Cord: 2.11 µg/L Maternal: 1.11 µg/L BIHg mean Cord: 0.84 µg/L Maternal: 1.22 µg/L Maternal UIHg mean: 0.76 µg/g Cr	Birth weight	↓ (BHg, BIHg, maternal) 0 (BMeHg, UIHg, maternal) 0 (BHg, BMeHg, BIHg, cord)
		Birth length	↓ (BHg, UIHg, maternal) 0 (BMeHg BIHg, maternal) 0 (BHg, BMeHg, BIHg, cord)
		12-month weight	0 (BHg, BMeHg, BIHg, UIHg, maternal) 0 (BHg, BMeHg, BIHg, cord)
		12-month height	↓ (BHg, BIHg, maternal) 0 (BMeHg, UIHg, maternal) ↓ (BIHg, cord) 0 (BHg, BMeHg, cord)
Papadopoulou et al. 2021 Prospective study; 2,277 mother-child pairs (n=227 in the 90th percentile maternal BHg), assessed from 1 month to 8 years of age (Norway)	BHg (maternal) Median: 1.03 µg/L 90th percentile: 2.23 µg/L	BMI, ages 1 month to 3 years	0 (BHg, 90th percentile, females) 0 (BHg, 90th percentile, males) 0 (BHg, 90th percentile, males and females combined)
		BMI, ages 4–8 years	↓ (BHg, 90th percentile, females) 0 (BHg, 90th percentile, males) 0 (BHg, 90th percentile, males and females combined)

Table 2-72. Overview of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Anthropometric Measures in Newborns in General Populations

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Taylor et al. 2016 Prospective; 4,044 mother-infant pairs (United Kingdom)	Maternal BHg: 2.07 µg/L	Birth weight	0 (BHg)
		Crown-heel length	0 (BHg)
		Head circumference	0 (BHg)
Vigeh et al. 2018 Prospective birth cohort; 334 mother-infant pairs (Japan)	Maternal BHg mean 1st trimester: 6.06 µg/L 2nd trimester: 4.99 µg/L 3rd trimester: 4.97 µg/L	Birth weight	↓ (BHg, log_{10}, 1st trimester) ↓ (BHg, log_{10}, 2nd trimester) 0 (BHg, log_{10}, 3rd trimester)
Wells et al. 2016 Cross-sectional; 271 newborns (Baltimore, Maryland)	Cord BHg Gmean BIHg: 0.13 µg/L BMeHg: 0.94 µg/L	Birth weight	0 (BMeHg)
		Birth length	0 (BMeHg)
		Head circumference	0 (BMeHg)
		Ponderal index	↓ (BMeHg)

↑ = positive association; ↓ = inverse association; 0 = no association; BHg = blood mercury; BIHg = blood inorganic mercury; BMeHg = blood methylmercury; Gmean = geometric mean; HHg = hair mercury; HMeHg = hair methylmercury; calculated as [(birth weight; g)/(birth length; cm)3] × 100; SGA = small for gestational age; UIHg = urine inorganic mercury

Few studies have evaluated effects of mercury exposure on postnatal growth in general populations; studies are summarized in Table 2-73. Results of studies on postnatal growth are inconsistent. In prospective studies, Kim et al. (2011) reported an inverse association between total BHg (maternal and umbilical cord) at age 24 months, although this effect was not observed at 12 months. Similar results were observed in infants assessed at 12 months, with no associations between exposure biomarkers and weight for age (Ou et al. 2015); however, inverse associations were observed for height for age and some exposure biomarkers. Cross-sectional studies did not find associations between BHg and/or HHg and measures of postnatal growth (weight, height) in infants or children ages 6 months to 6 years (Chang et al. 2015; Gao et al. 2018). Chang et al. (2015) observed an inverse association between child HHg and postnatal growth measured as the difference between body weight z-score at birth and at age of postnatal observation (6–20 months). However, the weight z-score difference was also independently inversely associated with duration of breastfeeding, and was no longer associated with child HHg when adjusted for duration of breastfeeding. Gao et al. (2018) observed a positive association between child BHg and BMI; however, other studies did not assess this endpoint. Results of these studies do not provide clear evidence that mercury exposure in general populations is associated with decreased postnatal growth.

Table 2-73. Overview of Epidemiological Studies Evaluating Associations between Mercury (Predominant Mercury Form Unknown) and Postnatal Growth in General Populations

Reference, study type, and population	Biomarker	Weight for age	Weight percent difference[a]	Height for age	BMI
Chang et al. 2015 Cross-sectional; 252 infants (age: 6–24 months) (Korea)	Gmean BHg: 0.94 µg/L HHg: 0.22 µg/g	0 (BHg) 0 (HHg)	0 (BHg ↓ (HHg)	0 (BHg 0 (HHg)	−
Gao et al. 2018 Cross-sectional; 14,202 children (age: 0–6 years) (China)	BHg mean: 1.39 µg/L	0 (BHg)	−	0 (BHg)	↑ (BHg)
Kim et al. 2011 Prospective; 921 mother-infant pairs (South Korea)	Gmean Maternal BHg: 3.1 µg/L Cord BHg Gmean: 5.2 µg/L	0 (BHg, M,C)[b] ↓ (BHg, M,C)[c]	−	−	−
Ou et al. 2015 Prospective; 50 mother-infant pairs (age: 12 months) (China)	Maternal mean BHg: 2.36 µg/L BIHg: 1.25 µg/L BMeHg: 1.11 µg/L UIHg: 0.76 µg/h Cr Cord mean BHg: 2.93 µg/L BIHg: 0.82 µg/L BMeHg: 2.11 µg/L	0 (BHg, M) 0 (BIHg, M) 0 (BMeHg, M) 0 (UIHg, M) 0 (BHg, C) 0 BIHg, C) 0 (BMeHg, C)		↓ (BHg, M) ↓ (BIHg, M) 0 (BMeHg, M) 0 (UIHg, M) 0 (BHg, C) ↓ (BIHg, C) 0 (BMeHg, C)	−

[a]Weight percentiles difference between birth weight and postnatal birth weight at time of study.
[b]Assessment at age 12 months.
[c]Assessment at age 24 months.

↑ = positive association; ↓ = inverse association; 0 = no association; BHg = blood mercury; BIHg = blood inorganic mercury; BMeHg = blood methylmercury; C = umbilical cord; Cr = creatinine; HHg = hair mercury; M = maternal; UIHg = urine inorganic mercury

Mechanisms of Action. Specific mechanisms for developmental effects of mercury exposure have not been established. Kim et al. (2013b) have shown that blood mercury is negatively associated with serum folate levels. Folate has an important role in preventing neural tube defects and intrauterine growth restriction; therefore, decreased folate levels could contribute to developmental effects, including neurotoxicity and decreased anthropometric measures. Prenatal exposure to mercury has been shown to alter DNA methylation in pregnant women and infants (Cardenas et al. 2017b; Weyde et al. 2021). General mechanisms of toxicity of mercury (reviewed in Section 2.21) are also likely involved in adverse developmental effects. Mercury is distributed to the fetus and has been measured in fetal tissues (see

Section 3.1.2, Distribution), providing a toxicokinetic mechanism for direct exposure of the placenta and fetus.

2.19 CANCER

Cancer Classifications of Mercury and Mercury Compounds. The U.S. Department of Health and Human Services (NTP 2016) has not categorized the carcinogenicity of mercury and mercury compounds. IARC (1993) has developed cancer classifications for metallic and inorganic mercury compounds and methylmercury compounds as follows.

- Metallic and inorganic mercury compounds: "not classifiable as to their carcinogenicity to humans (Group 3)," based on inadequate evidence in humans, inadequate evidence for elemental mercury in experimental animals, and limited evidence for mercuric chloride in experimental animals.
- Methylmercury compounds: "possibly carcinogenic to humans (Group 2B)," based on inadequate evidence in humans and sufficient evidence in experimental animals.

EPA IRIS (1995a, 1995b, 2001) classified the carcinogenicity of mercury and mercury compounds as follows:

- Elemental mercury: not classifiable as to human carcinogenicity (Group D), "based on inadequate human and animal data."
- Mercuric chloride: possible human carcinogen (Group C), "based on the absence of data in humans and limited evidence in rats and mice."
- Methylmercury: possible human carcinogen (Group C), "based on inadequate data in humans and limited evidence of carcinogenicity in animals."

Overview. Epidemiological studies have evaluated the potential carcinogenicity of mercury exposure. However, in general, studies did not report mercury biomarker levels as a measure of exposure or adjust results for confounding factors. Consistent with the IARC (1993) and IRIS (1995a, 1995b, 2001) classifications noted above, results of epidemiological studies results do not provide evidence that mercury exposure is associated with cancer in humans.

Carcinogenicity has been assessed in rats and mice following chronic oral exposure to mercuric chloride, methylmercury, and phenylmercuric acetate. Mercuric chloride induced forestomach and thyroid tumors in male rats and methylmercury induced renal tumors in male mice. There is limited evidence of renal

tumors in male rats exposed to phenylmercuric acetate. There are no animal inhalation cancer data available.

The following summarizes results of epidemiological and animal studies on cancer outcomes.

- ***Elemental mercury***
  - *Epidemiology studies*
    - No epidemiology studies on cancer outcomes associated with exposure to elemental mercury reporting data on mercury biomarkers were identified.
  - *Animal studies*
    - No studies evaluating cancer following exposure to elemental mercury were identified.
- ***Inorganic mercury salts***
  - *Epidemiology studies*
    - No epidemiological studies evaluating associations between exposure to inorganic mercury salts and cancer outcomes were identified.
  - *Animal studies*
    - Mercuric chloride showed some evidence of carcinogenicity in male rats (forestomach and thyroid tumors), equivocal evidence of carcinogenicity in female rats and male mice (low incidence of forestomach and renal tumors, respectively), and no evidence of carcinogenicity in female mice in an NTP (1993) bioassay.
- ***Organic mercury***
  - *Epidemiology studies*
    - Two studies on the Minamata population found elevated SMRs for liver cancer. However, results were not adjusted for alcohol consumption or other confounding factors, and mercury biomarkers were not reported.
  - *Animal studies*
    - Methylmercury is associated with induction of renal tumors in male mice.
    - Methylmercury did not induce tumors in female mice or male or female rats.
    - There are limited data that phenylmercuric mercury induces renal tumors in male rats.
- ***Predominant mercury form unknown (general populations)***
    - One epidemiological study did not find an association between mercury biomarkers and death due to cancer.

Confounding Factors. Numerous factors can influence results of epidemiological studies evaluating associations between mercury exposure and cancer if they are not homogenously distributed in the study

population. These factors include age, smoking status, family history of cancer, and co-exposure to other carcinogens that are also risk factors for cancer but may not be homogenous between exposure groups in the study population. The studies reviewed in this section did not adjust for these factors.

Elemental Mercury—Epidemiological Studies. Studies that evaluated associations between occupational exposure to elemental mercury and cancer did not report quantitative mercury biomarker data.

Elemental Mercury—Animal Studies. No studies were located regarding cancer in animals after exposure to elemental mercury.

Inorganic Mercury Salts—Animal Studies. The carcinogenicity of mercuric chloride was investigated in a 2-year gavage study in rats and mice (NTP 1993). In rats, statistically significant increases in the incidence of forestomach squamous cell papillomas in males (12/50 versus 0/50 in control) and thyroid follicular cell carcinomas in male rats (6/50 versus 0.50 control) were observed at 4 mg Hg/kg/day. Forestomach squamous cell papillomas were also observed in 3/50 males at 1.8 mg Hg/kg/day and in 2/50 females at 4 mg Hg/kg/day. In mice, potentially exposure-related tumors were limited to low incidence renal tumors in males at 7.4 mg Hg/kg/day, including renal tubule adenoma (2/50) and adenocarcinoma (1/50). NTP (1993) concluded that there was some evidence for carcinogenicity in male rats (increased forestomach tumors, marginally increased thyroid follicular cell tumors); equivocal evidence of carcinogenic activity in female rats (low incidence of forestomach tumors) and male mice (low incidence of renal tumors); and no evidence of carcinogenic activity in female mice.

Organic Mercury—Epidemiological Studies. No studies evaluating cancer in populations with high fish diets and reporting exposures based on mercury biomarkers were identified. Two studies evaluating cancer outcomes in the Minamata population found elevated SMRs for liver cancer (Futatsuka et al. 2005; Tamashiro et al. 1986). However, these studies are of limited usefulness as results were not adjusted for alcohol consumption or other confounding factors, and mercury biomarkers were not reported.

Organic Mercury—Animal Studies. Renal cell adenomas were increased in male rats exposed to phenylmercuric acetate at drinking water doses of 3.7 mg Hg/kg/day for 2 years (Solecki et al. 1991). The report is limited because the assay was not intended as a carcinogenicity assay and utilized small animal groups; however, renal tumors were observed in 10/20 treated males compared to 0/18 controls. In a 2-year methylmercury study, no increase in tumor incidence was observed in rats exposed to dietary doses as high as 0.18 mg Hg/kg/day (Verschuuren et al. 1976).

Chronic dietary exposure to methylmercury has resulted in significant increases in renal epithelial cell tumors in male mice in three cancer bioassays (Hirano et al. 1986; Mitsumori et al. 1981, 1990). In B6C3F1 mice, significant increases in renal epithelial cell adenomas and carcinomas were observed in males exposed to 0.686 mg Hg/kg/day for 2 years (Mitsumori et al. 1990). In ICR mice, a significant increase in the incidence of renal epithelial cell adenocarcinomas was observed in males exposed to 0.724 mg Hg/kg/day for 2 years (Hirano et al. 1986) and an increase in kidney adenomas and adenocarcinomas were observed in males exposed to 2.1 mg/kg/day for 78 weeks (Mitsumori et al. 1981). No exposure-related tumors were observed in similarly exposed female mice (Hirano et al. 1986; Mitsumori et al. 1981, 1990).

Predominant Mercury Form Unknown (General Populations). One study in general populations evaluated associations between mercury biomarkers and cancer death. A 20-year prospective study in 1,462 women from Sweden did not find an association between SHg (mean 17.0 µg/L) and death due to cancer (Ahlqwist et al. 1999).

Mechanisms of Action. As reviewed in Section 2.20 (Genotoxicity), elemental mercury has been shown to produce oxidative damage to DNA. There is limited evidence that inorganic and organic mercury are mutagenic. These findings provide a plausible mechanism for carcinogenesis. In addition, a recent review proposed that mercury may act as an epigenetic tumor promoter (Zefferino et al. 2017).

2.20 GENOTOXICITY

Overview. Available data indicate that elemental mercury may cause oxidative DNA damage; findings regarding chromosomal effects are inconclusive. There is limited evidence that inorganic and organic mercury are mutagenic. Inorganic and organic mercury are consistently clastogenic and DNA damaging in mammalian cells.

The following summarizes results of *in vitro* and *in vivo* studies on genotoxic effects.

- ***Elemental mercury (in vivo studies only)***
  - Inconclusive evidence for chromosome aberrations in exposed workers.
  - Limited evidence of oxidative DNA damage in the general population.
- ***Inorganic mercury salts***
  - *In vitro* studies
    - Limited evidence of mutagenicity in mammalian cells.
    - Consistent evidence of clastogenicity in mammalian cells.
    - Consistent evidence of DNA binding and damage in mammalian cells.
  - *In vivo* studies
    - Induced dominant lethal mutations in rats with oral exposure.
    - Inconclusive evidence for chromosome aberrations in exposed workers.
    - Oral, but not intraperitoneal, exposure is associated with chromosome aberrations and micronuclei in rodents.
    - Consistent evidence of DNA binding and damage in rodents following oral exposure.
- ***Organic mercury***
  - *In vitro* studies
    - Limited evidence of mutagenicity in mammalian cells.
    - Consistent evidence of clastogenicity in human, hamster, and rat cells; no evidence in mouse cells.
    - Consistent evidence of DNA damage in bacteria and mammalian cells.
  - *In vivo* studies
    - Induced dominant lethal mutations in one mouse strain with oral exposure.
    - Inconclusive evidence for chromosome aberrations from occupational and general population studies in humans and *in vivo* studies in animals.
    - Consistent evidence of DNA damage in mammals and chicken embryos.

Elemental Mercury. There is inconclusive evidence that occupational inhalation exposure to metallic mercury causes structural and numerical chromosome aberrations in human lymphocytes. However, most human studies have significant limitations, precluding clear conclusions. There is limited evidence that exposure to elemental mercury causes oxidative DNA damage. Available genotoxicity studies are reviewed in Table 2-74.

Table 2-74. Genotoxicity of Elemental Mercury in Epidemiological Studies

Species (exposure route)	Mercury compound	Endpoint	Results	Reference
Human (occupational exposure)	Metallic mercury	Aneuploidy in peripheral lymphocytes	–	Popescu et al. 1979
Human (occupational exposure)	Metallic mercury	Aneuploidy in peripheral lymphocytes	(+)	Verschaeve et al. 1976
Human (occupational exposure)	Metallic mercury	Aneuploidy in peripheral lymphocytes	–	Verschaeve et al. 1979
Human (occupational exposure)	Metallic mercury	Chromosome aberrations in peripheral lymphocytes	(+)	Popescu et al. 1979
Human (occupational exposure)	Metallic mercury	Chromosome aberrations in peripheral lymphocytes	(+)	Verschaeve et al. 1976
Human (occupational exposure)	Metallic mercury	Chromosome aberrations in peripheral lymphocytes	–	Verschaeve et al. 1979
Human (occupational exposure)	Amalgams	Chromosome aberrations in peripheral lymphocytes	(+)	Verschaeve et al. 1976
Human (occupational exposure)	Mercury amalgamated with zinc	Chromosome aberrations in peripheral lymphocytes	–	Mabille et al. 1984
Human (occupational exposure)	Mercury	Micronuclei induction in peripheral lymphocytes	+[a]	Barregard et al. 1991
Human (general population exposure)	Unspecified mercury	Oxidative DNA damage (urine 8-OHdG)	+	Al-Saleh et al. 2017
Human (oral)	Amalgams	Oxidative DNA damage (urine 8-OHdG)	+	Al-Saleh et al. 2012

[a]Positive response only in stimulated T-lymphocytes.

+ = positive result; – = negative result; (+) = reported as positive but study was either seriously compromised or findings did not provide valid evidence of a positive response; 8-OHdG = 8-hydroxydeoxyguanosine; DNA = deoxyribonucleic acid

One study reported increased aneuploidy in peripheral lymphocytes of 28 subjects exposed to various types of mercury (including 14 exposed to metallic mercury vapor and 3 exposed via amalgams), compared to 7 unexposed controls (Verschaeve et al. 1976). However, the study was not well controlled (i.e., not matched for sex, smoking habits, or sample size). Additionally, these data should also be interpreted with caution since age has an influence on aneuploidy, and in this study, there was a general trend toward a higher incidence of aneuploidy in the older exposed workers (ages 36–63 years). It is noteworthy that in a subsequent study performed by these investigators (Verschaeve et al. 1979), no adverse effect on the number of chromosomes was demonstrated in 28 workers exposed to moderate levels of metallic mercury (mean urine levels of 35 μg/L; range 7–175 μg/L), compared to 8 unexposed controls from the plant (e.g., clerks; urine level range <5–11 μg/L) and 12 general population controls (urine mercury levels not reported). The study authors concluded that the results from their 1976 study

suggesting a potential association between increased chromosomal aberrations and occupational exposure to mercury may have been affected by factors other than exposure to mercury compounds. No evidence of aneuploidy was observed in four workers exposed to high concentrations of metallic mercury (range 0.15–0.44 mg/m^3) (Popescu et al. 1979).

The study described above by Verschaeve et al. (1976) also reported an increase in structural chromosomal aberrations in mercury-exposed workers; as discussed above, data should be interpreted with caution. As with aneuploidy, no adverse effect on the structure of chromosomes was demonstrated in the subsequent study by Verschaeve et al. (1979) in 28 workers exposed to moderate levels of metallic mercury. Another study reported significant increases in the frequency of acentric fragments (chromosome breaks) in four workers exposed to high concentrations of metallic mercury (range 0.15–0.44 mg/m^3); the urinary excretion level of mercury for both exposed groups was 0.890 µg/L (Popescu et al. 1979). However, the findings of this study are suspect because the control group was not matched for sex, smoking habits, or sample size. Additionally, one of the four exposed individuals had a history of benzene poisoning, which was reflected in the unusually high frequency of abnormal chromosome morphology seen in this individual. Chromosomal aberrations were not observed in peripheral lymphocytes of 22 workers exposed to mercury amalgamated with zinc; the mean urine and blood mercury levels in the exposed group were 117 µg/g creatinine and 0.031 µg/mL, respectively (Mabille et al. 1984). Another study evaluated micronuclei induction in peripheral lymphocytes from 26 workers exposed to mercury vapors (25–50 µg/m^3) for a mean exposure time of 10 years, compared to 26 unexposed controls (Barregard et al. 1991). Groups were matched for age (±7 years) and smoking habits; plasma, erythrocyte, and urine mercury levels were determined. Parallel lymphocyte cultures from each donor group were incubated in the presence of pokeweed mitogen, which stimulates both B- and T-lymphocytes, and phytohemagglutinin, which primarily activates T-cells. The analysis showed no significant increase in the frequency or the size of micronuclei in the exposed versus the control group. Nor was there a correlation between micronuclei induction and plasma, erythrocyte, or urine levels of mercury. Within the exposed group, however, there was a significant correlation between micronuclei induction in phytohemagglutinin in stimulated lymphocytes and cumulative exposure (whole-blood mercury level over employment time); the response was independent of age or smoking habits. These results, suggesting a genotoxic effect on T-lymphocytes, are unusual since there is evidence that B-lymphocytes may be more sensitive indicators of chemically induced clastogenesis than T-lymphocytes (Högstedt et al. 1988). Barregard et al. (1991) stated that the evidence of a genotoxic response confined to T-lymphocytes could have been a random finding but hypothesized that long-term exposure to mercury may cause an accumulation of cytogenetic effects.

Oxidative DNA damage was significantly associated with the urine mercury levels in children aged 5–15.5 years with dental amalgam fillings (Al-Saleh et al. 2017). Oxidative DNA damage was also significantly associated with increased urine mercury levels in mothers and young children; however, environmental mercury exposure source(s) and form(s) are unknown in this study population (Al-Saleh et al. 2017).

Inorganic Mercury Salts. There is limited evidence that inorganic mercury salts are mutagenic in mammalian cells. *In vitro* data in mammalian cells and *in vivo* oral data in rodents show clear, consistent evidence of clastogenicity and DNA damage associated with inorganic mercury exposure. Available *in vitro* and *in vivo* genotoxicity studies for inorganic mercury salts are reviewed in Tables 2-75 and 2-76, respectively.

Table 2-75. Genotoxicity of Inorganic Mercury Salts *In Vitro* Studies

Species (test system)	Mercury compound	Endpoint	Results		Reference
			With activation	Without activation	
Prokaryotic organisms					
Salmonella typhimurium (TA1535, TA1537, TA98, TA102)	Mercuric chloride	Gene mutation	–	–	Wong 1988
Bacillus subtilis (H17, M45)	Mercuric chloride	DNA damage	NT	+	Kanematsu et al. 1980
Mammalian cells					
Mouse lymphoma cells L5178Y	Mercuric chloride	Gene mutation	+/–	–	Oberly et al. 1982
NIH 3T3 cells	Mercuric chloride	Gene mutation	NT	+	Schurz et al. 2000
Human (peripheral lymphocytes)	Mercuric chloride	Aneuploidy	NT	+	Patel and Rao 2018
Human (peripheral lymphocytes)	Mercuric chloride	Chromosome aberrations	NT	–	Rao et al. 2001
Human (peripheral lymphocytes)	Mercuric chloride	Chromosome aberrations	NT	+	Patel and Rao 2018
CHO cells	Mercuric chloride	Chromosome aberrations	NT	+	Howard et al. 1991
Human (peripheral lymphocytes)	Mercury nitrate	Sister chromatid exchange	NT	–	Lee et al. 1997
Human (peripheral lymphocytes)	Mercuric chloride	Sister chromatid exchange	NT	+	Patel and Rao 2015
Human (peripheral lymphocytes)	Mercuric chloride	Sister chromatid exchange	NT	+	Purohit and Rao 2014

Table 2-75. Genotoxicity of Inorganic Mercury Salts *In Vitro* Studies

Species (test system)	Mercury compound	Endpoint	Results		Reference
			With activation	Without activation	
Human (peripheral lymphocytes)	Mercuric chloride	Sister chromatid exchange	NT	+	Rao et al. 2001
CHO cells	Mercuric chloride	Sister chromatid exchange	NT	+	Howard et al. 1991
Human (peripheral lymphocytes)	Mercuric chloride	Micronuclei induction	NT	+	Patel and Rao 2018
Chinese hamster V79 cells	Mercuric chloride	Micronuclei induction	NT	+	Stoiber et al. 2004
Rat embryo fibroblasts	Mercuric chloride	DNA binding	NT	+	Rozalski and Wierzbicki 1983
CHO cells	Mercuric chloride	DNA binding	NT	+	Cantoni et al. 1984a
Human (U-937 monocyte-like cells)	Mercuric chloride	DNA damage	NT	+	Ben-Ozer et al. 2000
Human (WRL-68 hepatocytes)	Mercuric chloride	DNA damage	NT	+	Bucio et al. 1999
Human (TK6 lymphoblastoid cells)	Mercuric chloride	DNA damage	NT	+	Guillamet et al. 2008
Human (peripheral lymphocytes)	Mercuric chloride	DNA damage	NT	+	Patel and Rao 2018
Human (salivary gland tissue cells)	Mercuric chloride	DNA damage	NT	+	Schmid et al. 2007
Human (lymphocytes)	Mercuric chloride	DNA damage	NT	+	Schmid et al. 2007
Human KB cells	Mercuric acetate	DNA damage	NT	+	Williams et al. 1987
Rat embryo fibroblasts	Mercuric chloride	DNA damage	NT	+	Zasukhina et al. 1983
Mouse embryo fibroblasts	Mercuric chloride	DNA damage	NT	+	Zasukhina et al. 1983
CHO cells	Mercuric chloride	DNA damage	NT	+	Cantoni and Costa 1983
CHO cells	Mercuric chloride	DNA damage	NT	+	Cantoni et al. 1982, 1984a, 1984b
CHO cells	Mercuric chloride	DNA damage	NT	+	Christie et al. 1984, 1985

+ = positive result; – = negative result; +/– = weakly positive (2- to 3-fold increase in mutations); CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NT = not tested

Table 2-76. Genotoxicity of Inorganic Mercury Salts *In Vivo* Animal Studies

Species (exposure route)	Mercury compound	Endpoint	Results	Reference
Mammals				
(101xC3H)F1 mouse (intraperitoneal)	Mercuric chloride	Dominant lethal mutations in oocytes	+/–	Suter 1975
Rat (oral)	Mercuric chloride	Dominant lethal mutations in spermatogonia	+	Zasukhina et al. 1983
Human (occupational exposure)	Mixture of mercuric chloride, methylmercuric chloride, and ethylmercuric chloride	Aneuploidy in peripheral lymphocytes	–	Popescu et al. 1979
Swiss mouse (intraperitoneal)	Mercuric chloride	Aneuploidy in spermatogonia	–	Poma et al. 1981
Swiss mouse (intraperitoneal)	Mercuric acetate	Aneuploidy in oocytes	–	Jagiello and Lin 1973
Human (occupational exposure)	Mixture of mercuric chloride, methylmercuric chloride, and ethylmercuric chloride	Chromosome aberrations in peripheral lymphocytes	(+)	Popescu et al. 1979
Rat (gavage)	Mercuric chloride	Chromosome aberrations in bone marrow cells	+	Bhowmik and Patra 2015
Rat (drinking water)	Mercuric chloride	Chromosome aberrations in bone marrow cells	+	Boujbiha et al. 2012
Swiss mouse (intraperitoneal)	Mercuric chloride	Chromosome aberrations in bone marrow cells	–	Poma et al. 1981
Swiss mouse (gavage)	Mercuric chloride	Chromosome aberrations in bone marrow cells	+	Ghosh et al. 1991
Rat (gavage)	Mercuric chloride	Micronuclei induction in reticulocytes	+	Rozgaj et al. 2005
Golden Syrian hamsters (intraperitoneal)	Mercurous chloride	Micronuclei induction in bone marrow cells	–	Cortés-Gutiérrez et al. 2004
Swiss mouse (drinking water)	Mercuric chloride	DNA binding in liver	+	Bryan et al. 1974
Rat (gavage)	Mercuric chloride	DNA damage in lymphocytes	+	Bhowmik and Patra 2015
Rat (gavage)	Mercuric chloride	DNA damage in lymphocytes	+	Rozgaj et al. 2005
Rat (oral intubation)	Mercuric chloride	DNA damage in peripheral leukocytes	+	Grover et al. 2001

Table 2-76. Genotoxicity of Inorganic Mercury Salts *In Vivo* Animal Studies

Species (exposure route)	Mercury compound	Endpoint	Results	Reference
Non-mammalian eukaryotic organisms				
Drosophila melanogaster (diet)	Mercuric chloride	Somatic mutation and recombination	–	Carmona et al. 2008

+ = positive result; – = negative result; +/– = inconclusive; (+) = reported as positive but study was either seriously compromised or findings did not provide valid evidence of a positive response; DNA = deoxyribonucleic acid

Mercuric chloride is not mutagenic in bacteria (Wong 1988). In mammalian cells, mercuric chloride was weakly mutagenic with activation in mouse lymphoma cells (Oberly et al. 1982) and mutagenic without activation in mouse fibroblasts (Schurz et al. 2000). An *in vivo* study in rats showed dominant lethal mutations in spermatogonia following oral exposure to mercuric chloride (Zasukhina et al. 1983). Evidence for dominant lethal mutations in oocytes was inconclusive following intraperitoneal exposure to mercuric chloride in mice (Suter 1975). There is no evidence for somatic mutation or recombination in *Drosophila melanogaster* following dietary exposure to mercuric chloride (Carmona et al. 2008).

Several studies have reported clastogenic effects in human peripheral lymphocytes following exposure to mercuric chloride (without metabolic activation). One study reported aneuploidy (Patel and Rao 2018), one reported chromosomal aberrations (Patel and Rao 2018), three reported sister chromatid exchanges (Patel and Rao 2015; Purohit and Rao 2014; Rao et al. 2001), and one reported micronuclei induction (Patel and Rao 2018). However, one study reported a lack of chromosomal aberrations in human peripheral lymphocytes exposed to mercuric chloride (Rao et al. 2001) and another reported a lack of sister chromatid exchanges in human peripheral lymphocytes exposed to mercuric nitrate (Lee et al. 1997). In hamster cells, chromosome aberrations, sister chromatid exchanges, and micronuclei were induced following exposure to mercuric chloride in the absence of metabolic activation (Howard et al. 1991; Stoiber et al. 2004).

Evidence for clastogenicity of mercuric chloride is less consistent *in vivo*. In humans, one study reported significant increases in the frequency of acentric fragments (chromosome breaks) in 18 workers exposed to a mixture of mercuric chloride, methylmercuric chloride, and ethylmercuric chloride (Popescu et al. 1979). The urinary excretion level of mercury for the exposed group was 0.890 μg/L. The findings of this study should be interpreted with caution because the control group was not matched for sex, smoking habits, or sample size. No difference in the incidence of aneuploidy was found between the exposed workers and the controls. In rodents, there is no evidence of aneuploidy in spermatogonia or oocytes

following intraperitoneal exposure to mercuric chloride or acetate, respectively (Jagiello and Lin 1973; Poma et al. 1981). Chromosomal aberrations in bone marrow were reported in rats and mice following oral exposure to mercuric chloride (Bhowmik and Patra 2015; Boujbiha et al. 2012; Ghosh et al. 1991), but not in mice following intraperitoneal exposure (Poma et al. 1981). Oral exposure to mercuric chloride also induced micronuclei in rat reticulocytes (Rozgaj et al. 2005), but intraperitoneal exposure to mercurous chloride did not induce micronuclei in hamster bone marrow (Cortés-Gutiérrez et al. 2004).

Mercuric chloride does not cause DNA damage in bacteria (Kanematsu et al. 1980). However, numerous studies consistently reported DNA damage in human, rat, mouse, and hamster cells exposed to mercuric chloride (see Table 2-75 for citations), and mercuric chloride binds to rat and hamster DNA (Cantoni et al. 1984a; Rozalski and Wierzbicki 1983). Mercuric acetate also induced DNA damage in human cells (Williams et al. 1987). *In vivo* studies in rodents show DNA damage in rat lymphocytes and leukocytes and DNA binding in mouse liver following oral exposure to mercuric chloride (Bhowmik and Patra 2105; Bryan et al. 1974; Grover et al. 2001; Rozgaj et al. 2005).

Organic Mercury. There is limited evidence that exposure to organic mercury is mutagenic in mammalian cells. Evidence for clastogenicity is inconclusive in mammals following *in vivo* exposure; *in vitro* data in mammalian cells generally show evidence of clastogenicity associated with organic mercury exposure. DNA damage is consistently observed in both *in vivo* and *in vitro* studies in mammals; there is limited evidence for DNA damage in bacteria and chicken embryos. Available *in vitro* and *in vivo* genotoxicity studies for organic mercury are reviewed in Tables 2-77 and 2-78, respectively.

Table 2-77. Genotoxicity of Organic Mercury *In Vitro*

Species (test system)	Mercury compound	End point	Results		Reference
			With activation	Without activation	
Prokaryotic organisms					
Bacillus subtilis (H17, M45)	Methylmercury chloride	DNA damage	NT	+	Kanematsu et al. 1980
B. subtilis (H17, M45)	Phenylmercuric acetate	DNA damage	NT	+	Kanematsu et al. 1980
Non-mammalian eukaryotic organisms					
Saccharomyces cerevisiae	Methylmercury chloride	Gene mutation	NT	–	Nakai and Machida 1973
S. cerevisiae	Methylmercury chloride	Chromosome nondisjunction	NT	(+)	Nakai and Machida 1973

Table 2-77. Genotoxicity of Organic Mercury *In Vitro*

Species (test system)	Mercury compound	End point	Results		Reference
			With activation	Without activation	
S. cerevisiae	Methylmercury chloride	Recombination	NT	–	Nakai and Machida 1973
Mammalian cells					
Chinese hamster V79 cells	Methylmercury chloride	Gene mutation	NT	+/–	Fiskesjo 1979
Chinese hamster V79 cells	Methoxyethyl mercury chloride	Gene mutation	NT	+/–	Fiskesjo 1979
Human peripheral lymphocytes	Methylmercury chloride	Aneuploidy	NT	+	Betti et al. 1992
Human peripheral lymphocytes	Dimethyl mercury	Aneuploidy	NT	+	Betti et al. 1992
Human peripheral lymphocytes	Methylmercury chloride	Chromosome aberrations	NT	+	Betti et al. 1992
Human peripheral lymphocytes	Dimethyl mercury	Chromosome aberrations	NT	+	Betti et al. 1992
CHO cells	Methyl mercury chloride	Chromosome aberrations	NT	+	Ehrenstein et al. 2002
Human lymphocytes	Phenylmercury acetate	Sister chromatid exchange	NT	+	Lee et al. 1997
Human lymphocytes	Methylmercury chloride	Sister chromatid exchange	NT	+	Lee et al. 1997
Early mouse embryos (blastocysts)	Methylmercury	Sister chromatid exchange	NT	-	Matsumoto and Spindle 1982
CHO cells	Methyl mercury chloride	Sister chromatid exchange	NT	+	Ehrenstein et al. 2002
Human glioblastoma cell line	Methylmercury	Micronuclei induction	NT	+	Crespo-López et al. 2007
Human neuroblastoma cell line	Methylmercury	Micronuclei induction	NT	+	Crespo-López et al. 2007
Human lymphocytes	Methylmercury chloride	Micronuclei induction	NT	+	Migliore et al. 1999
Rat glioma C6 cells	Methylmercury	Micronuclei induction	NT	+	Crespo-Lopez et al. 2016
Human nerve cells	Methylmercury chloride	DNA damage	NT	+	Costa et al. 1991
Human lung cells	Methylmercury chloride	DNA damage	NT	+	Costa et al. 1991
Human leukocytes	Methyl mercury chloride	DNA damage	NT	+	Frenzilli et al. 2000
Human TK6 lymphoblastoid cells	Methyl mercury chloride	DNA damage	NT	+	Guillamet et al. 2008

Table 2-77. Genotoxicity of Organic Mercury *In Vitro*

Species (test system)	Mercury compound	End point	Results		Reference
			With activation	Without activation	
Rat glioblastoma cells	Methylmercury chloride	DNA damage	NT	+	Costa et al. 1991
Rat glioma C6 cells	Methylmercury	DNA damage	NT	+	Crespo-Lopez et al. 2016
Mouse wild-type and OGG1-null ($Ogg1^{-/-}$) embryonic fibroblasts	Methylmercury	DNA damage	NT	+	Ondovcik et al. 2012
Chinese hamster V79 cells	Methylmercury chloride	DNA damage	NT	+	Costa et al. 1991

+ = positive result; – = negative result; +/– = weakly positive at concentrations with >50% survival (2–3-fold increase in mutations); (+) = reported as slightly increased, but quantitative data were not reported; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NT = not tested

Table 2-78. Genotoxicity of Organic Mercury *In Vivo* Animal Studies

Species (exposure route)	Mercury compound	End point	Results	Reference
Mammals				
(101xC3H)F1 mouse (intraperitoneal)	Methylmercuric hydroxide	Dominant lethal mutations in spermatogonia	–	Suter 1975
(101xC3H)F1 mouse (intraperitoneal)	Mercuric chloride	Dominant lethal mutations in oocytes	–	Suter 1975
(SECxC57BL)F1 mouse (intraperitoneal)	Methylmercuric hydroxide	Dominant lethal mutations in spermatogonia	+	Suter 1975
Human (occupational exposure)	Mixture of mercuric chloride, methylmercuric chloride, and ethylmercuric chloride	Aneuploidy in peripheral lymphocytes	–	Popescu et al. 1979
Human (diet, fish consumption)	Methylmercury	Aneuploidy in peripheral lymphocytes	(+)	Skerfving et al. 1970
Human (diet, fish consumption)	Methylmercury	Aneuploidy in peripheral lymphocytes	(+)	Skerfving et al. 1974
Human (occupational exposure)	Ethylmercury	Aneuploidy in peripheral lymphocytes	(+)	Verschaeve et al. 1976
Human (occupational exposure)	Phenylmercury	Aneuploidy in peripheral lymphocytes	(+)	Verschaeve et al. 1976
Human (occupational exposure)	Mercury fulminate	Aneuploidy in peripheral lymphocytes	–	Anwar and Gabal 1991

Table 2-78. Genotoxicity of Organic Mercury *In Vivo* Animal Studies

Species (exposure route)	Mercury compound	End point	Results	Reference
Swiss mouse (intraperitoneal)	Dimethyl-mercury	Aneuploidy in oocytes	–	Jagiello and Lin 1973
Swiss mouse (intraperitoneal)	Mercaptomerin (as Thiomerin)	Aneuploidy in oocytes	–	Jagiello and Lin 1973
Syrian hamsters (intraperitoneal)	Methylmercury	Aneuploidy in oocytes	+	Mailhes 1983
Human (occupational exposure)	Mixture of mercuric chloride, methylmercuric chloride, and ethylmercuric chloride	Chromosome aberrations in peripheral lymphocytes	(+)	Popescu et al. 1979
Human (diet, fish consumption)	Methylmercury	Chromosome aberrations in peripheral lymphocytes	(+)	Skerfving et al. 1970
Human (diet, fish consumption)	Methylmercury	Chromosome aberrations in peripheral lymphocytes	(+)	Skerfving et al. 1974
Human (occupational exposure)	Ethylmercury	Chromosome aberrations in peripheral lymphocytes	(+)	Verschaeve et al. 1976
Human (occupational exposure)	Phenylmercury	Chromosome aberrations in peripheral lymphocytes	(+)	Verschaeve et al. 1976
Human (occupational exposure)	Mercury fulminate	Chromosome aberrations in peripheral lymphocytes	+[a]	Anwar and Gabal 1991
Cat (diet)	Methylmercury	Chromosome aberrations in bone marrow cells	+/-	Miller et al. 1979
Syrian hamsters (intraperitoneal)	Methylmercury	Chromosome aberrations in oocytes	–	Mailhes 1983
Human (diet, seal consumption)	Mercury	Sister chromatid exchange in peripheral lymphocytes	(+)	Wulf et al. 1986
Human (occupational exposure)	Mercury fulminate	Micronuclei induction in peripheral lymphocytes	+[a]	Anwar and Gabal 1991
Cat (diet)	Methylmercury	Micronuclei induction in bone marrow cells	–	Miller et al. 1979
CBA mouse (intraperitoneal)	Methylmercury hydroxide	Micronuclei induction in bone marrow cells	–	Jenssen and Ramel 1980
Human (diet, fish consumption)	Methylmercury	Mitochondrial DNA copy number and damage in white blood cells	–	Berky et al. 2019 (all regions)
Human (diet, fish consumption)	Methylmercury	Mitochondrial DNA copy number and damage in white blood cells	+	Berky et al. 2019 (outside capital region)
Cat (diet)	Methylmercury	UDS in peripheral leukocytes	–	Miller et al. 1979
Rat (gavage)	Methylmercury	DNA damage in peripheral leukocytes	+	Barcelos et al. 2011
Rat (gavage)	Methylmercury	DNA damage in hepatocytes	+	Barcelos et al. 2011

Table 2-78. Genotoxicity of Organic Mercury *In Vivo* Animal Studies

Species (exposure route)	Mercury compound	End point	Results	Reference
Rat (gavage)	Methylmercury	DNA damage in peripheral leukocytes	+	Barcelos et al. 2012
Rat (gavage)	Methylmercury	DNA damage in hepatocytes	+	Barcelos et al. 2012
Rat (oral)	Methylmercury	DNA damage in testes	+	Chen et al. 2019
Rat (gavage)	Methylmercury	DNA damage in whole blood	+	Grotto et al. 2009b
Rat (gavage)	Methylmercury	DNA damage in liver and kidneys	+	Jin et al. 2008
Rat (oral via intragastric catheter)	Methylmercury	DNA damage in liver, kidneys, and brain	+	Joshi et al. 2014
Rat (stereotaxic injection)	Methylmercury	DNA damage in frontal cortex	+	Juárez et al. 2005
Rat (gavage)	Methylmercury	DNA damage in leukocytes	+	Manzolli et al. 2015
Rat (gavage)	Methylmercury	DNA damage in hepatocytes	+	Manzolli et al. 2015
Non-mammalian eukaryotic organisms				
Drosophila melanogaster (diet)	Methyl mercury chloride	Somatic mutation and recombination	–	Carmona et al. 2008
Chicken embryos (injection)	Methylmercury	DNA damage	+	Ferreira et al. 2015

[a]Positive response but no correlation to urine mercury levels or duration of exposure.

+ = positive result; – = negative result; +/– = weakly positive or marginal result; (+) = reported as positive but study was either seriously compromised or findings did not provide valid evidence of a positive response;
DNA = deoxyribonucleic acid

Methylmercury is not mutagenic in yeast cells (Nakai and Machida 1973). In hamster cells, both methylmercury and methoxyethyl mercury chloride are weakly mutagenic without metabolic activation (Fiskesjo 1979). An *in vivo* study in (SEC × C57BL)F1 mice showed dominant lethal mutations in spermatogonia following intraperitoneal exposure to methylmercury; dominant lethal mutations were not induced in spermatogonia or oocytes in similarly exposed (101 × C3H)F1 mice (Suter 1975). There is no evidence for somatic mutation or recombination in *D. melanogaster* following dietary exposure to methylmercury (Carmona et al. 2008).

In yeast, methylmercury exposure is a weak inducer of chromosome nondisjunction, but does not cause recombination (Nakai and Machida 1973). *In vitro* studies show consistent evidence of clastogenicity (aneuploidy, chromosome aberrations, sister chromatid exchanges, and micronuclei) in human, rat, and hamster cell lines exposed to various organic mercury compounds in the absence of metabolic activation (Betti et al. 1992; Crespo-López et al. 2007; Ehrenstein et al. 2002; Lee et al. 1997; Migliore et al. 1999).

Sister chromatid exchanges were not observed in early mouse embryos (blastocysts) exposed to methylmercury in the absence of metabolic activation (Matsumoto and Spindle 1982).

The overall findings from cytogenetic monitoring studies of workers occupationally exposed to organic mercury compounds (Anwar and Gabal 1991; Popescu et al. 1979; Verschaeve et al. 1976) or the general population exposed via diet (Skerfving et al. 1970; Wulf et al. 1986) provided no convincing evidence that mercury adversely affects the number or structure of chromosomes in human somatic cells. Studies reporting a positive result (Anwar and Gabal 1991; Popescu et al. 1979; Skerfving et al. 1970, 1974; Verschaeve et al. 1976; Wulf et al. 1986) were compromised either by technical problems, a lack of consideration of confounding factors, or a failure to demonstrate a relationship between mercury exposure and induced aberrations. Therefore, none of these studies can be used to predict the potential genetic hazard to humans associated with exposure to mercury or mercury compounds. In hamsters, the number of aneuploid oocytes was significantly increased following intraperitoneal exposure to methylmercury, but not to dimethylmercury or mercaptomerin; structural chromosomal alterations were not induced (Jagiello and Lin 1973; Mailhes 1983). The number of chromosomal alterations was increased in cat bone marrow following oral exposure to methylmercury; however, findings were not clearly dose-related (Miller et al. 1979). Micronuclei were not induced in mouse bone marrow cells following intraperitoneal exposure to methylmercury (Mailhes 1983) or in cat bone marrow cells following oral exposure to methylmercury (Miller et al. 1979).

Methylmercury and phenylmercuric acetate both induced DNA damage in bacteria (Kanematsu et al. 1980). Various organic mercury compounds consistently induced DNA damage in human, rat, mouse, and hamster cells lines *in vitro* in the absence of metabolic activation (Costa et al. 1991; Crespo-Lopez et al. 2016; Frenzilli et al. 2000; Guillamet et al. 2008; Ondovcik et al. 2012). Oral exposure to organic mercury compounds consistently induced DNA damage in various tissues in rats (Barcelos et al. 2011, 2012; Chen et al. 2019; Grotto et al. 2009b; Jin et al. 2008; Joshi et al. 2014; Juárez et al. 2005; Manzolli et al. 2015). DNA damage was also observed in chicken embryos injected with methylmercury (Ferreira et al. 2015). Unscheduled DNA synthesis was not induced in cats following oral exposure to methylmercury (Miller et al. 1979).

The potential association between exposure to mercury and mitochondrial DNA copy number or damage in WBCs was assessed in Peruvian subjects living various distances from artisanal and small-scale gold mining operations outside the capital city of Puerto Maldonado (Berky et al. 2019). Exposure to mercury in these populations was attributed to consumption of methylmercury contaminated fish. Overall, hair

mercury levels were similar across regions and no associations were observed between hair mercury levels and mitochondrial DNA copy number or damage. Additionally, no associations were found when the data were stratified by relationship to mining operations (upriver, near Puerto Maldonado, downriver). However, when evaluated just in individuals who lived >20 miles outside of the capital city, hair mercury levels were significantly associated with increased mitochondrial DNA damage.

2.21 GENERAL MECHANISMS OF ACTION

A diverse list of toxic mechanisms for mercury compounds has been described. This includes alteration or disruption of regulation of: intracellular calcium homeostasis, cytoskeleton, mitochondrial function, oxidative stress, neurotransmitter release, and DNA methylation. Mercury is a soft electrophile and will interact with soft nucleophiles, including thiols (R-SH) and selenols (R-Se) in proteins (Carty and Malone 1979). A contributor to the diversity of activity of mercury in biological systems is the high affinity of Hg^{2+} and CH_3Hg^{2+} for thiolate ($R\text{-}S^-$) and selenolate ($R\text{-}Se^-$) groups in proteins (Carty and Malone 1979; Parks and Smith 2016; Ralston and Raymond 2018). This enables mercury to bind to and disrupt structure and activity of enzymes, transporters, and other proteins whose activity is dependent on functional thiol or selenol groups. These include a diverse set of important transporters and enzymes that participate in the regulation of cell structure and function such as ATPases; hemoglobin and myoglobin; tubulin; numerous oxidoreductases, transferases, hydrolases and isomerases; and selenoenzymes (Khan and Wang 2009; Nagahara 2011). Low molecular weight thiols also serve as important ligands for mercury transport in and out of cells. Conjugates of Hg^{2+} and CH_3Hg^{2+} with extracellular thiols (e.g., cysteine, glycinyl-cysteine, glutathione) are recognized by physiological transport systems for amino acids (e.g., molecular mimicry) and, once in cells, mercury can distribute to other critical intracellular thiol and selenol groups. Transport of mercury S-conjugates has been shown to be important in a variety of tissues, including, brain, intestines, kidneys, liver, placenta, and RBCs (Ballatori 2002; Bridges and Zalups 2010, 2017; Clarkson et al. 2007; Lohren et al. 2015). Molecular mimicry may contribute to tissue target specificity of methylmercury and inorganic mercuric mercury, primarily to brain, fetus, and kidneys (Bridges and Zalups 2017). General mechanisms by mercury form (elemental, inorganic, organic) are discussed in more detail below.

Elemental Mercury. Toxic actions of elemental mercury are related to mercury levels in the target tissues, primarily (e.g., brain). The relatively high lipid solubility of Hg^0 contributes to the partitioning of inhaled mercury vapor into blood and delivery of Hg^0 and Hg^{2+}-thiol conjugates to the central nervous system. Vascular proximity of the brain, coupled with a limiting oxidation rate of Hg^0 in blood,

contributes to a first-pass effect on uptake of mercury into the brain following inhalation of Hg^0 (Magos et al. 1989). Transfer of inhaled Hg^0 into the brain results from several processes: (1) diffusion of Hg^0 vapor into blood; (2) physical partitioning (dissolving) of Hg^0 into plasma, RBCs, and other tissues; (3) extracellular and intracellular oxidation of Hg^0 to Hg^{2+}; (4) formation of Hg^{2+} complexes with proteins and non-protein species (primarily with sulfhydryls, including sulfhydryl amino acids); and (5) transport and distribution of Hg^{2+} complexes. Toxicity of absorbed Hg^0 in target tissues is related to inorganic mercury (primarily mercuric) levels in the target tissues (see discussion of mechanisms of toxicity of inorganic mercuric mercury below).

Inorganic Mercuric Mercury. Toxic actions of inorganic mercuric mercury are related to mercury levels in the target tissues (e.g., brain, kidneys, red blood cells). Delivery of inorganic mercuric mercury to target tissues is facilitated by membrane transporters that recognize S-conjugates of Hg^2. The Hg^{2+} ion has a strong tendency to form conjugates with two sulfur ligands (e.g., R-S-Hg-S-R′) (Carty and Malone 1979; Parks and Smith 2016). This distinguishes S-conjugates of inorganic Hg^{2+} from those formed by CH_3Hg^{2+} (CH_3Hg-S-R). Transporters implicated in the uptake of Hg^{2+}-S conjugates in the mammalian renal proximal tubule include the organic anion transporter, OAT1, located in the basolateral membrane of the proximal tubule and amino acid transporter system, $b^{0,+}$, located in the luminal membrane (Bridges and Zalups 2005; Bridges et al. 2004; Wei et al. 1999; Zalups and Ahmad 2004; Zalups et al. 2004). Both systems transport thiol conjugates of Hg^{2+} with the amino acid cysteine (Cys-S-Hg-S-Cys). On the luminal side of the proximal tubule, formation of the cysteine S-conjugate is facilitated by the catabolism of a glutathione S-conjugate (GluGlyCys-S-Hg-S-CysGlyGlu), which is catalyzed by the luminal membrane enzymes, GGT and cysteinylglycinase (Berndt et al. 1985; de Ceaurriz et al. 1994; Tanaka et al. 1990; Tanaka-Kagawa et al. 1993; Zalups 1995; Zalups and Lash 1997). Kinetics of reversible binding of Hg^{2+} to thiols is sufficiently fast enough to allow the Hg^{2+} in transported S-conjugates of Hg^{2+} to exchange with other thiol or selenol ligands, including thiolate or selenolate groups in proteins (Carty and Malone 1979; Parks and Smith 2016; Ralston and Raymond 2018).

Interactions of mercury with transporters, enzymes, and other proteins are thought to be the primary mechanisms by which inorganic mercuric mercury disrupts cell function. Several specific systems have been identified as targets of inorganic mercuric mercury. Mercuric mercury binds to and inhibits selenoenzymes, including thioredoxin reductases, enzymes that function in regulation of the oxidation state of protein thiols (Branco and Carvalho 2019). Inhibition of thioredoxin reductases is considered to be an important mechanism by which inorganic mercuric mercury impairs cellular antioxidant systems and produces oxidative damage to cells (Branco et al. 2012). Disruption of antioxidant systems leads to

formation of ROS, lipid peroxidation, necrosis, and apoptosis, and in RBCs, promotes the formation of methemoglobin (Ahmad and Mahmood 2019; dos Santos et al. 2016; Branco et al. 2012). Mercuric mercury binds to thiol groups in heme-thiolate proteins, which include cytochrome P450 and nitric oxide synthase (Ynalvez et al. 2016). Inhibition of nitric oxide synthase is thought to be an important mechanism by which mercuric chloride disrupts regulation of vascular resistance (Omanwar et al. 2014; Vassallo et al. 2011; Wiggers et al. 2008). Altered expression of cytochrome P450 in cardiac tissue is thought to be a contributing mechanism to mercuric chloride-induced cardiotoxicity (Amara et al. 2014).

The Hg^{2+} ion can displace cationic metals (copper, zinc) from binding sites on metallothionein (and other metalloproteins) and induces the synthesis of metallothionine (Aschner et al. 2006; Kagi et al. 1984, Yasutake and Nakamura 2011).

Methylmercury. Toxic actions of methylmercury are related to mercury levels in the target tissues, which primarily include the brain and kidneys. Delivery of methylmercury to target tissues is facilitated by membrane transporters that recognize S-conjugates of methylmercury with cysteine and other thiols (Ballatori 2002; Bridges and Zalups 2010, 2017; Clarkson et al. 2007; Lohren et al. 2015). The high affinity of CH_3Hg^{2+} for thiols enables mercury to bind to and perturb the function of a wide variety of proteins. These include ATPases; globins (e.g., hemoglobin, myoglobin); tubulin; and numerous oxidoreductases, transferases, hydrolases, and isomerases (Nagahara 2011). Methylmercury also forms stable complexes with selenols (R-Se) (Khan and Wang 2009). Formation of complexes with selenocysteine residues can alter the function of selenoenzymes (e.g., GPX and thioreductase). Direct complexation of selenium with methylmercury may also sequester selenium, making it unavailable for incorporation into protein or other selenium-dependent physiological processes (Ralston and Raymond 2018).

Interactions of mercury with transporters and enzymes are thought to be the primary mechanisms by which methylmercury disrupts cell differentiation and function. Several specific systems have been identified as targets of methylmercury. Methylmercury disrupts cellular antioxidant systems and promotes generation of ROS (Aaseth et al. 2020; Farina and Aschner 2017; Garza-Lombo et al. 2018). Several mechanisms contribute to the pro-oxidative action of mercury, including direct binding to cysteine and glutathione, depletion of glutathione, and inhibition of selenoenzymes that function in maintaining cell redox potential (Farina and Aschner 2017; Ralston and Raymond 2018; Spiller 2018). These include the selenoenzymes, GPX and thioreductase. In mitochondria, disruption of antioxidant systems leads to loss of mitochondrial membrane integrity, apoptotic cell cytokine cascade, and cell death

(Ceccatelli et al. 2010; Roos et al. 2012). Methylmercury stimulates neuronal excitatory N-methyl-D-aspartate (NMDA) glutamate receptors (Aaseth et al. 2020; Colon-Rodriguez et al. 2017; Farina and Aschner 2017). This can lead to dysregulation of intracellular calcium levels and production of ROS (Aschner et al. 2007). Methylmercury binds to thiols on neuronal gamma-aminobutyric acid (GABA) receptors and inhibits GABA signaling (Basu et al. 2010; Fonfria et al. 2001). Methylmercury disrupts cell signaling pathways, including phospholipase C, calcium, and phosphatidylinosito-3-kinases/protein kinases (Fretham et al. 2012; Kang et al. 2006). Disruption of cell signaling is thought to contribute to increased production of ROS and inflammatory responses to methylmercury in neuronal tissues (Chang 2011; Hwang et al. 2011). Methylmercury forms complexes with thiols in microtubule-associated proteins, disrupting tubulin organization, and cellular architecture dependent on microtubules (Aaseth et al. 2020, Sager et al. 1983; Vogel et al. 1985). Methylmercury changes expression and post-translational modification of genes involved in neuronal cell differentiation, antioxidant responses, and inflammation (Fujimura and Usuki 2014; Hwang et al. 2011; Ke et al. 2019; Onishchenko et al. 2008; Robinson et al. 2011; Theunissen et al. 2011).

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Overview. Humans are exposed to a variety of forms of mercury that exhibit route-dependent and chemical species dependent toxicokinetics. The major categories discussed in this section include:

- elemental mercury (Hg^0, e.g., mercury vapor);
- inorganic mercuric compounds (Hg^{2+}, e.g., mercuric chloride);
- inorganic mercurous compounds (Hg^+, calomel); and
- organic mercuric compounds (Hg^{2+}, e.g., methylmercury, dimethylmercury, phenylmercury).

Elemental Mercury

- *Absorption:*
  - Respiratory tract: Absorption of inhaled mercury vapor was estimated to range from 69 to 85% in human adults.
  - Gastrointestinal tract: Absorption of elemental mercury ingested as mercury amalgam was estimated to be 0.04% in human adults.
  - Dermal: Systemic absorption of mercury has been shown to occur in adult humans following skin exposure to mercury vapor. Systemic dermal absorption during a full-body immersion in mercury vapor was estimated to be 2% of the amount absorbed from inhalation during the immersion.
- *Distribution:*
  - Following inhalation exposure to mercury vapor, mercury distributes throughout the body, with the highest concentrations occurring in the kidneys.
  - Vascular proximity of the heart and brain coupled with a limiting oxidation rate of Hg^0 in blood contributes to a first-pass effect on uptake of Hg^0 in these tissues following inhalation of mercury vapor.
  - Mercury from inhalation exposure to mercury vapor can be transferred from the mother to the fetus and also from the mother to infants via maternal milk.
- *Metabolism:*
  - Absorbed Hg^0 is rapidly oxidized in blood and tissues to mercuric mercury (Hg^{2+}).
  - The major oxidative pathway for Hg^0 is catalyzed by the enzyme catalase.

- Oxidation removes Hg^0 from blood, limiting its transfer from blood to exhaled air and its distribution to other tissues.

- *Excretion:*
  - The major routes of excretion of absorbed mercury vapor are excretion of unmetabolized Hg^0 in exhaled air and urinary and fecal excretion of mercuric Hg^{2+} following oxidation of Hg^0 in blood and other tissues.
  - Kinetics of elimination of mercury following exposure to inhalation mercury vapor shows multiple phases. The terminal half-time, thought to largely reflect urinary and fecal excretion of Hg^{2+}, has been estimated in humans to range from 30 to 90 days.
- *Toxicokinetics models:*
  - Several pharmacokinetics models of inorganic mercury have been published. Of these, two models were developed to predict the absorption and distribution of inhaled mercury vapor (Jonsson et al. 1999; Leggett et al. 2001).

Inorganic Mercuric Mercury

- *Absorption:*
  - Respiratory tract: Following accidental inhalation exposures to mercuric oxide (^{203}HgO), mercury was detected in various body regions, including the head, kidneys, pelvis, and legs; indicating systemic absorption.
  - Gastrointestinal tract: Absorption of ingested inorganic mercuric mercury was estimated to range from 1 to 16% in human adults. Studies conducted in rodents have found that gastrointestinal absorption is higher in younger rats (age 8 weeks compared to adults).
  - Dermal: Inorganic mercuric mercury was absorbed across isolated human and pig skin.
- *Distribution:*
  - Following ingestion of inorganic mercuric mercury (e.g., mercuric chloride), mercury distributes throughout the body, with the highest concentrations occurring in the kidneys and liver.
  - Inorganic mercury is found in human cord blood, placenta, and breast milk indicating potential routes of transfer to the fetus and nursing infant.
- *Metabolism:*
  - Exhaled Hg^0 was observed in mice following parenteral doses of mercuric chloride, suggesting that Hg^{2+} had been reduced to Hg^0.

- Salivary and gastrointestinal bacteria have been shown to methylate Hg^{2+}; however, the quantitative significance of methylation in the disposition of absorbed Hg^{2+} remains uncertain.

- *Excretion:*
  - The major routes of excretion of absorbed mercuric mercury are feces and urine.
  - Kinetics of elimination of absorbed inorganic mercuric mercury exhibits multiple phases.
  - The terminal half-time has been estimated in humans to range from 49 to 120 days.
- *Toxicokinetics models:*
  - Several pharmacokinetics models for inorganic mercury have been published. These models are based on studies of the pharmacokinetics of absorbed inorganic mercuric mercury.

Inorganic Mercurous Mercury

- No studies were located that provide quantitative information on the absorption, distribution, metabolism, or excretion of inorganic mercurous mercury.
- Pharmacological and cosmetic use of calomel (mercurous sulfide) ointments (skin lightening, acne) has resulted in elevated urinary mercury levels and mercury poisoning, indicating that absorption of mercury can occur following oral and/or dermal exposure to inorganic mercurous mercury.
- Toxicity may have been from absorbed inorganic mercuric mercury, as the low pH and high chloride concentration of the gastric environment favor oxidation of ingested Hg^{1} to Hg^{2+}.

Organic Mercuric Mercury

- *Absorption:*
  - Respiratory tract: No studies were found that have estimated absorption of inhaled organic mercuric mercury.
  - Gastrointestinal tract: Studies conducted in humans, monkeys, and rodents have shown that gastrointestinal absorption of mercury is close to 100% following ingestion of methylmercury as the chloride salt or when incorporated into fish or other ingested protein.
  - Dermal: Dimethylmercury is rapidly absorbed through human skin. A study conducted in guinea pigs showed that mercury was absorbed following application of methylmercuric dicyandiamide.
- *Distribution:*
  - Following ingestion of methylmercury, mercury distributes throughout the body, with the highest concentrations occurring in the liver, kidneys, and brain.

  - Methylmercury is found in human cord blood, placenta, and breast milk indicating potential routes of transfer to the fetus and nursing infants.
- *Metabolism:*
  - Studies conducted in humans and in a variety of other mammalian species have observed methylmercury and inorganic mercury in tissues and excreta following exposure to methylmercury.
  - During repeated exposures to methylmercury, the rate of demethylation is not sufficient to completely eliminate the entire absorbed dose of methylmercury. As a result, a mix of methylmercury and inorganic mercuric mercury occurs in the body following exposures to methylmercury.
- *Excretion:*
  - The major routes of excretion of absorbed methylmercury are feces, urine, and hair.
  - Following exposure to phenylmercury, absorbed mercury is eliminated in bile, feces, urine, and hair.
  - Kinetics of elimination of absorbed methylmercury exhibits multiple phases. The terminal half-time has been estimated in humans to be 80 days (2.5–97.5 percentile range: 64–97).
- *Toxicokinetics models:*
  - Pharmacokinetics models of methylmercury have been developed for humans and a variety of other animal species.

3.1.1 Absorption

Inhalation Exposure

Elemental Mercury. Inhaled elemental mercury vapor (Hg^0 vapor) is absorbed from the respiratory tract. Absorption has been estimated in human clinical studies in which subjects (adults) inhaled measured amounts of Hg^0 vapor over periods of several minutes and retention was estimated from blood or whole-body mercury elimination kinetics. Absorption was estimated to range from 69 to 85% in humans exposed to concentrations ranging from 0.05 to 0.4 mg Hg/m^3 (Hursh et al. 1976, 1980; Nielsen-Kudsk 1965a, 1965b; Sandborgh-Englund et al. 1998; Teisinger and Fiserova-Bergerova 1965). Kinetics of absorption from the respiratory tract exhibits multiple phases: a more rapid phase attributed to diffusion and partitioning into blood and a slower phase attributed to absorption of mercury oxidized to Hg^{2+} in lung tissues (Hursh 1985; Leggett et al. 2001; Sandborgh-Englund et al. 1998). Based on sequential measurements of plasma mercury following a 15-minute inhalation exposure to Hg^0 vapor (0.4 mg/m^3),

an absorption half-time was estimated to be approximately 4.5 hours (Sandborgh-Englund et al. 1998). Leggett et al. (2001) assigned three components to absorption of Hg^0 from the lung with approximate half-time values of 1 minute, 8 hours, and 5 days (see Section 3.1.5 for a more description of the Leggett et al. 2001 respiratory tract model).

Mercury vapor released from dental amalgams can be absorbed by inhalation (Clarkson et al. 1988). Evidence that mercury released from amalgams can be absorbed comes from numerous studies that have shown associations between amalgam number and other factors that affect release of mercury from amalgams, and blood or urine mercury levels. For example, levels of mercury in these biological media increased with increasing number of dental amalgams (Al-Saleh et al. 2011; Barany et al. 2003; Gul et al. 2016; Maserejian et al. 2008; Yin et al. 2016). Children who received amalgam restorations showed higher urinary mercury levels than children who received resin restorations (Woods et al. 2007). Plasma and urinary levels of mercury declined after replacement of amalgams with resin restorations (Halbach et al. 2000). Studies conducted in rodents have also shown that mercury released from dental amalgam restorations is excreted in urine (Galic et al. 2001). Quantification of absorption of amalgam mercury from the inhalation pathway is complicated by multiple routes of absorption, including ingestion of Hg^0 dissolved in saliva and Hg^0 particulate (Bjorkman et al. 1997; Halbach et al. 2000; Leistevuo et al. 2001; Mackert and Berglund 1997). Based on results from measurements of releases of Hg^0 vapor and particulate Hg^0 from amalgams and models of intake and absorption of mercury released from amalgams, the inhalation pathway was estimated to account for approximately two-thirds of total absorption of amalgam mercury (Mackert and Berglund 1997). Rates of absorption from inhalation were estimated to be 2 µg Hg/day (range 0.3–6.1 µg Hg/day; 33 adults). Estimated rates of absorption of mercury from inhalation ranged from 3 to 18 µg Hg/day for four studies of Hg^0 release from dental amalgams (Clarkson et al. 1988). The wide range reflects, at least in part, the methodological differences used in estimating Hg^0 release rates and different conditions of the amalgams (e.g., number, wear, active chewing during measurement) (Clarkson et al. 1988).

Inter-species variation in regional deposition of inhaled Hg^0 vapor has been observed (Leggett et al. 2001). A larger fraction of inhaled mercury was deposited in bronchial regions of the respiratory tract in rodents and monkeys compared to humans (Berlin et al. 1969a; Hayes and Rothstein 1962; Khayat and Dencker 1984). Absorption kinetics of inhaled Hg^0 exhibits multiple phases in monkeys, guinea pigs, mice, rabbits, and rats (Berlin et al. 1966, 1969b; Hayes and Rothstein 1962; Hursh et al. 1980; Khayat and Dencker 1983, 1984; Nordberg and Serenius 1969). In general, all species show a rapid phase of

absorption of most of the deposited mercury (50–70% with a half-time of several minutes) with a slower component accounting for the remaining portion.

Mechanisms of absorption. The primary mechanism contributing to absorption of inhaled Hg^0 vapor is thought to be deposition primarily in alveolar and bronchial regions of the respiratory tract followed by diffusion and partitioning of mercury vapor into blood (Leggett et al. 2001). Transfer to blood is facilitated by the relatively high solubility of Hg^0 in blood and a diffusion gradient maintained by uptake and oxidation of Hg^0 in RBCs (Hursh 1985; Magos et al. 1978).

Inorganic Mercuric Mercury. Retention of mercury was measured in two adult workers following three incidents of accidental inhalation exposures to ^{203}HgO (Newton and Fry 1978). The total inhaled dose could not be estimated as the exposures were discovered from urinary measurements several days following the actual inhalation exposures. Whole-body and regional mercury retentions were estimated from measurements of external gamma activity over periods extending from 3 to 256 days following exposure. In one subject, based on thorax measurements made between days 3 and 212 following exposure, lung retention kinetics exhibited two phases with half-times of approximately 2 days for the fast phase and 20–26 days for the slow phase. Following all three incidents, absorption of mercury was indicated from measurements of ^{203}Hg in the head, kidney, pelvis, and leg regions. Following nose-only exposures of dogs to aerosols of mercuric oxide (^{202}HgO, 5 mg/m^3, count median diameter 0.16 μm), approximately 45% of the of the deposited mercury was cleared from the lower respiratory tract with a half-time that was <24 hours and the remaining portion was cleared with a half-time of 33 days (Morrow et al. 1964). Absorption of more soluble mercuric compounds (e.g., mercuric chloride) following inhalation is also expected but has not been studied.

Inorganic Mercurous Mercury. No information was located on absorption of mercury following inhalation exposures to inorganic mercurous mercury,

Organic Mercuric Mercury. No information was located on absorption of mercury following inhalation exposures to methylmercury. In mice, approximately 100% of inhaled dimethylmercury (4.5–9.0 mg Hg/kg) was initially retained during the first 5 minutes following the inhaled dose (Ostlund 1969).

Oral Exposure

Elemental Mercury. Ingested Hg^0 is absorbed from the gastrointestinal tract (af Geijersstam et al. 2001; Engqvist et al. 1998; Sandborgh-Englund et al. 2004). Following ingestion of water that had been equilibrated with Hg^0 vapor, approximately 40% of the mercury dose (0.03 mg, one adult subject) was excreted in feces over a 12-hour observation period (Engqvist et al. 1998). An elevation of plasma mercury concentrations was observed following ingestion of liquid Hg^0 contained in a rubber bile-sampling balloon, indicating that Hg^0 vapor that diffused out of the sampling balloon was absorbed (Sandborgh-Englund et al. 2004). Gastrointestinal absorption of ingested Hg^0 vapor is greater than absorption of mercury from ingested mercury amalgam.

Fecal excretion in two adult subjects who ingested powdered mercury amalgam (0.31–0.56 mg Hg) accounted for approximately 80% of the ingested dose of mercury (Engqvist et al. 1998). Absorption was estimated in a human clinical study in which 11 adult subjects ingested capsules containing powdered mercury amalgam and absorption was estimated from mercury elimination kinetics (af Geijersstam et al. 2001). Following a single dose of 1 mg amalgam mercury, absorption was estimated to be 0.04% of the ingested dose and was sufficient to result in transient elevations of plasma mercury concentrations. In rats, absorption of mercury was detected (but not quantified) as elevated tissue mercury levels following 4 weeks of exposure to diets amended with pulverized mercury amalgam (8.3 or 25 mg amalgam per week) (Song et al. 2002). Based on results from measurements of releases of Hg^0 vapor and particulate Hg^0 from amalgams and models of intake and absorption of mercury released from amalgams, the ingestion pathway was estimated to account for approximately one-third of total absorption of amalgam mercury (Mackert and Berglund 1997). Rates of absorption from inhalation were estimated to be 1 µg Hg/day (range 0.2–3.2 µg Hg/day; 33 adults).

Mechanisms of absorption. Following ingestion of Hg^0, absorption of mercury is likely to occur, in part as Hg^{2+} and in part as Hg^0 vapor released from Hg^0 particulates (Mackert and Berglund 1997). The low pH and high chloride concentration of the gastric environment favor oxidation of ingested Hg^0 to Hg^{2+} (Mousavi 2015; Nikolaychuk 2016). Mechanisms that contribute to absorption of Hg^{2+} are summarized in the section on absorption of inorganic mercuric mercury. Mechanisms that contribute to gastrointestinal absorption of Hg^0 vapor are likely to be those that operate in absorption across the lung. These include diffusion and partitioning of mercury vapor into blood, with diffusion gradients maintained by oxidization to Hg^{2+} and uptake of Hg^{2+} into tissues.

Inorganic Mercuric Mercury. Few studies quantify mercury absorption in humans following ingestion of Hg^{2+}. Rahola et al. (1972, 1973) measured whole-body elimination kinetics and excretion in adult subjects following ingestion of a single tracer dose of mercury (6 µg), as $^{203}Hg(NO_3)_2$, in drinking water (two subjects) or mixed with calf liver paste (eight subjects). Based on the mean recovery of 85% of the mercury dose in feces during the first 4–5 days following dosing (range 75–92 days), absorption was estimated to have been approximately 15%. This estimate would not have accounted for mercury that was excreted in feces following absorption. Rahola et al. (1973) also reported for each subject the parameters for a two-compartment model of elimination of whole-body radioactivity. If it is assumed that the fast elimination component consisted entirely of fecal excretion of unabsorbed mercury, occurring largely during the first 10–15 days after the dose, then extrapolation of the slow component to zero time yields an estimate of the absorbed dose fraction. Parameter estimates from the study are presented in Table 3-1. The mean value for absorbed dose fraction (percent of administered dose) for the subjects who consumed mercury in calf liver was 6.2±2.7% (range 4–8.7%; n=7); the mean values for the two subjects who consumed mercury in drinking water were 4.7 and 15.6%. The mean value for all subjects (n=10) was 7.0% (range 1.4–15.6%).

Table 3-1. Whole-Body Retention and Excretion of Mercuric Chloride in Human Subjects

Medium	Subject	Sex	Age	BW	$T_{1/2}a$	$\%T_{1/2}a$	$T_{1/2}b$	$\%T_{1/2}b$	FE	UR
Food	AE	F	35	60	1.7	32	29	4	82	0.11
Food	AN	F	23	48	3.0	22	36	7.4	ND	0.21
Food	TP	F	23	51	2.2	54	39	6.6	ND	ND
Food	AH	M	32	75	1.9	19	50	4.0	91	0.06
Food	PK	M	40	72	1.9	27	60	8.7	75	0.15
Food	JM	M	49	85	2.9	6	51	1.4	88	0.05
Food	MR	M	30	56	3.3	8	45	8.5	91	0.21
Food	IV	M	29	69	1.0	5	32	8.7	92	0.23
Water	MG	F	48	72	2.5	45	38	4.7	ND	0.11
Water	KR	F	29	61	2.5	35	41	15.6	75	0.38
AM			34	65	2.3	25	42	7.0	85	0.17
SD			9.2	12	0.7	17	9.5	3.9	7.5	0.10
SE			2.9	3.7	0.2	5.3	3.0	1.2	2.8	0.03
AM food			33	65	2.2	22	43	6.2	87	0.15
SD food			8.7	13	0.8	16	11	2.7	6.7	0.07
SE food			3.1	4.5	0.3	5.8	3.8	1.0	2.7	0.03
AM water			39	67	2.5	40	39.5	10	75	0.30

AM = arithmetic mean; F = female; FE = cumulative fecal excretion measured on days 4–5 after the dose; M = male; ND = no data; SD = standard deviation; SE = standard error; $T_{1/2}a$ = first-order elimination half-time for the rapid

Table 3-1. Whole-Body Retention and Excretion of Mercuric Chloride in Human Subjects

Medium	Subject	Sex	Age	BW	$T_{1/2}a$	$\%T_{1/2}a$	$T_{1/2}b$	$\%T_{1/2}b$	FE	UR
Food	AE	F	35	60	1.7	32	29	4	82	0.11
Food	AN	F	23	48	3.0	22	36	7.4	ND	0.21
Food	TP	F	23	51	2.2	54	39	6.6	ND	ND
Food	AH	M	32	75	1.9	19	50	4.0	91	0.06
Food	PK	M	40	72	1.9	27	60	8.7	75	0.15
Food	JM	M	49	85	2.9	6	51	1.4	88	0.05
Food	MR	M	30	56	3.3	8	45	8.5	91	0.21
Food	IV	M	29	69	1.0	5	32	8.7	92	0.23
Water	MG	F	48	72	2.5	45	38	4.7	ND	0.11
Water	KR	F	29	61	2.5	35	41	15.6	75	0.38
AM			34	65	2.3	25	42	7.0	85	0.17
SD			9.2	12	0.7	17	9.5	3.9	7.5	0.10
SE			2.9	3.7	0.2	5.3	3.0	1.2	2.8	0.03
AM food			33	65	2.2	22	43	6.2	87	0.15
SD food			8.7	13	0.8	16	11	2.7	6.7	0.07
SE food			3.1	4.5	0.3	5.8	3.8	1.0	2.7	0.03
AM water			39	67	2.5	40	39.5	10	75	0.30

phase of elimination, respectively; $T_{1/2}b$ = first-order elimination half-time for the slower phase of elimination; %T = fractions of the body burden attributed to fast or slow phase of elimination; UR = urinary excretion measured on days 4–5 after the dose; the administered dose was 6 µg Hg, as [^{203}Hg]-mercuric chloride.

Source: Rahola et al. 1973

Absorption of Hg^{2+} has been studied more extensively in rodents. Studies that provide quantitative estimates of the fraction of dose absorbed are summarized in Table 3-2. The estimates for ingested mercuric chloride range from 0.4 to 42%. Differences in methods used to arrive at these estimates make it difficult to compare values across studies. For example, mass balance studies that estimate absorption as the difference between the oral dose and cumulative fecal excretion are likely to underestimate absorption because mercury excreted in feces after absorption cannot be distinguished from excretion of unabsorbed mercury. Within-study comparisons provide some insights about variables that affect absorption of Hg^{2+}. In rats, absorption was substantially higher in nursing pups (38%) compared to adults maintained on rat chow (1%) (Kostial et al. 1978). Young rats (130 g or 8 weeks of age) also showed higher absorption than older rats (Kostial et al. 1997; Piotrowski et al. 1992). A repeated-dose study in which rats were exposed to mercuric chloride in drinking water estimated the absorption fraction to range from 31 to 43% (Morcillo and Santamaria 1995). Estimates of the absorption fraction following ingestion of mercuric chloride in mice also showed wide variability (2–30%). The large difference in the estimates provided by Nielsen and Andersen (1990), 17–30%, and Revis et al. (1990), 2.1%, may reflect the

substantial underestimate of the absorption fraction provided by fecal mass-balance studies on the lower end of the range (Revis et al. 1990). Of the mouse studies reported in Table 3-2, the Nielsen and Andersen (1990) study would not have been biased downward by fecal excretion of absorbed mercury and may represent a more accurate estimate of the absorption fraction in adult mice (17–30%). Estimates from the Revis et al. (1990) study suggest that the absorption fraction for ingested mercuric chloride (2.1%) is larger than that for mercuric sulfide (0.4%). This is supported by studies in mice that have found lower tissue levels of mercury following ingestion of mercuric sulfide and/or cinnabar in which the predominant mercury species is mercuric sulfide, compared to tissue levels following ingestion of mercuric chloride (Sin et al. 1983, 1989; Wang et al. 2013). The lower absorption fraction is likely to result from the lower solubility of mercuric sulfide and the higher stability of the Hg^{2+}-S^{-2} complex under physiological conditions (Carty and Malone 1979).

Mechanisms of absorption. Studies conducted in mice and rats indicate that the predominant site of absorption of Hg^{2+} is the small intestine (Endo et al. 1984, 1986, 1990, 1991; Foulkes 1993; Foulkes and Bergman 1993; Nielsen et al. 1992; Zalups 1998). The mechanism of absorption of Hg^{2+} has not been fully characterized. Bile flow and bile constituents increase absorption in the rat (Endo et al. 1984; Nielsen et al. 1992; Zalups 1998). Absorption is dependent on pH of the luminal contents of the intestine (Endo et al. 1986). In a study in rats that compared intestinal absorption of a series of Hg^{2+} compounds, absorption decreased with increasing stability constant of the Hg^{2+} complex (Endo et al. 1990). These observations suggest that ligand interactions are important variables affecting absorption. These interactions include formation of Hg^{2+} S-conjugates, which have been found to be important in the transport of Hg^{2+} in kidneys, liver, and brain (Bridges and Zalups 2017). Studies conducted in mice and in cultured enterocytes have shown that Hg^{2+} can be a substrate for the divalent metal transporter, DMT1, which resides on the apical membrane of enterocytes and, therefore, may participate in the absorption of Hg^{2+} (Ilback et al. 2008; Vazquez et al. 2015). Analogous to Hg^{2+} transport in kidneys, amino acid transporters may also participate in the uptake of Hg^{2+} into hepatocytes (Bridges and Zalups 2017).

Inorganic Mercurous Mercury. No studies were located that provide estimates of absorption of ingested mercurous mercury compounds, although pharmacological use of calomel (mercurous sulfide) as a purgative and teething ointment has resulted in mercury poisoning (Davis 2000). Mercurous sulfide has a substantially lower solubility than mercuric chloride, which is likely to limit absorption of Hg^{1+}. However, the low pH and high chloride concentration of the gastric environment favor oxidation of solubilized Hg^{1+} to Hg^{2+}; therefore, absorption of Hg^{2+} may have contributed to toxicity observed in cases of calomel poisoning (Mousavi 2015; Nikolaychuk 2016).

Table 3-2. Summary of Estimates of Gastrointestinal Absorption in Mice and Rats

Species	Sex	Age or BW	Hg Form	EF	Dose	Route	Diet	AF (%)	Source
Mouse	F	7–8 weeks	$HgCl_2$	1 dose	0.2–1 mg/kg	Gavage	Standard diet	17–30[b]	Nielsen and Andersen 1990
Mouse	ND	3 months	$HgCl_2$	1 dose	Trace	Gavage (in feed)	Standard diet	2.1[b]	Revis et al. 1990
Mouse	ND	3 months	HgS	1 dose	Trace	Gavage (in feed)	Standard diet	0.4[c]	Revis et al. 1990
Mouse	FM	3 months	Soil[a]	1 day	0.002–0.4 mg	5% soil in diet	Standard diet	4–16[c]	Revis et al. 1990
Mouse	FM	1–21 days	$HgCl_2$	21 days	0.0002 mg/pup	Nursing	Nursing	15[d]	Sundberg et al. 1999
Rat	ND	1 weeks	$HgCl_2$	1 dose	ND	Gavage	Nursing	38[e]	Kostial et al. 1978
Rat	ND	18 weeks	$HgCl_2$	1 dose	ND	Gavage	Cow milk diet	7[e]	Kostial et al. 1978
Rat	ND	18 weeks	$HgCl_2$	1 dose	ND	Gavage	Standard diet	1[e]	Kostial et al. 1978
Rat	F	8 weeks	$HgCl_2$	1 dose	0.5 mg/kg	Gavage	Standard diet	42[f]	Kostial et al. 1997
Rat	M	130 g	$HgCl_2$	Daily for 8 weeks	0.1–7.3 mg/kg day	Drinking water	Standard diet	31–43[g]	Morcillo and Santamaria 1995
Rat	F	160–250 g	$HgCl_2$	1 dose	0.2–12.5 mg/kg	Gavage	Standard diet	3–4[h]	Piotrowski et al. 1992
Rat	F	160–250 g	$HgCl_2$	1 dose	17–20 mg/kg	Gavage	Standard diet	6–9[h]	Piotrowski et al. 1992

AF = absorption fraction; BW = body weight; EF = exposure frequency; F = female; FM = female and male; M = male; ND = no data

[a]5% soil in diet.
[b]Oral/intraperitoneal ratio of whole-body retention.
[c]Dose minus cumulative excretion in feces measured over a period of 96 hours, minus mercury in gastrointestinal tract mercury at termination of exposure.
[d]Whole-body minus gastrointestinal tract/cumulative dose from nursing.
[e]Whole-body retention 6 days after dosing.
[f]Whole-body retention 4 days after dosing.
[g]Whole-body retention/whole-body elimination rate.
[h]Whole-body retention minus gastrointestinal tract 4 hours after dosing.

Organic Mercuric Mercury. Studies conducted in humans, monkeys, and rodents have shown that gastrointestinal absorption of mercury is close to 100% following ingestion of methylmercury as the chloride salt or when incorporated into fish or other ingested protein (Aberg et al. 1969; Berlin et al. 1975; Clarkson 1971; Clarkson and Shapiro 1971; Miettinen et al. 1971; Mori et al. 2012; Nielsen 1992; Nielsen and Andersen 1991; Nielsen et al. 1992; Sundberg et al. 1999; Yannai and Sachs 1993).

Mechanisms of absorption. Studies conducted in rats and intestinal cell cultures have shown that absorption of methylmercury from the small intestine involves facilitated transport of S-conjugates of methylmercury out of the intestinal lumen (Bridges and Zalups 2017; Mori et al. 2012; Urano et al. 1990; Vazquez et al. 2014). The CH_3Hg-S-CysGly and CH_3Hg-S-Cys were more avidly taken up from the lumen of the rat small intestine than CH_3Hg-S-CysGlyGlu, suggesting that the transported species may be CH_3Hg-S-CysGly and CH_3Hg-S-Cys (Urano et al. 1990). In rats, orally administered methylmercury and CH_3Hg-S-Cys had similar absorption fractions and absorption kinetics (Mori et al. 2012), and inhibition of intestinal GGT suppressed absorption of orally administered methyl mercury (Urano et al. 1990).

Dermal Exposure

Elemental Mercury. Hg^0 vapor is absorbed through the skin. Absorption was estimated in a human clinical study in which the forearms of subjects (adults) were exposed to $^{203}Hg^0$ vapor (0.88–2.14 mg Hg/m^3) and absorption was estimated from whole-body gamma counting (Hursh et al. 1989). Absorption into skin was estimated to range from 0.01 to 0.04 ng Hg/cm^2 skin per mg Hg/m^3 air. Approximately one-half of the mercury uptake into skin was eliminated by desquamation (skin shedding) over a period of 60 days. The remaining portion was absorbed into the systemic circulation, with the highest amounts of systemic mercury observed 10–30 days post-exposure. The rate constant for systemic absorption from skin was estimated to be approximately 0.05 day^{-1}, which corresponds to a half-time of 14 days. Based on the measured rate of dermal absorption and 80% absorption of inhaled mercury vapor, the relative contributions of the dermal and inhalation absorption routes during a full body immersion in mercury vapor were estimated to be 2.6 and 97.4%, respectively (Hursh et al. 1989).

Inorganic Mercuric Mercury. Dermal penetration of Hg^{2+} has been studied in preparations of isolated human and pig skin and in guinea pigs (Moody et al. 2009; Sartorelli et al. 2003; Skowronski et al. 2000). These studies showed that mercury from mercuric chloride was transferred across the skin and retained in skin, and that retention substantially exceeded transdermal transfer over the period of observation (16–72 hours). Transdermal transfer was of similar magnitude in the three studies. Sartorelli et al. (2003)

estimated the permeability coefficient (K_p) for transdermal transfer across isolated human breast skin to be $1.4x10^{-2}$ cm/hour when the initial mercury concentration was 0.0088 nmol/cm^3 (1.8 µg Hg/L) and $3.0x10^{-3}$ cm/hour when the initial concentration was 0.0607 nmol/cm^3 (12.2 µg/L). At the lower concentration, 4.8% of the applied dose was transferred across the skin over a 72-hour period (1.64% over a 24-hour period) and 19% was retained in skin. At the higher concentration, transdermal transfer was 0.93% over a 72-hour period (0.34% in 24 hours) and 45% was retained in skin. In a study of isolated human abdomen skin, transdermal transfer over a 24-hour period was 1.4% of the applied mercury dose (1.1 µg hg/cm^2), while 77% was retained in the skin (Moody et al. 2009). Transdermal transfer across pig skin was 0.18% of the applied dose (0.25 µg/cm^2) when measured over a period of 16 hours and 66% of the applied dose was retained in skin. Transdermal transfer and skin retention were lower after mixing mercuric chloride with soil, and more substantially decreased if the mercury-soil mixture was allowed to age (stored in the dark in a sealed vial) for a period of 3 months (Sartorelli et al. 2003, Skowronski et al. 2000). In guinea pigs, a dermal dose of 95 mg mercury as mercuric chloride applied to a 3.1 cm^2 area of skin resulted in 65% mortality (Wahlberg 1965).

Inorganic Mercurous Mercury. No studies were located that estimated absorption of dermally applied inorganic mercurous mercury. Pharmacological and cosmetic use of calomel (mercurous sulfide) ointments (skin lightening, acne) has resulted in elevated urinary mercury levels and mercury poisoning (Copan et al. 2015; Davis 2000).

Organic Mercuric Mercury. A study conducted in guinea pigs showed that methylmercuric dicyandiamide (a fungicide) applied to skin was absorbed (Friberg et al. 1961). Following dermal exposures to 2.6 or 5.3 mg Hg/cm^2, absorption was estimated to be 0.44 and 1.2% per hour. Methylmercuric dicyandiamide is not a dissociable salt of methylmercury.

Dimethylmercury is rapidly absorbed through human skin. A lethal dose of dimethylmercury occurred following accidental contact of the dorsal surface of a latex gloved hand to “a few drops” of liquid dimethylmercury (Nierenberg et al. 1998; Siegler et al. 1999). The applied dose was reconstructed based on measurements of blood mercury made approximately 5 months following the accident and the estimated half-time of 75 days for hair mercury in the subject (Nierenberg et al. 1998). The applied dose was estimated to have been approximately 1,344 mg mercury contained in approximately 0.48 mL of liquid dimethylmercury (density 3.2 g dimethylmercury/mL) (Nierenberg et al. 1998).

Phenylmercury is absorbed through the skin. Estimates of the magnitude of absorption were not located; however, cases of mercury toxicity (acrodynia) and elevated urinary mercury excretion have been reported in infants exposed to phenylmercury that had been applied to cloth diapers as a fungicide (Gotelli et al. 1985).

3.1.2 Distribution

Elemental Mercury. The distribution of absorbed mercury following inhalation of Hg^0 vapor reflects several processes: (1) diffusion of Hg^0 vapor into blood; (2) physical partitioning (dissolving) of Hg^0 into plasma, RBCs, and other tissues; (3) extracellular and intracellular oxidation of Hg^0 to Hg^{2+}; (4) formation of Hg^{2+}complexes with proteins and non-protein species (primarily with sulfhydryls, including sulfhydryl amino acids); and (5) and transport and distribution of Hg^{2+} complexes. Although Hg^{2+} is the dominant species of mercury retained in tissues, the distribution of mercury following exposure to Hg^0 vapor differs from the distribution observed following exposure to inorganic Hg^{2+} compounds (Berlin et al. 1966, 1969b; Khayat and Dencker 1983; Magos et al. 1989). These differences are attributed, in part, to the high solubility of Hg^0 in lipid as well its affinity for proteins such as hemoglobin (Hursh 1985; Magos 1967; Magos et al. 1978; U.S. Atomic Energy Commission 1961). Particularly relevant to the vulnerability of the nervous system to Hg^0 vapor is the pronounced distribution of mercury in the brain following Hg^0 vapor exposure. The distribution of inorganic Hg^{2+} is discussed in greater detail in the section on inorganic mercuric mercury.

Whole-body distribution. Following inhalation exposure to Hg^0 vapor, mercury distributes to the blood and other tissues. Hursh et al. (1978) measured regional external gamma activity following 14–24-minute exposures to $^{203}Hg^0$ vapor (0.1 mg Hg/m^3) and estimated that approximately 7% (range 6.3–8.3%; five adult subjects) initially distributed to the head region and that mercury levels in the kidney region were approximately 10-fold higher than levels in the head region. Studies conducted in monkeys and rodents have found that the largest portion of the absorbed dose and highest concentrations of mercury occur in the kidneys following inhalation exposure to Hg^0 vapor (Berlin et al. 1969b; Hayes and Rothstein 1962; Khayat and Dencker 1984). In monkeys, immediately after a 1-hour exposure to Hg^0 vapor, the rank order of mercury concentration in tissues was kidneys, lungs, myocardium, spleen, thymus, liver, brain, salivary glands, pancreas, skeletal muscles, whole blood, and testes (Khayat and Dencker 1984). Following a 4-hour exposure in mice (4–50 mg/m^3), the rank order of mercury concentration in tissues was lungs, kidneys, thyroid, myocardium, adrenal glands, brain, eyes, liver, plasma, blood, testes, and abdominal fat (Khayat and Dencker 1983).

Vascular proximity of the heart and brain, coupled with a limiting oxidation rate of Hg^0 in blood, contributes to a first-pass effect on uptake in these tissues following inhalation of Hg^0 (Magos et al. 1989). In rats, uptake into the lungs, brain, and heart and exhalation of mercury were greater when Hg^0 was injected directly into the jugular vein than when the same dose was injected into the tail vein (Magos et al. 1989). The time of first appearance of mercury in exhaled air, indicative of the transit time to the lungs, was 0.6 seconds following jugular vein injection and 1.8 seconds following tail vein injection, whereas the half-time for oxidation of Hg^0 in rat blood was estimated to be 3.3 seconds. The first-pass effect is also evident from differences in tissue distribution observed in monkeys and rodents following inhalation of Hg^0 vapor compared to similar doses of Hg^{2+} administered intravenously (Berlin et al. 1966, 1969b; Khayat and Dencker 1983; Magos et al. 1989). Studies conducted in monkeys and rodents have found that uptake of mercury into the brain and heart tissues is greater following an inhalation exposure to Hg^0 vapor compared to the same intravenous dose of mercuric chloride (Berlin et al. 1966, 1969b). In rats, higher initial mercury levels were observed in the adrenal cortex, brown fat, epididymides, eyes, ovaries, and thyroid gland following inhalation of Hg^0 vapor compared to the distribution following an intravenous dose of mercuric chloride (Khayat and Dencker 1983).

Distribution in blood. Mercury absorbed following inhalation of Hg^0 vapor distributes into plasma and RBCs (Berlin et al. 1969b; Cherian et al. 1978; Hursh et al. 1980; Khayat and Dencker et al. 1983). Concentrations in the RBC fraction of blood exceeds that of plasma. The RBC-to-plasma ratio (RBC/plasma) has been measured in human clinical studies and in studies conducted in monkeys and rodents (Berlin et al. 1969b; Cherian et al. 1978; Hursh et al. 1980). In a human clinical study, the RBC/plasma ratio was >10 within minutes of inhaling Hg^0 vapor (0.1 mg/m^3 for 14–24 minutes), after which the ratio declined to a value of approximately 2 within 20 hours following exposure and remained at that ratio over the 5-day observation period. (Cherian et al. 1978). An RBC/plasma ratio of approximately 1.3 for total mercury was observed in Hg^0 workers (Suzuki et al. 1970). An RBC/plasma ratio of 2 corresponds to a whole blood/plasma ratio of approximately 1.45 if the hematocrit is 0.45. Sandborgh-Englund et al. (1998) measured whole blood and plasma concentrations in human subjects over a 30-day period following inhalation of mercury vapor (0.4 mg/m^3 for 25 minutes). The ratio of the area under the curve (AUC) for mercury in the RBCs to that in plasma (AUC_{RBC}/AUC_{plasma}) was approximately 1.33, consistent with an RBC/plasma ratio of approximately 1.7. A whole blood/plasma ratio of 1.3 was observed in workers exposed to Hg^0 vapor (Lundgren et al. 1967). The RBC/plasma ratios immediately after exposure to Hg^0 vapor were 2 in monkeys and >5 in rabbits (Berlin et al. 1969b). Following exposure of whole blood or plasma to Hg^0 vapor, mercury was found to be associated with

proteins, including albumin, hemoglobin and other globulins, and non-protein sulfhydryls (NPSH) (Cember et al. 1968; U.S. Atomic Energy Commission 1961).

The decrease in the RBC/plasma ratio observed in the initial few minutes following exposure to Hg^0 vapor is thought to reflect an initial partitioning of Hg^0 into blood followed by distribution of its oxidation product, Hg^{2+}, between plasma, RBCs, and other tissues (Hursh et al. 1976; Magos 1967; Magos et al. 1978; U.S. Atomic Energy Commission 1961). Partitioning of Hg^0 into blood involves both the physical dissolving of Hg^0 into aqueous and lipid components of blood as well as an interaction with hemoglobin (Hursh et al. 1976; Magos 1967; U.S. Atomic Energy Commission 1961). The blood:air partition coefficient for Hg^0 in human whole blood ranged from approximately 10 to 4.2 over a range of temperatures extending from 10 to 37°C and ranged from 5.6 to 2.4 in plasma over the same temperature range (Hursh et al. 1980). The partition coefficient in lipid (sunflower oil) was approximately 80 (Hursh et al. 1980).

Distribution in brain and nervous tissue. Studies of regional and cellular distribution of mercury in the brain principally have relied on two techniques imaging the distribution of mercury. In studies in which exposures were to ^{203}Hg, the regional distribution of mercury can be observed by autoradiography, which maps the location of gamma emission from ^{203}Hg. Spatial resolution of this technique is limited by the path length between the tissue section and the radiography plate. Detection is also limited by the gamma emission decay of ^{203}Hg, which has a half-life of 37 days. Mercury can be visualized at the cellular and subcellular levels using autometallography. In this technique, the tissue section is placed in contact with a developing agent containing silver ion and a reducing agent. The silver reacts with Hg-sulfides in the tissue to form localized deposits of elemental silver that can be imaged by light or electron microscopy (Danscher and Moller-Madsen 1985; Nørgaard et al. 1989).

Mercury does not uniformly distribute in all areas of the brain following inhalation exposure to Hg^0 vapor. Studies conducted in monkeys and rodents have found higher levels in gray matter compared to white matter and heterogenous distribution among brain nuclei (Berlin et al. 1969b; Nordberg and Serenius 1969; Warfvinge 2000; Warfvinge et al. 1994a). Higher mercury levels were found in the dentate nucleus in the cerebellum, inferior olivary nucleus, subthalamic nucleus, choroid plexus, and superior colliculus. Within the cerebral cortex, higher levels were found in the ganglionic layer, and mercury was found in both neurons and astrocytes. In the cerebellum, uptake was higher in the granular and Purkinje cell layers, and mercury was found in neurons and glial cells. In monkeys and mice, mercury was observed in the spinal cord following inhalation exposure to Hg^0 vapor, in association with

motor neurons (Pamphlett and Coote 1998; Roos and Dencker 2012; Stankovic 2006). In a study conducted in mice, mercury was observed in association with spinal motor neurons 30 weeks after a single 12-hour exposure to 0.025 mg/m^3 or a 30-minute exposure to 0.5 mg/m^3 (Pamphlett and Coote 1998). Studies conducted in monkeys have shown uptake of mercury into the retina, including optic disk, pigment epithelium, ganglion cells, and vessel walls (Khayat and Dencker 1983, 1984; Warfvinge and Bruun 1996, 2000). Analyses of tissues from autopsies of mercury minors have found concentrations in the thyroid and pituitary higher than in the kidneys, liver, or whole brain (Kosta et al. 1975).

Maternal-fetal-infant transfer. Mercury is transferred to the fetus and to nursing infants from breast milk following exposures to Hg^0. Concentrations of inorganic mercury in maternal blood, cord blood, placenta, and breast milk were higher in women who had been occupationally exposed to vapor compared to a control group, and the inorganic fraction of breast milk mercury was higher in the exposed group (Yang et al. 1997). Studies conducted in monkeys and rodents have shown that mercury absorbed following maternal inhalation exposures to Hg^0 vapor distributes to the placenta and fetus, including the fetal brain, kidneys, and liver (Clarkson et al. 1972; Ishitobi et al. 2010; Morgan et al. 2002; Pamphlett and Kum-Jew 2001: Pamphlett et al. 2019; Shimada et al. 2004; Warfvinge 2000; Yoshida et al. 2002). In mice, mercury was found associated with neonatal brain vasculature, sensory ganglia, and facial and spinal motor neurons following maternal exposure (0.5 mg/m^3, 4 hours/day) during GDs 14–18, but not when exposure occurred earlier in pregnancy (GDs 1–10) (Pamphlett and Kum-Jew 2001). A study conducted in monkeys exposed animals to 0.5 or 1 mg/m^3, 5 days/week during gestation (Warfvinge 2000; Warfvinge and Bruun 2000). In this study, mercury was detected in maternal and offspring cerebellum 3 years after maternal exposure. Mercury was found in Bergmann glia and Purkinje cells, granular and Golgi cells, and medullary astrocytes. The highest amounts of mercury were found in cerebellar nuclei. Areas of the retina where mercury distributed in adult monkeys were also sites of accumulation of mercury in offspring of monkeys exposed to Hg^0 vapor (Warfvinge and Bruun 2000). These areas included the optic nerve, retinal pigment epithelium, inner plexiform layer, ganglion cells, and vessel walls. Studies conducted in mice have examined eye tissues of mouse neonates following maternal exposures in late pregnancy (0.5 mg/m^3, 4 hours/day, GDs 14–18) and found deposits of mercury in the retinal ganglion cells, endothelial cells, and retinal pigment epithelium and optic nerve (Pamphlett et al. 2019).

Mercury released from dental amalgam restorations can be transferred to the placenta, fetuses, and newborns during nursing. Dental amalgam restorations in pregnant women increased placenta and cord levels of mercury compared to a control group with no amalgam restorations (Bedir Findik et al. 2016).

In rats and sheep, dental amalgam restorations installed during gestation increased mercury levels in the placenta and amniotic fluid; fetal brain, kidneys, and liver; and maternal milk (Takahashi et al. 2001; Vimy et al. 1990).

Elimination from tissues. Kinetics of elimination of mercury from plasma following exposure to Hg^0 vapor exhibits multiple phases. In a human clinical study, following a 15-minute inhalation exposure to Hg^0 vapor (0.4 mg/m^3), half-times for elimination from plasma were estimated to be 1.2 days (range 0.26–2.5 days) and 10.4 days (range 0.6–2.5 days; n=9 adult subjects) (Sandborgh-Englund et al. 1998). In another human clinical study in which subjects (adults) ingested capsules containing powdered mercury amalgam, the terminal elimination half-time for plasma mercury was estimated to be 37 days (af Geijersstam et al. 2001). In workers exposed to mercury vapor and monitored for a 600-day period following cessation of exposure, the elimination half-time for mercury in blood was estimated to be 45 days and the half-time for mercury in urine was estimated to be 56 days (Bluhm et al. 1992).

Studies conducted in rats have found that mercury concentrations decrease faster in most tissues compared to the kidneys and, as a result, several weeks following exposure, most of the body burden of mercury resides in the kidneys (Berlin et al. 1969b; Hayes and Rothstein 1962). In rats, mercury concentrations in the brain declined more slowly than either the body burden or the concentrations in the kidneys (Magos 1967). The same may not apply to humans. Following a brief exposure to $^{203}Hg^0$ (0.1 mg/m^3), the mean half-time for externally measured gamma activity in the head region was estimated to be 21 days (range 16–29 days; n=5 subjects) compared to 64 days (range 47–83 days) in the kidneys region (Hursh et al. 1976).

Inorganic Mercuric Mercury. The distribution of absorbed Hg^{2+} reflects formation of Hg^{2+}complexes with proteins and non-protein species (primarily sulfhydryls, including sulfhydryl amino acids) and transport and distribution of Hg^{2+} complexes.

Whole-body distribution following inhalation. Retention of mercury was measured in two adult workers following three incidents of accidental inhalation exposures to ^{203}HgO (Newton and Fry 1978). Whole-body and regional mercury retention were measured from external gamma activity over periods extending from 3 to 256 days following exposure. Following all three incidents, ^{203}Hg was detected in the lungs, head, kidneys, pelvis, and leg regions. Whole-body elimination exhibited multiple phases, with terminal half-times estimated to have been 39, 78, and ~400 days for each incident. Mercury levels declined more slowly in region of the kidneys compared to the lung and head regions and, as a result, >25 days following exposure, most of the retained mercury was located in the kidney region. The estimated

elimination half-time for the region of the kidneys ranged from 35 to 53 days and from 23 to 26 days for the head region.

Whole-body distribution following ingestion. Studies conducted in rodents have found that the kidneys and liver retain the largest fractions of the absorbed dose following an oral dose of mercuric chloride and mercuric sulfide (Ekstrand et al. 2010; Feng et al. 2004; Hojbjerg et al. 1992; Khan et al. 2001; Kostial et al. 1978, 1984; Nielsen and Andersen 1990, Nielsen et al. 1992; Nielsen and Hultman 1998; Nielsen et al. 1992; Piotrowski et al. 1992; Sin et al. 1983, 1989; Zhang et al. 2017). In mice, on day 14 following a single oral dose of mercuric chloride (1 mg Hg/kg), 40–50% of the residual body burden was in the kidneys, 10–20% in the liver, and 1% the in brain; other tissues retained <1% (Hojbjerg et al. 1992; Nielsen and Andersen 1990, Nielsen et al. 1992). Following repeated exposure of mice to mercuric chloride (2 or 3.7 mg Hg/L in drinking water for 6–12 weeks), mercury levels in the kidneys ranged from 10 to 100 times that of the liver, depending on the mouse strain and sex (Ekstrand et al. 2010; Nielsen and Hultman 1998). In some mouse strains, differences in whole-body retention of mercury has been shown to be associated with increased retention of mercury in the kidneys (Ekstrand et al. 2010; Nielsen 1992; Nielsen and Andersen 1990; Nielsen and Hultman 1998). Within-strain sex differences in whole-body and kidney retention have also been observed in mice, with males showing greater whole-body and kidney retention than females (Ekstrand et al. 2010). Following 14 days of daily gavage dosing of rats with mercuric chloride (2 mg/kg/day), the highest quantifiable concentration of mercury was found in the kidneys and liver, with the concentration in the kidneys approximately 60 times that of the liver (Khan et al. 2001).

Distribution in blood. The distribution of absorbed Hg^{2+} is strongly influenced by the high affinity of Hg^{2+} for the thiolate anion and formation of Hg^{2+} S-conjugates (Carty and Malone 1979). In plasma, the predominant sulfhydryls available to form S-conjugates with Hg^{2+} include albumin (approximately 1 mM) (Brown and Shockley 1982; Ikegaya et al. 2010) and low molecular weight thiols such as glutathione and cysteine (approximately 10 µM) (Lash and Jones 1985). Within cells, Hg^{2+} forms complexes with intracellular thiols, including glutathione, cysteine, glycinyl-cysteine, metallothionein, and RBC hemoglobin (Cherian and Clarkson 1976; Hursh 1985; Kagi et al. 1984; Komsta-Szumska et al. 1976; Magos 1967; Magos et al. 1978; Piotrowski et al. 1974a, 1974b; U.S. Atomic Energy Commission 1961). The Hg^{2+} ion has a strong tendency to form conjugates with two sulfur ligands (e.g., R-S-Hg-S-R′) (Carty and Malone 1979). This distinguishes S-conjugates of inorganic Hg^{2+} from those formed by CH_3Hg^{2+} (CH_3Hg-S-R). In rats that received an injection of mercuric chloride (0.02 or 0.2 mg Hg) approximately half of the mercury in blood was associated with RBCs, and mercury bound to protein in

plasma was associated with albumin and globulins (Cember et al. 1968). In mice administered mercuric chloride, the concentration of Hg^{2+} in plasma was similar to that in whole blood (Sundberg et al. 1998). In workers who were exposed to Hg^0 for varying lengths of time, the RBC/plasma mercury ratio was observed to be approximately 1.3 (Suzuki et al. 1970). This ratio probably reflects the distribution of Hg^{2+} formed from oxidation of absorbed Hg^0.

Distribution in the kidneys. Following a dose of mercuric chloride, absorbed mercury distributes to the renal cortex and outer strip of the outer medulla in association with proximal tubules (Bergstrand et al. 1958; Berlin and Ullberg 1963a, 1963b, 1963c; Hultman and Enestrom 1986; Hultman et al. 1985; Rodier et al. 1988; Zalups and Barfuss 1990). This non-uniform distribution within the kidney is the result of membrane transporters in the proximal tubule that participate in the bi-directional transport of Hg^{2+} (Cannon et al. 2000, 2001; Wei et al. 1999; Zalups and Lash 1997; Zalups and Minor 1995; Zalups et al. 1993). Transporters implicated in the uptake of Hg^{2+} in the mammalian proximal tubule include the organic anion transporter, OAT1, located in the basolateral membrane of the proximal tubule and amino acid transporter system, $b^{0,+}$, located in the luminal membrane (Bridges and Zalups 2005; Bridges et al. 2004; Wei et al. 1999; Zalups and Ahmad 2004; Zalups et al. 2004). Both systems transport sulfhydryl conjugates of Hg^{2+} with the amino acid cysteine (Cys-S-Hg-S-Cys). On the luminal side of the proximal tubule, formation of the cysteine S-conjugate is facilitated by the catabolism of a glutathione S-conjugate (GluGlyCys-S-Hg-S-CysGlyGlu), which is catalyzed by the luminal membrane enzymes, GGT and cysteinylglycinase (Berndt et al. 1985; de Ceaurriz et al. 1994; Tanaka et al. 1990; Tanaka-Kagawa et al. 1993; Zalups 1995; Zalups and Lash 1997). Luminal uptake of Hg^{2+} in the rat has been estimated to be approximately half of total uptake (Zalups and Minor 1995). Within kidney cells, Hg^{2+} forms conjugates with non-protein and protein sulfhydryls, including metallothionein (Cherian and Clarkson 1976; Komsta-Szumska et al. 1976; Piotrowski et al. 1974a, 1974b).

Distribution in the liver. Studies conducted in rodents dosed with mercuric chloride have found higher accumulation in the periportal region of the liver (Berlin and Ullberg 1963a, 1963c). Mercury can distribute to the liver from the systemic circulation by way of the hepatic artery or from the gastrointestinal tract by way of the portal vein. Either route, in addition to transport of mercury into the bile duct, could contribute to higher concentrations in the periportal region. Several mechanisms may contribute to the uptake of mercury into the liver, including endocytosis of Hg^{2+} conjugates with albumin or other proteins in the sinusoidal space, and transport of Hg^{2+} or Hg^{2+} S-conjugates by carriers in the hepatic sinusoidal membrane (Bridges and Zalups 2017). Several transporters in the hepatic sinusoidal

membrane may participate in transfer of Hg^{2+} from the sinusoidal space into hepatocytes; these include organic anion transporter, OAT2, and amino acid transporters (Bridges and Zalups 2017).

Maternal-fetal-infant transfer. Inorganic mercury is found in human cord blood, placenta, and breast milk, indicating potential routes of transfer to the fetus and infant (Ask et al. 2002; Bjornberg et al. 2003, 2005; Ou et al. 2014; Sakamoto et al. 2013; Sandborgh-Englund et al. 2001; Vahter et al. 2000). The appearance of inorganic mercury in fetal or neonatal tissues could represent direct transfer of inorganic mercuric mercury absorbed into the maternal system or could result from transfer of Hg^0 or methylmercury and subsequent oxidation and demethylation, respectively. Studies conducted in rodents dosed with mercuric chloride provide direct evidence of placental and lactational transfer of inorganic mercuric mercury (Dock et al. 1994; Feng et al. 2004; Mansour et al. 1974; Oliveira et al. 2001, 2015; Sundberg et al. 1998, 1999; Suzuki et al. 1967). Mechanisms of placental transfer of inorganic mercuric mercury have not been characterized and may involve transport of Hg^{2+} and Hg^{2+} S-conjugates in the kidneys and other tissues (Bridges and Zalups 2017).

Elimination from tissues. Whole-body retention kinetics of absorbed inorganic mercuric mercury in humans was estimated in a clinical study in which five adult subjects received a single intravenous dose of $^{203}Hg(NO_3)_2$ (0.6–2.8 Hg) (Hall et al. 1995). Although short-term kinetics following intravenous administration of Hg^{2+} may differ from that following the oral route of administration, the terminal half-time can be expected to reflect the elimination kinetics of inorganic mercuric mercury following its initial systemic distribution. The whole-body elimination half-time in the five subjects ranged from 49 to 96 days based on observations made over the period of 13–73 days following dosing. The corresponding blood half-time ranged from 23 to 66 days. Farris et al. (2008) reanalyzed the data from Hall et al. (1995) and reported the whole-body half-time for the interval 21–70 days following dosing; based on the combined data for the five subjects, the whole-body half-time was 75.9 days (range 49–120 days).

Whole-body elimination of mercury following ingestion of mercuric chloride exhibited multiple phases in rodents (Ekstrand et al. 2010; Nielsen and Hultman 1998). Three half-times estimated in four different mouse strains were 1.5–2.5 days for the fast phase, 10–12 days for the second phase, and 44–83 days for the slowest phase, when mice were observed for a period of 10 weeks following a 12-week period of exposure to mercuric chloride in drinking water (3.7 mg Hg/L) (Nielsen and Hultman 1998). Whole-body elimination half-times in four strains of mice were 0.98–2.04 days for the fast phase and 3.97–5.39 days for the slower phase, when measured over a 5-week period following 6 weeks of exposure to mercuric chloride in drinking water (2 mg Hg/L) (Ekstrand et al. 2010). The fast phase of elimination is

due, in part, to excretion of unabsorbed mercury in feces and the slow phase is attributed to elimination from the kidneys and other tissues (Piotrowski et al. 1992). Since the kidneys are the major site of accumulation of mercury following ingestion of inorganic mercuric mercury, the rate of elimination of mercury from the kidneys is the major determinant of the rate of elimination of the absorbed dose.

Inorganic Mercurous Mercury. No studies were located that provide information on the distribution of absorbed inorganic mercurous mercury.

Organic Mercuric Mercury Similar to Hg^{2+}, CH_3Hg^{2+} has a high affinity for the thiolate anion and readily forms CH_3Hg^{2+} S-conjugates with protein and non-protein sulfhydryls (Carty and Malone 1979; see discussion of the distribution and elimination of inorganic mercuric mercury from blood). However, the CH_3Hg^{2+} ion has a strong tendency to form conjugates with a single sulfur ligand (e.g., CH_3Hg-S-R), unlike inorganic Hg^{2+}, which tends to form ligands with two sulfur ligands (R-S-Hg-S-R′) (Carty and Malone 1979). The difference in structure of S-conjugates may explain, at least in part, differences in the toxicokinetics of methylmercury and inorganic mercuric mercury. In particular, the larger oral absorption fraction of methylmercury, greater accumulation of methylmercury in the brain, and greater accumulation of inorganic mercury in the kidneys (Berlin et al. 2015; Bridges and Zalups 2005; Clarkson and Magos 2006).

Whole-body distribution. Studies of postmortem tissue mercury concentrations have revealed a non-uniform distribution of mercury and the methylmercury fraction in tissues (Bjorkman et al. 2007; Magos 1967; Matsuo et al. 1989; Sumino et al. 1975). Most notably, concentrations of methylmercury were highest in the liver (approximately 2–3-fold higher than in other tissues, including the brain, heart, kidneys, and spleen); however, the methylmercury fraction was highest in the brain, heart, and spleen (80%) and lower in the liver (38%) and kidneys (11–16%) (Matsuo et al. 1989). Postmortem measurements of mercury in tissues reflect the combined effects of exposure to inorganic and methylmercury as well as changes to mercury concentrations that may have occurred postmortem. Postmortem measurements of mercury in tissues made after formalin fixation (embalming) are subject to errors from loss of mercury to tissue leakage and demethylation of methylmercury (Matsuo et al. 1989).

In three adult subjects who ingested a single oral dose of ^{203}Hg-labeled methylmercuric nitrate (9 µg Hg), measurements of external radiation indicated that approximately 10% of the body burden was detected in the head region and approximately 50% was in the region of the liver (Aberg et al. 1969). Studies conducted in monkeys and rodents have found that the liver, kidneys, and brain retain the largest fractions

of the absorbed dose following an oral dose of methylmercury, while the highest concentrations occurred in the kidneys (Berlin et al. 1975; Clarkson and Shapiro 1971; Nielsen and Andersen 1991; Nielsen et al. 1992; Rice et al. 1989; Sundberg et al. 1999; Yasutake et al. 1997).

The distribution of absorbed mercury following dosing with methylmercury has been studied in a variety of other mammalian species (Young et al. 2001), including cats (Charbonneau et al. 1976; Hollins et al. 1975), cows (Ansari et al. 1973; Sell and Davison 1975), goats (Sell and Davison 1975), guinea pigs (Iverson et al. 1973), hamsters (Omata et al. 1986), pigs (Gyrd-Hansen 1981), rabbits (Petersson et al. 1991), and sheep (Kostyniak 1983).

Dimethylmercury distributed to the brain, kidneys, and liver following a lethal dose of dimethylmercury resulting from accidental contact of the dorsal surface of a latex gloved hand to liquid dimethylmercury (Nierenberg et al. 1998; Siegler et al. 1999). In mice, absorbed dimethylmercury that was not exhaled distributed to tissues, with highest concentrations in the liver and kidneys (Ostlund 1969). Other sites of retention in mice were adipose tissue, adrenal cortex, brain, Harderian glands, lens of the eyes, intestines, oral mucosa, salivary glands, pituitary, spleen, and hair follicles (Ostlund 1969).

Distribution in blood. Most of the mercury in blood (>90%) following absorption of methylmercury is found in RBCs (Berglund et al. 2005; Kawasaki et al. 1986). Several factors contribute to the accumulation of methylmercury in RBCs. The S-conjugates of methylmercury with cysteine (CH_3Hg-S-Cys) and glutathione (CH_3Hg-S-CysGlyGlu) are substrates for organic anion transporters that facilitated uptake and concentration of methylmercury in the RBC (Wu 1995, 1996, 1997). Methylmercury readily exchanges between sulfhydryl ligands, which allows it to complex with hemoglobin, trapping methylmercury (temporarily) in the RBCs (Carty and Malone 1979; Rabenstein et al. 1982).

Distribution of mercury in blood following ingestion of methylmercury has been studied in several human clinical and occupational studies in which adult subjects ingested a tracer dose of ^{203}Hg-labeled methylmercury, or methylmercury incorporated in fish (Aberg et al. 1969; Birke et al. 1972; Kershaw et al. 1980; Lundgren et al. 1967; Miettinen et al. 1971; Sherlock et al. 1984), or received an intravenous dose of ^{203}Hg-labeled methylmercury (Smith et al. 1994). Following a fish meal (18–20 µg Hg/kg body weight), the concentration of mercury in blood increased above baseline; however, the concentration of inorganic mercury remained unchanged, indicating that the mercury absorbed from the fish meal was predominantly methylmercury (Kershaw et al. 1980). Blood mercury accounted for approximately 5–7% of the absorbed dose (Kershaw et al. 1980; Sherlock et al. 1984; Smith et al. 1994). Within blood, most

of the mercury was located in RBCs (Birke et al. 1972; Kershaw et al. 1980; Lundgren et al. 1967; Miettinen et al. 1971). The RBC/plasma ratio ranged from 17 to 26 and was nearly identical to the ratio for organic mercury, indicating that nearly all of the mercury in the RBC was organic mercury (Kershaw et al. 1980).

Following a lethal dermal dose of dimethylmercury (estimated dose approximately 1344 mg Hg), mercury concentrations in RBCs were approximately10–20-fold higher than concentrations in plasma (Nierenberg et al. 1998).

Distribution in the brain. In monkeys, methylmercury was observed in the cerebral cortex and cerebellum located on the exterior of neurons and glial cells (Berlin et al. 1975; Kawasaki et al. 1986; Rice 1989b). Mercury concentrations in the cerebral cortex and cerebellum ranged from 2 to 7 times that of blood. Rice (1989c) measured regional brain levels of mercury in brains of monkeys 210–260 days following cessation of 800–1,000 days of oral dosing with methylmercury (25 or 50 µg Hg/kg). Mercury was distributed throughout the brain, with highest concentrations found in the hypothalamus and pons. Following exposure to methylmercury, mercury in the brain was found to be associated with protein and as S-conjugates with non-protein sulfhydryls, including glutathione, cysteine, homocysteine, and N-acetylcysteine (Clarkson 1993; Thomas and Smith 1979). Entry of methylmercury into the brain is facilitated by transport of the cysteine S-conjugate (CH_3Hg-S-Cys) by a neutral amino acid transporter (system L) in brain capillary endothelial cells (Aschner and Clarkson 1988, 1989; Aschner et al. 1990, 1991; Bridges and Zalups 2017; Kerper et al. 1992; Mokrzan et al. 1995; Simmons-Willis et al. 2002). The S-cysteine conjugate may be as substrate for system L as a structural analog of methionine (Bridges and Zalups 2017; Kerper et al. 1992; Simmons-Willis et al. 2002).

Autopsy findings 10 months following a lethal dermal dose of dimethylmercury (estimated dose approximately 1,344 mg Hg), showed elevated levels of mercury in the frontal lobe and visual cortex (3.1 µg/g), atrophy of the cerebral cortex and cerebellum, and neuron loss in the visual and auditory cortices (Nierenberg et al. 1998).

Distribution in the kidneys. A large fraction (60–70%) of the mercury found in monkey kidneys following an oral dose of methylmercuric hydroxide (0.8 mg/kg, 0.7 mg Hg/kg) was identified as inorganic mercury (Berlin et al. 1975). Mercury concentrations in the renal cortex of monkeys were approximately 20 times higher than in the blood 210–260 days following cessation of 800–1,000 days of oral dosing (25 or 50 µg Hg/kg) (Rice 1989b). In a study conducted in rats, 40–50% of the mercury

administered as methylmercury (5 mg Hg/kg) was identified in the kidneys as inorganic mercury, whereas <1% of mercury in blood was inorganic (Zalups et al. 1992). In mice, organic mercury in the kidneys has been identified as methylmercury protein complexes and S-conjugates with glutathione and cysteine (Yasutake et al. 1989). This suggests the possibility that renal uptake of absorbed methylmercury may reflect a combination of the renal handling of methylmercury and inorganic mercuric mercury formed from methylmercury in or external to the kidneys. Mercury accumulates in the renal cortex following exposures to methylmercury (Rice 1989b; Zalups et al. 1992). Studies conducted in rats that received doses of methylmercury (5 mg Hg/kg) found the distribution of mercury within the kidneys to be similar to that following a dose of inorganic mercuric mercury, with the highest concentrations in the renal cortex and outer stripe of the outer medulla (Zalups et al. 1992). Uptake of methylmercury into the kidneys is facilitated by transporters in the luminal (system $b^{0,+}$) and basolateral (OAT1) membranes of the proximal tubules that transport S-conjugates of methylmercury with cysteine or homocysteine (Berlin et al. 2015; Bridges and Zalups 2017; Koh et al. 2002; Tanaka et al. 1992; Zalups and Ahmad 2005a, 2005b, 2005c).

Autopsy findings 10 months following a lethal dermal dose of dimethylmercury (estimated dose of approximately 1,344 mg Hg) showed elevated levels of mercury in the renal cortex (34.8 μg/g) (Nierenberg et al. 1998).

In rats that received a subcutaneous dose of phenylmercury (2.95 mg phenylmercuric acetate, 1.76 mg Hg), the inorganic fraction of mercury in the kidneys increased from 41% at 2 hours to 80% at 24 hours after the administered dose (Daniel et al. 1972). Total mercury concentration in the kidneys at 24 hours was 22 μg/g.

Distribution in the liver. A large fraction (70–90%) of the mercury found in monkey liver following an oral dose of methylmercuric hydroxide (0.8 mg/kg, 0.7 mg Hg/kg) was identified as organic mercury (Berlin et al. 1975). This suggests the possibility that hepatic uptake of absorbed methylmercury may reflect a combination of the hepatic handling of methylmercury and inorganic mercuric mercury formed from methylmercury in or external to the liver. Several mechanisms may contribute to the uptake of methylmercury into liver, including endocytosis of S-conjugates with albumin or other proteins in the sinusoidal space, and transport of S-conjugates by carriers in the hepatic sinusoidal membrane (Ballatori and Truong 1995; Berlin et al. 2015; Bridges and Zalups 2017; Thomas and Smith 1982; Wang et al. 2000).

Autopsy findings 10 months following a lethal dermal dose of dimethylmercury (estimated dose of approximately 1,344 mg Hg), showed elevated levels of mercury in the liver (20.1 μg/g) (Nierenberg et al. 1998).

In rats that received a subcutaneous dose of phenylmercury (2.95 mg phenylmercuric acetate, 1.76 mg Hg), the inorganic fraction of mercury in the liver increased from 26% at 2 hours to 76% at 24 hours after the administered dose (Daniel et al. 1972). Total mercury concentration in the liver at 24 hours was 7.4 μg/g.

Maternal-fetal-infant transfer. Methylmercury is found in human cord blood, placenta, and breast milk, indicating potential routes of transfer to the fetus and nursing infant (Ask et al. 2002; Bjornberg et al. 2003, 2005; Iwai-Shimada et al. 2014; Kim et al. 2011; Marques et al. 2013c; Ou et al. 2014; Sakamoto et al. 2018; Stern and Smith 2003; Vahter et al. 2000; Wells et al. 2016). Studies conducted in monkeys and rodents provide direct evidence of placental and lactational transfer of mercury following exposure to methylmercury (Gilbert et al. 1993, 1996; Harry et al. 2004; Hu et al. 2010; Kajiwara et al. 1997; Newland and Reile 1999; Nordenhall et al. 1998; Oliveira et al. 2001, 2017; Oskarsson et al. 1995; Rice 1992; Stern et al. 2001; Sundberg et al. 1991, 1998, 1999). A cross-fostering study conducted in hamsters found that *in utero* transfer of mercury following gestational exposure to methylmercury was approximately 0.9% of the maternal mercury dose (0.32 mg Hg/kg) and lactational transfer was approximately 4.5% of the maternal body burden at the start of nursing (Nordenhall et al. 1998).

Studies conducted in rodents have shown that methylmercury transferred to the fetus distributes to the brain, liver, and kidneys, with the highest concentrations in these tissues observed in the liver (Inouye et al. 1986; Nordenhall et al. 1998; Oliveira et al. 2001; Sundberg et al. 1999). In mice and rats, *in utero* exposure to methylmercury resulted in mercury concentrations in the fetal brain that exceeded concentrations in fetal blood or the maternal brain (Inouye et al. 1986; Stern et al. 2001). In rats following *in utero* exposure to methylmercury, the rank order of mercury concentrations in the fetal brain was cerebrum > cerebellum > hippocampus (Hu et al. 2010). Mechanisms of placental transfer of methylmercury have not been fully characterized; however, a contributing mechanism involves transport of the cysteine S-conjugate, CH_3Hg-S-Cys (Berlin et al. 2015; Bridges and Zalups 2017; Bridges et al. 2012; Kajiwara et al. 1996).

Mercury can be transferred to the fetus following absorption of dimethylmercury. In mice, following an intravenous dose of ^{203}Hg-labeled dimethylmercury, mercury distributed to the fetus, with highest levels detected in the bronchi, nasal and oral mucosa, and lens of the eyes (Ostlund 1969).

Elimination from tissues. A human clinical study measured whole-body mercury for a period of 3 months following an oral dose of ^{203}Hg-labeled methylmercuric nitrate (9 µg Hg). The whole-body half-time ranged from 70.4 to 74.3 days (three adult subjects) (Aberg et al. 1969). The whole-body half-time was estimated to be 134 days (SD 2.7 days, n=7) in monkeys that were monitored for a period of 115 days following an oral dose of 0.8 mg/kg methylmercuric hydroxide (0.7 mg Hg/kg) (Berlin et al. 1975). Whole-body retention kinetics of absorbed methylmercury in humans was estimated in a clinical study in which seven adult subjects received a single intravenous dose of ^{203}Hg-labeled methylmercury (0.6–2.8 Hg) (Smith et al. 1994). Although short-term kinetics following intravenous administration may differ from that following the oral route of administration, the terminal elimination half-time can be expected to reflect the elimination kinetics of mercury following its initial systemic distribution. Whole-body elimination half-time in the seven subjects ranged from 40 to 53 days (geometric mean 42.7±1.2 SD) based on observations made over the period of 10–70 days following dosing. The whole-body elimination half-time corresponded to elimination of 1.6±1.2% of the total mercury body burden per day.

Several clinical studies have estimated blood elimination half-times of mercury following exposure to methylmercury. Elimination of mercury from blood was biphasic; the estimated half-time for the fast phase was 7.6 days (SE 0.8) and 51.9 days (SE 3.7) for the slower phase (Kershaw et al. 1980). The terminal half-time was estimated to be 50 days based on measurements of blood mercury in 20 adult subjects during and following cessation of consumption of mercury in fish (43–233 µg Hg/day) (Sherlock et al. 1984). Terminal-plasma elimination half-times for mercury following ingestion of methylmercury ranged from 47 to 130 days (Birke et al. 1972) and from 99 to 120 days for RBCs (Birke et al. 1972). A human clinical study measured clearances of mercury from the whole body and of total mercury and methylmercury from blood in seven adult subjects following a single intravenous dose of ^{203}Hg-labeled methylmercury (0.6–2.8 Hg) (Smith et al. 1994). Blood was estimated to contain 7.5% of the injected mercury dose, of which >90% was identified as methylmercury. The blood elimination half-time for methylmercury measured from day 10 to day 70 following the dose, ranged from 32 to 60 days (seven adult subjects; geometric mean 44.8±1.2 days) and was nearly identical to the whole-body mercury elimination half-time (43.7±1.2 days). A study conducted in monkeys estimated the elimination half-time to be 49.1 days (SD 2.8) for mercury in blood monitored for a period of 115 days following an oral dose

of methylmercury (0.8 mg/kg, 0.7 mg Hg/kg) (Berlin et al. 1975). Similar to humans, the RBC/plasma mercury concentration ratio in monkeys was approximately 20 (Berlin et al. 1975).

A population study estimated blood half-times for methylmercury in 125 pregnant women (Albert et al. (2010). Scalp and whole hair mercury levels were measured at weeks 12 and 32 of pregnancy. Dietary mercury intakes were estimated in each subject from a food frequency questionnaire with seafood items paired to a national (France) database on methylmercury content of foods (Verger et al. 2007). The following one-compartment model was solved to estimate blood half-time:

$$MeHg_b = \frac{d \cdot t_{1/2} \cdot Abs \cdot f_b \cdot w}{\ln(2) \cdot V_b}$$

where *d* is the daily dietary intake (μg/kg body weight/day), $t_{1/2}$ is the blood methylmercury half-time (day), *Abs* is the gastrointestinal absorption fraction, f_b is the fraction of methylmercury body burden in blood in the blood, *w* is the body weight (kg), and V_b is the blood volume (L). Values for parameters were assigned prior distributions based on various sources (Albert et al. 2010) and posterior distributions were estimated in Markov Chain Monte Carlo simulations. When estimated assuming a point estimate for the population dietary intake, the mean half-time was 65.4 days (SD 6.0; 95% CI 54, 78). When interindividual variability in dietary mercury intake was included in the estimation of the half-time, the population mean half-time was 103 days (SD 9.5; 95% CI 83, 121).

Jo et al. (2015) used a similar approach to estimate half-times in 304 adults who were randomly selected from blood mercury quartiles of the Korean Research Project on Integrated Exposure Assessment to Hazardous Materials for Food Safety (KRIEFS) cohort (Jo et al. 2015). Values for parameters were assigned prior distributions (based on Albert et al. 2010; Stern 1997) and posterior distributions were estimated in Markov Chain Monte Carlo simulations. The estimated population mean half-time (n=304) was 80.2 days (2.5^{th}–97.5^{th} percentile range: 64.0–97.4 days). The estimated mean half-time for males (n=167) was 81.6 days (range 66.0–98.8 days); for females (n=137), the estimated mean half-time was 78.9 days (range 62.8–96.4 days).

In monkeys, elimination of mercury from blood following oral doses of methylmercury was biphasic (Rice 1989a, 1989b; Rice et al. 1989). Terminal blood mercury half-times in monkeys ranged from 10 to 15 days when followed for a period of 50 days following a single dose of 50 or 500 g Hg/kg as methylmercury. With repeated dosing of 10, 20, or 50 g Hg/kg/day, time to 95% of blood mercury steady

state was estimated to range from 76 to 103 days. In monkeys followed for a period of 210–260 days following cessation of 800–1,000 days of oral dosing with methylmercury (25 or 50 µg Hg/kg), the estimated blood mercury half-time ranged from 9 to 17 days (9 monkeys) and the mean was 14 days. Estimated elimination half-times for the brain ranged from 38 to 79 days (nine monkeys) and were substantially greater than estimated half-times for blood, which ranged from 9 to 14 days (Rice 1989b).

Elimination of mercury from blood was measured following a lethal dermal dose of dimethylmercury (estimated dose of approximately 1,344 mg Hg) (Nierenberg et al. 1998). Measurements began approximately 170 days following the exposure and continued for a period of 95 days. The estimated elimination half-times were 33 days in whole blood, 37 days in RBCs, and 29 days in plasma. In mice, the whole-body elimination half-time was estimated to be 70 days when measured over a 25-day period following an inhaled dose of dimethylmercury (from 4–5 to 9 Hg/kg) and 95 days following an intravenous dose (12–15 mg Hg/kg) (Ostlund 1969).

3.1.3 Metabolism

Elemental Mercury. Absorbed Hg^0 is rapidly oxidized to mercuric mercury (Hg^{2+}) in tissues. Oxidation removes Hg^0 from blood and limits its distribution to other tissues and elimination in exhaled air. Oxidation occurs in the brain, RBCs, lungs, liver, and other tissues (Clarkson 1989; Dencker et al. 1983; Hursh et al. 1980; Magos et al. 1978; Satoh et al. 1981). The major oxidative pathway for Hg^0 is catalyzed by the enzyme, catalase (Halbach and Clarkson 1978; Hursh et al. 1980; Nielsen-Kudsk 1973; Magos et al. 1978). Metabolism of Hg^0 through the catalase pathway is saturable, in part, due to limitations in availability of intracellular hydrogen peroxide (Magos et al. 1989; Nielsen-Kudsk 1973). Saturation of metabolism in RBCs alters the distribution of absorbed Hg^0, increasing its distribution to extravascular tissues (Magos et al. 1989).

Inorganic Mercuric Mercury. Exhaled Hg^0 was observed in mice following parenteral doses of mercuric chloride, suggesting that Hg^{2+} had been reduced to Hg^0 (Clarkson and Rothstein 1964; Dunn et al. 1978). The mechanism for reduction of Hg^{2+} in mammalian tissues has not characterized and may be non-enzymatic or of bacterial origin. A Hg^{2+} reductase is found in various forms of bacteria (Boyd and Barkay 2012; Fox and Walsh 1982). Salivary and gastrointestinal bacteria have been shown to methylate Hg^{2+}; however, the quantitative significance of methylation in the disposition of absorbed Hg^{2+} remains uncertain (Barregard et al. 1994b; Li et al. 2019; Rowland et al. 1975a, 1975b).

Inorganic Mercurous Mercury. No studies were located that provide information on the metabolism of absorbed inorganic mercurous mercury. The low pH and high chloride concentration of the gastric environment favor oxidation of ingested Hg^{1} to Hg^{2+} (Mousavi 2015; Nikolaychuk 2016).

Organic Mercuric Mercury. Studies conducted in humans and in a variety of other mammalian species have observed methylmercury and inorganic mercury in tissues and excreta following exposure to methylmercury (Berlin et al. 1975; Farris et al. 1993; Havarinasab et al. 2007; Iverson and Hierlihy 1974; Norseth 1971; Norseth and Clarkson 1970; Oliveira et al. 1998; Smith et al. 1994; Zorn and Smith 1989). In rats that received a single oral dose of ^{203}Hg-labeled methylmercury (4.5 µg Hg), 69% of the administered dose was demethylated over a 98-day observation period (Farris et al. 1993). Gastro-intestinal bacteria are a major contributor to demethylation and degrade ingested methylmercury as well as absorbed methylmercury that is secreted into the small intestine (Caito et al. 2018; Farris et al. 1993; Li et al. 2019; Norseth and Clarkson 1970). Demethylation also occurs in the liver, phagocytes, brain, and other tissues (Charleston et al. 1995; Nagano et al. 2010; Shapiro and Chan 2008; Suda et al. 1992, 1993; Uchikawa et al. 2016; Vahter et al. 1995; Yasutake and Hirayama 2001). In the liver, demethylation occurs in the microsomal fraction catalyzed by NADPH-cytochrome P-450 reductase and by other free radical driven mechanisms (Suda and Hirayama 1992). Salivary and gastrointestinal flora can methylate Hg^{2+}; however, the quantitative significance of this pathway to net methylmercury production remains uncertain (Barregard et al. 1994b; Li et al. 2019). Methylmercury can react with hydrogen sulfide and hydrogen persulfide produced by gastrointestinal tract bacteria to form thiol complexes of methylmercury (Seki et al. 2021).

Dimethylmercury has been shown to be demethylated in mice. Following inhalation or intravenous exposure to ^{203}Hg-labled dimethylmercury (20 mg Hg/kg), mercury retained in the kidneys and liver 24 hours following exposure was identified as methylmercury, while mercury excreted in exhaled air was identified as dimethylmercury (Ostlund 1969).

A study conducted in rats showed that following a subcutaneous dose of phenylmercury (2.95 mg phenylmercuric acetate, 1.76 mg Hg), approximately 80–90% of the mercury excreted (bile, urine, feces) and retained in the kidneys and liver was inorganic mercury (Daniel et al. 1972). The time for conversion to inorganic mercury was approximately 1 day, based on measurements of the inorganic fraction in excreta and tissues. In the kidneys and liver, the inorganic fraction increased during the first day after dosing to 80 and 76% in the kidneys and liver, respectively (Daniel et al. 1972). Phenylmercury was

demethylated in the soluble fraction of rat liver homogenates, in a reaction that did not require NADPH or NADH (Daniel et al. 1972).

3.1.4 Excretion

Elemental Mercury. The major routes of excretion of absorbed Hg^0 are excretion of unmetabolized Hg^0 in exhaled air and urinary and fecal excretion of mercuric Hg^{2+} following oxidation of Hg^0 in blood and other tissues. A more detailed discussion of the excretion of mercuric mercury is present in the section on mercuric compounds. Mercury has also been detected in sweat following exposure to Hg^0 (Bjorkman et al. 1997; Lovejoy et al. 1973; Sunderman 1978). Mercury excretion following inhalation of Hg^0 has been measured in several clinical studies conducted in adults (Cherian et al. 1978; Hursh et al. 1976, 1980; Sandborgh-Englund et al. 1998; Teisinger and Fiserova-Bergerova 1965). Exhaled air was the dominant excretion pathway shortly after inhalation of Hg^0 vapor and accounted for approximately 10% of the inhaled dose (Cherian et al. 1978; Hursh et al. 1976, 1980; Sandborgh-Englund et al. 1998). Over a 7-day observation period following a 14–24-minute inhalation exposure to Hg^0 vapor (1 mg Hg/m^3), 7% of the initially retained dose was exhaled, 2.4% (range 1.9, 2.5%, n=5 adults) was excreted in urine, and 9.2% (range 7.7=11.9%) was excreted in feces (Cherian et al. 1978). When monitored over longer periods that exceed the time for excretion of Hg^0 vapor in exhaled air, a larger fraction of the inhaled dose is excreted in urine (Sandborgh-Englund et al. 1998). This later phase represents mercury (primarily inorganic mercuric mercury) excreted from blood, kidneys, and other tissues. In a study that monitored subjects for 30 days postexposure (0.4 mg Hg/m^3 for 15 minutes), 7.5–12% (n=9 adults) of the inhaled dose was exhaled during the first 3 days following dosing and approximately 1% was excreted in urine, whereas 13% (range 8–40%) was excreted in urine over the 30-day observation period (Sandborgh-Englund et al. 1998). Based on the data from the Sandborgh-Englund et al. (1998) study, Jonsson et al. (1999) estimated that, over a period of 1 year, 14% of the initially retained dose of inhaled Hg^0 vapor would be exhaled and 55% would be excreted in urine.

Half-times for decline in urinary excretion of mercury following inhalation of Hg^0 vapor have been measured in human clinical studies and in workers exposed to Hg^0 vapor (Barregard et al. 1992, 1996; Harari et al. 2012; Jonsson et al. 1999; Sallsten et al. 1994). Jonsson et al. (1999) estimated the urinary excretion half-time to be 63.1 days (range 12.8–98.9 days; eight adult subjects) over a 30-day period following a 15-minute exposure to 0.4 mg Hg/m^3 Hg^0 vapor (data from Sandborgh-Englund et al. 1998). These estimates are consistent with half-times estimated in chloralkali workers (range 10–210 days) who were exposed to Hg^0 vapor (Barregard et al. 1992, 1996; Sallsten et al. 1994). The half-time for decrease

in urinary mercury following a decrease in exposure to Hg^0 vapor varied with genotype of the enzyme glutamate-cysteine ligase modifier subunit (GCLM-588). The half-time was estimated to be 77 days for the CC genotype and 34 days for the CT/TT genotype (Harari et al. 2012).

Fecal excretion of mercury following inhalation of Hg^0 vapor has been observed in human clinical studies and in rats (Hayes and Rothstein 1962; Hursh et al. 1980). In a human clinical study, cumulative excretion over a 7-day period following exposure to Hg^0 vapor (range 0.06–0.08 mg Hg/m^3, n=2 adult subjects) was approximately 4% in urine and 11% in feces (Hursh et al. 1980). In rats, fecal excretion was the dominant excretory pathway during the first 6 days following exposure (6% of body burden per day); however, some of fecal excretion may have derived from ingestion of mercury that adhered to the body surface following whole-body exposure (Hayes and Rothstein 1962). After 6 days, fecal and urinary excretion occurred at similar rates (approximately 0.7–1% of the body burden per day).

Based on human clinical studies and animal studies, fecal and urinary excretion are dominant long-term routes of excretion and elimination of mercury absorbed following inhalation of Hg^0 vapor (Barregard et al. 1992, 1996; Hayes and Rothstein 1962; Hursh et al. 1980; Jonsson et al. 1999; Sallsten et al. 1994; Sandborgh-Englund et al. 1998). Therefore, long-term kinetics of the body burden (e.g., terminal half-time) provide estimates of the combined rates of excretion in feces and urine. The terminal whole-body half-time has been measured in humans and rodents (Hayes and Rothstein 1962; Hursh et al. 1976). The half-time in humans was estimated to be 58 days (range 35–90 days, n=5 adult subjects) when assessed over a period that ranged from 9 to 48 days (Hursh et al. 1976). This value is close to the terminal half-time estimated for the decline in urinary mercury after an exposure to Hg^0 vapor (Jonsson et al. 1999). In rats, the terminal whole-body half-time was estimated to be 15–24 days when assessed over a period of 1–16 days (Hayes and Rothstein 1962).

Inorganic Mercuric Mercury. Absorbed inorganic mercuric mercury is excreted in feces and urine. In a clinical study in which five adult subjects received a single intravenous dose of $^{203}Hg(NO_3)_2$ (0.6–2.8 Hg), fecal excretion measured over a 70-day period following dosing ranged from 18 to 38% of the administered dose and urinary excretion ranged from 6 to 35% of the dose (Hall et al. 1995). Farris et al. (2008) reanalyzed the data from Hall et al. (1995) and, based on the combined data for the five subjects, estimated that approximately 30% of the dose was excreted in feces and 25% was excreted in urine. In humans, absorbed mercury is also excreted in sweat (Genuis et al. 2011; Robinson and Skelly 1983; Sears et al. 2012) and saliva (Bjorkman et al. 1997; Joselow et al. 1968). Studies conducted in rodents have found that mercury absorbed following an oral dosing with mercuric chloride is excreted in feces and

urine (Morcillo and Santamaria 1995). In rats, mercury has been observed in salivary and lacrimal glands following exposure to mercuric chloride (Warfvinge et al. 1994b). Absorbed inorganic mercuric mercury is not appreciably accumulated in hair (Berglund et al. 2005; George et al. 2010; Yasutake and Hachiya 2006).

Excretion following inhalation. Following an accidental inhalation exposure to ^{203}HgO, urinary excretion was estimated to account for elimination of all absorbed mercury (Newton and Fry 1978). Following nose-only exposures of dogs to aerosols of mercuric oxide (^{203}HgO, 5 mg/m^3, count median diameter 0.16 µm), mercury was excreted in feces and urine. The fecal/urine ratio ranged from 0.06 on the first day following exposure to 0.3 on day 5 of exposure (Morrow et al. 1964).

Excretion following ingestion. Rahola et al. (1972, 1973) measured mercury excretion in adult subjects following ingestion of a single tracer dose of $^{203}Hg(NO_3)_2$ (6 µg) mercury in drinking water (two subjects) or mixed with calf liver paste (eight subjects). Immediately after dosing and during the absorption phase, feces was the dominant route of excretion of mercury. Within 5 days following dosing, the rate of fecal excretion declined to be similar to the rate of urinary excretion (0.05–0.15% of the administered dose per day). At 50 days following the administered dose, fecal and urinary excretion were each approximately 0.02% of the administered dose per day. Fecal mercury observed following an oral dose of inorganic mercuric mercury results from a combination of unabsorbed and absorbed mercury.

Mechanisms of fecal and urinary excretion. Studies conducted in rodents have shown that fecal excretion of absorbed inorganic mercuric mercury derives from secretion from the liver into bile as well as secretion from blood across the gastrointestinal epithelium (Ballatori and Clarkson 1984, 1985; Sugawara et al. 1998; Zalups 1998; Zalups et al. 1999). Secretion into bile is dependent on intracellular glutathione, suggesting that mercury may be transported in the liver as a Hg^{2+} S-conjugate of glutathione (Ballatori and Clarkson 1984, 1985). Several transporters in the bile canalicular membrane may participate in the transfer of Hg^{2+} from hepatocytes into bile; these include multidrug resistance proteins, MDR1, MRP2, and MRP3; and the breast cancer resistant protein, BCRP (Bridges and Zalups 2017).

Studies conducted in rodents and mammalian kidney cell cultures have shown that several processes in the kidneys contribute to excretion of inorganic mercuric mercury in urine. These include glomerular filtration of Hg^{2+} S-conjugates (e.g., albumin cysteine, glutathione), transport of Hg^{2+} S-conjugates (e.g., Cys-Hg-Cys) out of the tubular fluid into proximal tubule cells, and transport of Hg^{2+} S-conjugates (e.g., Cys-Hg-Cys) from peritubular blood into proximal tubule cells (Berlin et al. 2015). The relative

contributions of these three processes may vary with dose and other factors that may affect such variables as binding of Hg^{2+} to plasma proteins, glomerular sieving of protein, levels of intra- and extracellular glutathione and metallothionein in proximal tubule cells, and presence of other non-physiological ligands that can form transportable S-conjugates with Hg^{2+} (Berlin et al. 2015; Zalups 2000; Zalups and Bridges 2012). Net secretion of Hg^{2+} from blood to urine has been shown to be mediated by the multidrug resistance protein, MRP2 (Bridges et al. 2011, 2013).

Organic Mercuric Mercury. Following a dose of methylmercury, the major routes of excretion of mercury are feces, urine, and hair (Berlin et al. 1975; Cernichiari et al. 1995; Farris et al. 1993; Johnsson et al. 2005; Kawasaki et al. 1986; Kershaw et al. 1980; Mottet et al. 1987; Nordenhall et al. 1988; Smith et al. 1994; Yaginuma-Sakurai et al. 2012). Most of the mercury excreted in feces and urine is inorganic mercury, while the dominant form in hair is organic mercury (Berlin et al. 1975; Caito et al. 2018; Cernichiari et al. 1995; Farris et al. 1993; Giovanoli-Jakubczak et al. 1974; George et al. 2010; Ishihara 2000; Norseth and Clarkson 1970; Rothenberg et al. 2016b; Smith et al. 1994). A human clinical study measured excretion of mercury in seven adult subjects following a single intravenous dose of ^{203}Hg-labled methylmercury (0.6–2.8 Hg) (Smith et al. 1994). During the 70-day observation period, 31% of the dose was excreted in feces and 4% was excreted in urine. A study conducted in monkeys found that 85 days following a single oral dose of methylmercury (0.8 mg/kg, 0.7 mg Hg/kg), approximately 70% of the initial body burden remained in the body, of which 50% of the total body burden was in hair (Berlin et al. 1975). In rats, 98 days following a single oral dose of methylmercury (4.5 µg Hg), 90% of the remaining body burden (12% of the dose) was associated with hair (Farris et al. 1993).

Methylmercury is secreted from the liver into bile and transported into the gastrointestinal tract, where it can be reabsorbed into the blood or demethylated and excreted in feces as inorganic mercuric mercury (Ballatori and Clarkson 1984; Dutczak and Ballatori 1994; Dutczak et al. 1991). Biliary secretion of methylmercury is dependent on glutathione and metabolism of glutathione by the enzyme, GGT (Ballatori and Clarkson 1982, 1985; Omata et al. 1978; Refsvik 1983; Refsvik and Norseth 1975). In rats, development of biliary secretion of methylmercury occurs at age 2–4 weeks, in association with the development of biliary secretion of glutathione (Ballatori and Clarkson 1982). Inhibition of (or absence of) hepatic GGT disrupts biliary secretion of methylmercury and accelerates excretion of methylmercury in urine (Ballatori et al. 1998). Secretion of methylmercury is thought to involve the following processes: formation of an S-conjugate of methylmercury with glutathione (CH_3Hg-S-CysGlyGlu), metabolism of the CH_3Hg-S-CysGlyGlu by GGT, and transport of CH_3Hg S-Cys or CH_3Hg-S-CysGlyGlu across the canalicular membrane (Dutczak and Ballatori 1994; Wang et al. 2000). CH_3Hg-Cys in bile can be

reabsorbed in the gall bladder or small intestine (Dutczak and Ballatori 1992; Dutczak et al. 1991). Demethylation of methylmercury by intestinal bacteria contributes to the excretion of inorganic mercuric mercury in feces (Farris et al. 1993; Li et al. 2019; Norseth and Clarkson 1970).

Most of the mercury excreted in urine following absorption of methylmercury is inorganic mercury (Berlin et al. 1975; Farris et al. 1993; Smith et al. 1994). Urinary excretion of methylmercury is limited by a resorptive pathway for methylmercury in the proximal tubule facilitated by metabolism of the S-conjugate of glutathione (CH_3Hg-S-CysGlyGlu) and reabsorptive transport of the S-conjugate of cysteine (CH_3Hg-S-Cys). Inhibition of GGT increases urinary excretion of glutathione and methylmercury (Berndt et al. 1985; Gregus et al. 1987; Mulder and Kostyniak 1985a, 1985b; Tanaka et al. 1992; Tanaka-Kagawa et al. 1993; Yasutake et al. 1989).

In a case of dimethylmercury poisoning, mercury was excreted in urine following dermal absorption of dimethylmercury (Nierenberg et al. 1998). In mice, respiratory exhalation was the major route of excretion of mercury following an intravenous injection of radiolabeled ^{203}Hg-labeled dimethylmercury and accounted for approximately 65% of the dose (1.3 µg Hg) (Ostlund 1969). Following inhalation of ^{203}Hg-labeled dimethylmercury (20 mg/kg) in mice, all exhaled mercury was identified as dimethylmercury (Ostlund 1969).

Methylmercury enters hair follicles and is incorporated into hair during keratinization and remains associated with hair as the hair strand grows (Cernichiari et al. 2007; Shi et al. 1990; Zareba et al. 2008). Mercury in hair collected from women in a marine fish-eating population was shown to be predominantly CH_3Hg-S-Cys (80% of total mercury) and inorganic Hg^{2+} S-conjugates (20%) (George et al. 2010). A study of hair mercury in a sample for a general population found that >90% of the mercury in hair was organic mercury (Berglund et al. 2005). Following exposures to methylmercury, hair mercury concentrations exceed that of blood and approach a steady-state ratio of 200–400 (Clarkson et al. 1988; Yaginuma-Sakurai et al. 2012). Hair appears to uptake mercury corresponding to methylmercury blood concentrations at the time of hair keratinization. As a result, the kinetics of accumulation and elimination of mercury in hair is similar to that of methylmercury in blood (Clarkson et al. 1988; Yaginuma-Sakurai et al. 2012). Interspecies variability in uptake of methylmercury into hair has been observed (Farris et al. 1993; Kawasaki et al. 1986; Mottet et al. 1987). The hair/blood ratio is lower in monkeys compared to humans (Kawasaki et al. 1986; Mottet et al. 1987). Species differences may arise from several different variables including cysteine content of keratins and hair growth patterns and rates (Mottet et al. 1987).

Mercury levels in hair were measured following a lethal dermal dose of dimethylmercury (estimated dose of approximately 1,344 mg Hg) (Nierenberg et al. 1998). Sequential analysis of mercury in a single hair strand provided a time series of hair mercury concentrations. Levels of mercury became elevated after approximately 17 days following exposure and reached the highest observed level (1,100 μg/g) at approximately 40 days following exposure; the half-time to peak hair level was 5.6 days. Based on the declining phase of hair mercury (40–170 days), the elimination half-time was estimated to have been 75 days.

Following exposure to phenylmercury, absorbed mercury is eliminated in bile, feces, urine, and hair (Daniel et al. 1972; Gotelli et al. 1985). Phenylmercury was detected in hair of infants exposed to phenylmercury that had been applied to cloth diapers as a fungicide (Gotelli et al. 1985). More than 90% of the mercury excreted in urine in the exposed infants was inorganic mercury. In rats that received a subcutaneous dose of phenylmercury (2.95 mg phenylmercuric acetate, 1.76 mg Hg), 13% of the administered mercury dose was excreted in urine and 52% was excreted in feces over an 8-day observation period (Daniel et al. 1972). Approximately 80% of the mercury in urine or bile was inorganic mercury.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

Several pharmacokinetics models of inorganic mercury have been published (Abass et al. 2018; Farris et al. 2008; Jonsson et al. 1999; Leggett et al. 2001). Of these, three models were developed to predict the absorption and distribution of inhaled mercury vapor (Jonsson et al. 1999; Leggett et al. 2001; Pierrehumbert et al. 2002) and one model (Abass et al. 2018) includes an absorption fraction for Hg^0 and simulates the kinetics of absorbed Hg^0 as inorganic mercury using the Farris et al. (2008) model. Pharmacokinetic models of methylmercury have been developed for humans (Byczkowski and Lipscomb

2001; Carrier et al. 2001a; Gearhart et al. 1995; Young et al. 2001) and a variety of other animal species (Carrier et al. 2001b; Farris et al. 1993; Young et al. 2001).

Farris et al. 2008 Model

Farris et al. (2008) developed a model to simulate the pharmacokinetics of intravenously injected inorganic mercuric mercury. The model includes a mobile compartment that receives the intravenous dose and an immobile compartment that exchanges mercury with the mobile compartment. Exchange between compartments is governed by first-order rate coefficients (day^{-1}). Both compartments contribute to excretion of mercury in feces and urine (day^{-1}). The model was calibrated with data on fecal and urinary mercury excretion measured over a period of 70 days in five adult subjects who received intravenous injections of tracer amounts of $^{203}Hg(NO_3)_2$ (0.6–2.8 µg Hg) (Hall et al. 1995). The model was then evaluated for predicting whole body burden measured in the same study. The model predicted observed kinetics and cumulative fecal excretion (approximately 30% of the administered dose) and urinary excretion of mercury (approximately 25% of the administered dose) when parameters were fit to the individual subject data on fecal and urinary mercury. The model also predicted the observed whole-body elimination kinetics for each subject. Terminal elimination half-times for the five subjects ranged from 56 to 120 days, based on data for days 21–70 following the dose. When data for individual subjects were averaged, the terminal half-time was estimated to be 75.9 days.

The Farris et al. (2008) model was incorporated into a model for simulating pharmacokinetics of inorganic and organic mercury (Abass et al. 2018; Carrier et al. 2001a, 2001b). The Abass et al. (2018) model included a blood compartment for inorganic mercury, which transferred absorbed mercury (from food and mercury amalgams) to tissues with a half-time of 2 days. The absorption fractions used in the model were 0.8 for inhaled Hg^0 and 0.15 for inorganic mercury in food.

Jonsson et al. 1999 Model

Jonsson et al. (1999) developed a model to simulate the pharmacokinetics of inhaled Hg^0 vapor in humans. The model includes compartments representing the respiratory tract, a central distributing compartment in equilibrium with blood plasma, kidney (referred to as the excretion depot), and a lumped peripheral tissue compartment representing mercury in all other tissues. Transfers of mercury between compartments are governed by first-order rate coefficients (k, day^{-1}) and deposition fractions (f). Values for these parameters are presented in Jonsson et al. (1999).

Inhaled mercury deposits in the respiratory compartment and is removed from the respiratory tract by absorption and exhalation. Mercury in the central compartment exchanges with mercury in the peripheral compartment and is eliminated by direct transfer to urine, transfer to kidney and then to urine, or to a lumped elimination compartment representing other elimination pathways. Total clearance from the central compartment was estimated to be 0.123 L/day/kg body weight. The ratio of the rate coefficients for exchange between the central and peripheral compartments leads to a steady state in which the amount of mercury in the peripheral compartment is approximately 20 times the amount in the central compartment.

Total transfer from the central compartment to excretory pathways is apportioned approximately as follows: transfer to kidney (60%), direct transfer to urine (3%), and transfer to other excretory pathways (37%). The model predicts that over a period of 1 year following an acute exposure to Hg^0 vapor, 14% of the initially retained inhaled mercury dose is lost to exhaled air (half-time 1.81 days) while 55% is excreted in urine (half-time 63.2 days). The remining portion, 31%, is retained in tissues or eliminated by other pathways (Jonsson et al. 1999).

The model was calibrated using data collected in a clinical study in which eight adult subjects inhaled Hg^0 (0.4 mg Hg/m^3) for a single 15-minute period and mercury levels in plasma and urine were measured over a period of 30–35 days (Sandborgh-Englund et al. 1998). The calibrated model was evaluated against observations of urinary mercury excretion in two clinical studies of acute-duration inhalation exposures to Hg^0 vapor (Cherian et al. 1978; Hursh et al. 1980). Simulations of the Cherian et al. (1978) study (0.1 mg Hg/m^3 for 14–24 minutes) predicted a daily rate of mercury excretion of approximately 0.5%/day from days 2 to 12 post-exposure compared to observed rates which ranged from approximately 0.2 to 0.45%. The model predicted cumulative urinary mercury excretion to be approximately 3.5% of the dose 7 days post-exposure compared to observations that ranged from 1.9 to 3% (n=4 subjects). Simulations of the Hursh et al. (1980) study predicted cumulative excretion of approximately 5% of the dose at day 10 post-exposure, compared to observations that ranged from approximately 3.6 to 4.2% (n=2 subjects).

Leggett et al. 2001 (ICRP 1980) Model

Leggett et al. (2001) developed a respiratory tract model for depositions and absorption of inhaled Hg^0 in humans. The respiratory tract model was developed to predict absorbed doses from inhalation as inputs to the International Commission on Radiological Protection (ICRP) Human Respiratory Tract Model

(HRTM, ICRP 1994) and a systemic biokinetics model for inorganic mercury (ICRP 1980). The generic ICRP HRTM model simulates transport and absorption of inhaled particles or vapors deposited in regions of the respiratory tract. The model simulates surface transport (e.g., mucociliary) and sequestration into tissues.

The Leggett et al. (2001) model assumes that 80% of inhaled Hg^0 is deposited in the respiratory tract with the following apportionments: 2% to the extrathoracic region, 1% to the bronchial region, 2% to the bronchiolar region, and 75% to the alveolar-interstitial region. Absorption to blood is governed by three first-order rate coefficients (day^{-1}) that simulate a slower phase of absorption from all regions and a faster phase of absorption from the alveolar-interstitial region. The alveolar-interstitial pathway absorbs 70% of total deposition with a half-time of approximately 1 minute. Of the remaining mercury in all regions, 80% is absorbed with a half-time of 8 hours and 20% with a half-time of 5 days.

In the systemic model, mercury absorbed from the respiratory tract is transferred to a central compartment, which distributes 8% of the mercury in the central compartment to the kidney and 92% to a lumped compartment representing all other tissues (ICRP 1980). Mercury is eliminated from both the kidney and other tissue compartments at the same rates: 95% is eliminated with a half-time of 40 days and 5% with a half-time of 10,000 days.

The model was developed based on the results of human clinical studies in which adult subjects were exposed acutely to Hg^0 vapor (Cherian et al. 1978; Hursh et al. 1976, 1980; Nielsen-Kudsk 1965a, 1965b; Sandborgh-Englund et al. 1998; Teisinger and Fiserova-Bergerova 1965). The model was evaluated against data on retention of mercury in the respiratory tract following exposures to Hg^0 vapor in humans (Hursh et al. 1976), monkeys (Berlin et al. 1969b; Khayat and Dencker 1984), and rodents (Berlin et al. 1966, 1969a, 1969b; Hayes and Rothstein 1962; Hursh et al. 1980; Khayat and Dencker 1984; Magos 1967; Nordberg and Serenius 1969). The model predicted the observed temporal pattern of elimination over a period of 30 days following acute-duration exposure in which approximately 70% of mercury initially deposited in the respiratory tract was absorbed within minutes of exposure and, of the remaining 30%, 80% was absorbed with a half-time of 8 hours and 20% was absorbed with a half-time of 5 days (Leggett et al. 2001).

Pierrehumbert et al. 2002 Model

Pierrehumbert et al. (2002) developed a model to simulate the pharmacokinetics of inorganic mercury absorbed from inhalation of Hg^0 vapor in humans. The model is a modification of a generic model for simulating the pharmacokinetics of several other chemicals (lead, phenol, inorganic mercury, toluene). The model includes compartments representing a central distributing compartment in equilibrium with blood and kidney. Transfers of mercury between compartments are governed by compartment blood flows, partition coefficients, and permeability coefficients. Values for these parameters are presented in Pierrehumbert et al. (2002).

Although Pierrehumbert et al. (2002) describes parameters governing alveolar absorption and excretion (alveolar ventilation, blood/air partition coefficients), values for the blood/air partition coefficient for mercury are not reported; therefore, it is not clear how the alveolar exchange of mercury is actually represented in the model. Two pathways of excretion are simulated. Excretion in urine occurs from the kidney compartment and is governed by a first-order rate constant ($minute^{-1}$). Biliary excretion is represented as first-order transfer from the central compartment.

Pierrehumbert et al. (2002) do not report or cite evaluations of the mercury model against observations made in humans. Berthet et al. (2010) applied the Pierrehumbert et al. (2002) model to predict blood urinary mercury levels for hypothetical workweek exposures and compared the results to American Conference of Governmental Industrial Hygienists (ACGIH) Biological Exposure Indices (BEI) corresponding to the same workweek exposure assumptions. The predicted levels were similar to the BEIs.

Farris et al. 1993 Model

Farris et al. (1993) developed a PBPK model for simulating the kinetics of methylmercury in rats. The model includes compartments for blood, brain, gastrointestinal tract, liver, kidney, skin, hair, and a lumped compartment representing all other tissues (carcass). Growth is simulated as a time-dependent increase in compartment volumes (expressed in units of g), governed by a rate coefficient ($minute^{-1}$). The model simulates the disposition of absorbed methylmercury as well as inorganic mercury formed from demethylation in the liver and lumen of the gastrointestinal tract. Transfers of mercury between blood and tissue compartments are governed by first-order clearance coefficients (mL/minute/g tissue) and the concentration gradients between systemic blood and tissue blood, where the tissue blood concentrations

are calculated as the ratio of the tissue concentration and tissue/blood concentration equilibrium ratios (*R*).

The gastrointestinal tract has two compartments representing lumen and tissue. Absorption of methylmercury and inorganic mercury are simulated as direct transfers from gastrointestinal tissue to the liver and exchanges between gastrointestinal tissue and blood. Methylmercury is assumed to undergo bidirectional transfer between gastrointestinal tissue and the gastrointestinal lumen, with transfer governed by a first-order clearance coefficient (mL/minute/g tissue) and concentration gradient between systemic blood and tissue blood, where the tissue blood concentration is calculated as the ratio of the tissue concentration and a lumen/tissue concentration equilibrium ratio. The gastrointestinal lumen also receives methylmercury from the oral dose, methylmercury and inorganic mercury from bile, and inorganic mercury from demethylation of methylmercury in the gastrointestinal lumen. Demethylation in the gastrointestinal lumen is assumed to occur in regions of the gastrointestinal tract distal to the site of absorption and is not reabsorbed. Unabsorbed methylmercury and inorganic mercury are cleared to feces at a rate governed by a fecal flow rate (mL/minute/g lumen).

Flows of methylmercury and inorganic mercury in the liver compartment include exchange with blood, transfer from gastrointestinal tissue, transfer to bile, and demethylation in the liver. Biliary transfers of methylmercury and inorganic mercury are governed by clearance coefficients (mL/minute/g tissue) and the biliary clearance of non-protein sulfhydryls (Ballatori and Clarkson 1985). Flows of methylmercury and inorganic mercury in the kidney compartment include exchange with blood and transfer to urine. Two pathways for urinary excretion are simulated representing “filtration clearance” and “exfoliation of renal tubular cells.” The exfoliation pathway is governed by the kidney concentration, urine flow rate mL/minute/g kidney and a urine/kidney equilibrium concentration ratio. The filtration pathway applies only to inorganic mercury and is governed by the inorganic mercury concentration in the kidneys and a filtration clearance term (mL blood/minute/g kidney).

The model includes a skin compartment, which exchanges methylmercury and inorganic mercury with blood and through which methylmercury and inorganic mercury can be transferred to hair. Skin-to-hair transfer is governed by a clearance coefficient (mL/minute/g skin). Mercury is assumed to be retained in hair until the hair is shed. Hair shedding is represented as a first-order elimination rate constant ($minute^{-1}$). Hair mercury is assumed to be partially ingested during fur grooming in rats at a rate also governed by a rate coefficient ($minute^{-1}$).

The model was developed and calibrated to simulate results from a study in which adult rats were administered a single oral dose of ^{203}Hg-labeled methylmercuric chloride (4.5 µg, approximately 14.9 µg Hg/kg) and monitored for methylmercury and inorganic mercury in tissue, feces, and urine; and mercury in hair and skin for a period of 98 days (Farris et al. 1993). Comparisons of observed and predicted mercury levels are reported in figures with no statistical evaluation of model fit to the observations. Based on the figures, the models simulated the observed levels (percent dose/g) and rates of decline of methylmercury and inorganic mercury in the blood, brain, kidney, and liver, as well as the distinct differences between kinetics of methylmercury and inorganic mercury in these tissues. For example, levels of inorganic mercury in the kidney peaked 28 days after the time of peak levels of methylmercury (day 1) and, by day 98, levels of inorganic mercury exceeded that of methylmercury in the kidney. The model also predicted the observed pattern of cumulative fecal and urinary excretion of methylmercury and inorganic mercury in which inorganic mercury was the dominant form of mercury in feces (65% of dose) compared to methylmercury (15% of dose), whereas urine was a relatively minor excretory route, accounting for approximately 4% of the dose (methylmercury 3.5%, inorganic mercury 1%). The model predicted the observed levels of mercury in hair as approximately 1–2% of the dose/g hair, with little attenuation during the 98-day observation period.

Carrier et al. 2001 Model

Carrier et al. (2001a, 2001b) developed a PBPK model for simulating the kinetics of methylmercury in rats and humans. The model includes compartments for blood, brain, gastrointestinal tract, kidney, liver, hair, and a lumped compartment representing all other tissues. The model is structured as two submodels, which simulate the disposition of absorbed organic mercury and inorganic mercury formed from demethylation.

The organic mercury model simulates whole-body elimination of organic mercury as the sum of the elimination rates for fecal and urinary excretion, transfer to hair, and demethylation, with each elimination pathway governed by a first-order rate coefficient (day^{-1}). Organic mercury in tissue compartments is apportioned from whole-body organic mercury based on proportionality constants (tissue/blood) for each tissue. The gastrointestinal tract compartment receives organic mercury from the ingested dose as well as from organic mercury in hair ingested during fur grooming (rat model only). Absorption of organic mercury is simulated as a direct transfer from gastrointestinal tissue to whole body governed by a rate coefficient (day^{-1}). Demethylation of inorganic mercury is assumed to occur in the liver and brain.

The inorganic mercury submodel simulates the disposition of inorganic mercury formed in the brain and liver from organic mercury transferred to these compartments from blood (passed to the inorganic mercury submodel). Transfers of organic mercury to the brain and blood are governed by rate coefficients (day^{-1}) that combine rates for transfer and demethylation. Bi-directional exchanges of inorganic mercury between blood and tissues are governed by rate coefficients (day^{-1}). Hair receives inorganic mercury from blood and loses inorganic mercury to feces, representing ingestion of hair during fur grooming (i.e., ingested hair inorganic mercury is not absorbed). Excretion of inorganic mercury in feces includes direct transfer from blood, transfer from liver representing biliary transfer, and transfer from hair (rodent only), each governed by rate coefficients (day^{-1}). Urinary excretion of inorganic mercury includes direct transfer from blood and transfer from the kidney compartment, both governed by rate coefficients (day^{-1}). Mass balance between the organic mercury and inorganic mercury submodels is achieved by setting the transfer rate coefficients to ensure that the blood-to-brain and blood-to-liver mass transfers for inorganic mercury equal the rate of demethylation of whole-body organic mercury.

The model was developed and calibrated to simulate results from a study in which adult rats were administered a single oral dose of ^{203}Hg-labeled methylmercuric chloride (4.5 µg, approximately 14.9 µg Hg/kg) and monitored for methylmercury and inorganic mercury in tissue, feces, and urine; and total mercury in hair and skin for a period of 98 days (Farris et al. 1993). Comparisons of observed and predicted mercury levels are reported in figures with no statistical evaluation of model fit to the observations. Based on the figures, the models simulated the observed levels (percent dose/g) and rates of decline of methylmercury and inorganic mercury in the blood, brain, kidney, and liver, as well as the distinct differences between kinetics of methylmercury and inorganic mercury in these tissues. The model also predicted the observed pattern of cumulative fecal and urinary excretion of methylmercury and inorganic mercury in which inorganic mercury was the dominant form of mercury in feces (65% of dose) compared to methylmercury (15% of dose), whereas urine was a relatively minor excretory route, accounting for approximately 4% of the dose (methylmercury 3.5%, inorganic mercury 1%). The model predicted the observed levels of mercury in hair, approximately 1–2% of the dose/g hair, with little attenuation during the 98-day observation period.

The rat model was evaluated by comparing predictions to observations made in studies conducted in rats that were not used in model development (Norseth and Clarkson 1970; Thomas et al. 1986). In the Norseth and Clarkson (1970) study, rats received single intravenous doses of 1 mg of mercury as ^{203}Hg-labeled methylmercury and were monitored for a period of 60 days. In the Thomas et al. (1986) study,

rats received a single subcutaneous dose of 0.2 mg Hg/kg as ^{203}Hg-labeled methylmercury and were monitored for a period of 98 days. Comparisons of observed and predicted mercury levels are reported in figures with no statistical evaluation of model fit to the observations. Based on the figures, the model predicted the observed patterns of elimination of total mercury (percent of dose) in the blood, brain, kidney, and liver, and the cumulative excretion in feces, urine, and hair, observed in both studies.

The human model was developed by adjusting transfer coefficients (Carrier et al. 2001b). The model was calibrated to simulate results from a study conducted in which three adult subjects ingest a single oral dose of ^{203}Hg-labeled methylmercury (9 µg Hg) and whole body ^{203}Hg and ^{203}Hg in blood urine and feces were measured over a period of 3 months (Aberg et al. 1969). The calibrated model was evaluated by comparing predictions to observations made in studies conducted in humans that were not used in model development (Birke et al. 1972; Kershaw et al. 1980; Miettinen et al. 1971; Sherlock et al. 1984; Smith et al. 1994). In the Birke et al. (1972) study, 26 adults consumed fish meals for doses of 5–800 µg mercury as methylmercury.

Total mercury and organic mercury were measured in blood. Mercury was measured before and following switching to a diet having a lower mercury level. In the Kershaw et al. (1980) study, six adults consumed a meal of fish (6–10 µg Hg/g fish) for an oral mercury dose of 18–20 µg Hg/kg body weight, and total mercury and organic mercury in blood were measured for a period of 160 days following the meal. In the Miettinen et al. (1971) study, 15 adults consumed a meal of fish that had been fed ^{202}Hg-labeled methylmercury for an oral dose of 22 µg mercury and ^{203}Hg in whole body and blood were measured periodically over a period of 28 weeks.

In the Sherlock et al. (1984) study, 20 adults consumed fish periodically for a period of 96 days for an average oral dose that ranged from 43 to 233 µg Hg/day. In the Smith et al. (1994) study, seven adults received a single intravenous dose of ^{203}Hg-labeled methylmercury (0.6–2.8 Hg) and whole-body retention kinetics of absorbed methylmercury in humans was measured for a period of 70 days. Comparisons of observed and predicted mercury levels are reported in figures with no statistical evaluation of model fit to the observations. Based on the figures, the model predicted the observed patterns of whole body and blood retention of mercury observed in all of the above studies. The model predicted the observed buildup of total mercury blood concentration during a 3-month period of fish ingestion and the elimination kinetics in the subjects following cession of fish meals that ranged from 43 to 223 µg Hg/day (Sherlock et al. 1984).

Gosselin et al. (2006) applied the Carrier et al. (2001b) model to reconstruct methylmercury intakes from measurements of hair mercury in high fish and marine mammal consumers in the Inuvik region of Canada and the Amazonian River Basin. Reconstructed methylmercury intakes in the Inuvik population (mean 0.03±0.05 SD μg/kg/day) were lower than intakes estimated from food questionnaires (0.20±0.35 μg/kg/day). Blood mercury-time profiles predicted with the model from hair mercury-time profiles agreed with observed blood mercury levels.

Reconstructed methylmercury intakes for two Amazonian subjects ranged from approximately 0.5 to 1.4 μg/kg/day and were substantially higher than the intakes reconstructed for the Inuvik population. Noisel et al. (2011) applied the Carrier et al. (2001b) model to reconstruct methylmercury intakes from measurements of hair mercury in fishermen in northern Quebec. Reconstructed methylmercury intakes (mean 0.07 μg/kg/day, range 0–0.26 μg/kg/day) were lower than intakes estimated from food questionnaires (0.43 μg/kg/day, range 0.09–2.78 μg/kg/day).

Abass et al. (2018) combined the Carrier et al. (2001b) human model with a model of inorganic mercury (Farris et al. 2008) to estimate dietary mercury intakes corresponding to mercury blood concentrations and methylmercury/inorganic mercury ratios from the diet measured in a Norwegian food consumption survey (Jenssen et al. 2012). The correlation was 0.38 between dietary mercury intakes predicted from the PBPK model (median 0.043 μg Hg/kg/day) and the food consumption survey (median 0.050 μg Hg/kg/day). Residuals for estimates of dietary intake from the PBPK model indicated the model provided estimates that tended to be higher than the estimates from the food consumption survey, particularly at ages >40 years.

Gearhart et al. 1995 Model

Gearhart et al. (1995; Clewell et al. 1999) developed a PBPK model to simulate maternal-fetal transfer of methylmercury in humans. The Clewell et al. (1999) model is the same as the Gearhart et al. (1995) human model, with parameter values representing U.S. women (age 14–45 years) derived from an analysis of NHANES (1988–1994). Population parameter values for the model were subsequently re-estimated for U.S. women ages 16–49 years based on Bayesian analysis of NHANES (1999–2000) and data on dietary intake of methylmercury in the U.S. population for the same population stratum (Allen et al. 2007; Carrington and Bolger 2002). The PBPK model has been applied to human methylmercury dosimetry (Allen et al. 2007; Clewell et al. 1999; Gearhart et al. 1995; Lee et al. 2017b; Shipp et al. 2000).

The PBPK model includes maternal compartments for blood (with plasma and RBC compartments), brain, fat, intestine, kidney, liver, placenta, hair, and lumped compartments representing all other rapidly and slowly-perfused tissues. The fetal model includes compartments for plasma, RBCs, brain, and a lumped compartment representing all other fetal tissues (fetal body). The model simulates demethylation of methylmercury in the brain, intestine, and liver as elimination pathways; disposition of the inorganic mercury produced from demethylation is not simulated.

Exchanges between plasma and all tissues are either flow- or diffusion-limited. Flow-limited exchanges are governed by tissue plasma flows (L/hour), the tissue-plasma partition coefficient, and the concentration gradient for methylmercury between plasma and tissue. Diffusion-limited exchanges are governed by first-order plasma-tissue diffusion coefficients (L/hour), tissue-plasma concentration gradients, and tissue/plasma partition coefficients. Exchanges between plasma and all tissues except RBCs and the brain are flow-limited. The diffusion-limited (L/hour) RBC-plasma model results in a steady state of approximately 88% of blood mercury residing in RBCs and a plasma/RBC concentration ratio of approximately 0.08. Approximately 6% of the post-absorption mercury body burden resides in whole blood.

Maternal model. Methylmercury enters brain tissue by diffusion (L/hour) from brain blood, which receives methylmercury from central plasma by flow-limited exchange. Mercury in the brain has several possible fates: conversion of methylmercury to inorganic mercury (L/hour); incorporation of inorganic mercury in brain tissue (L/hour); and loss of incorporated inorganic mercury from brain (L/hour). Incorporated inorganic mercury can be lost from the brain; however, it cannot become unincorporated. As a result, incorporated inorganic mercury that is lost from the brain is lost from systemic distribution (e.g., it is not returned to central plasma), and its fate is not described in the model.

Exchanges of methylmercury between the liver and central plasma are flow-limited. Methylmercury in the liver has two potential fates: biliary secretion into the intestine (L/hour) or conversion to inorganic mercury (L/hour). Demethylation in the liver serves solely as an elimination pathway for methylmercury in the model. The fate of the inorganic mercury produced in the liver is not simulated. Exchanges of methylmercury between the kidneys and central plasma are flow-limited.

Exchanges of methylmercury between plasma and all other tissues (fat, richly perfused, slowly perfused) are flow-limited. Urinary excretion of methylmercury is simulated as clearance from central plasma

(L/hour). The default value for the clearance coefficient is zero, representing typical conditions in which methylmercury makes a negligible contribution to urinary mercury.

Elimination pathways for methylmercury from the maternal system include: (1) fecal excretion of unabsorbed or biliary methylmercury and inorganic mercury produced in the intestine; (2) demethylation of methylmercury in the brain and liver; (3) transfer of methylmercury to hair; (4) transfer of methylmercury from plasma to urine (nominally set to zero); (5) transfer of methylmercury to the fetus; and (6) transfer to breast milk. The demethylation and urinary pathways were described previously in Section 3.1.1, in the discussions of absorption in the brain, kidneys, and liver. Conversion of methylmercury to mercury is simulated in the brain and liver with rate coefficients ($hour^{-1}$). All demethylation not occurring in the brain is attributed to the liver.

There are no atomic/molecular weight conversions in the model so the rate coefficients account for the mass fraction of mercury in methylmercury. Methylmercury enters hair from the slowly perfused tissue compartment (which includes skin). The transfer is assumed to be diffusion-limited and governed by a clearance coefficient (L/hour), concentration of methylmercury in slowly perfused venous plasma, and a hair/blood partition coefficient. Appearance of methylmercury in hair is subject to a time delay (day), representing the time for between-exposure of the hair follicle and appearance of hair on the body surface. The nominal delay is set to 7 days. The model also includes a first-order elimination pathway for methylmercury in hair (L/hour), representing loss from hair to the environment. Methylmercury lost from hair is lost from the systemic distribution. The nominal value for the clearance rate from hair is set equal to the clearance rate from slowly perfused tissue to hair.

Pregnancy-fetal model. The duration of pregnancy is nominally set to 270 days. Pregnancy initiates growth of the placenta and fetus, and expansion of the maternal blood volume by approximately 50%. Exchange of methylmercury between maternal plasma and the placenta is flow-limited, with plasma flow to the placenta scaled to the growing placenta volume (L).

The fetal model includes compartments representing central plasma, RBCs, and a lumped compartment representing all other fetal tissues. Volumes of these compartments scale with the fetal blood volume, which scales with fetal volume (L). Entry of methylmercury into the fetus is from the placenta to fetal central plasma. Transfer to fetal plasma is diffusion limited and governed by a clearance coefficient (L/hour) and the concentration gradient between placenta and fetus.

Similar to the maternal model, exchange between fetal plasma and RBCs is diffusion-limited (L/hour). The fetal brain compartment is simpler than the maternal model and includes only a single compartment. Exchanges of methylmercury between plasma and brain, and between plasma and the lumped other fetal tissue (body) compartment, are flow-limited.

The model was calibrated with data from studies conducted in monkeys (Kawasaki et al. 1986; Rice et al. 1989) and humans (Birke et al. 1972; Sherlock et al. 1984). In the Kawasaki et al. (1986) study, monkeys received oral doses of methylmercury (10, 30, or 100 µg Hg/kg/day) for periods ranging from 18 to 54 months. In the Rice et al. (1989) study, monkeys received oral doses of methylmercury (10, 25, or 50 µg Hg/day, 3 days/week) for a period of 35–100 weeks. The model predicted the observed buildup to steady state of blood methylmercury observed in the Rice et al. (1989) study and the buildup of hair mercury observed in the Kawasaki et al. (1986) study. The model predicted the buildup and decline in blood methylmercury levels observed in adults who consumed fish periodically for a period of 96 days for an average oral dose that ranged from 43 to 233 µg Hg/day (Sherlock et al. 1984), and the decline in methylmercury concentrations in plasma, RBCs, and hair in an adult following cessation of consumption of methylmercury in fish (2.14 µg Hg/kg/day) (Birke et al. 1972).

Byczkowski and Lipscomb 2001 Model

Byczkowski and Lipscomb (2001) extended the Gearhart (1995; Clewell et al. 1999) model to include parameters for simulation of lactational transfer of methylmercury to a nursing human infant. The lactation model simulates transfer of methylmercury into breast milk, transfer to the nursing infant, and biokinetics of methylmercury in the infant. Transfer of methylmercury into breast milk begins on the day of conception. The model can be run with or without a nursing infant. Transfer to breast milk is flow-limited, with plasma flow to breast tissue being a fraction (10%) of flow to rapidly perfused tissue, and a breast/plasma partition coefficient of 0.172. Production of breast milk is an exponential function of infant body weight. Milk consumption by the infant is a fraction of total milk production (nominally set to 1).

The infant model includes compartments representing plasma, RBCs, brain, kidney, gastrointestinal tract, and other tissues (body). Infant growth is simulated using the same body weight growth algorithm applied to the maternal model, with separate parameters for F0 and F1 generations, allowing maternal and infant growth to be independently controlled. Weight at conception can be set to represent the fetal volume at the end conception. Infant tissue plasma flows and volumes are scaled from maternal values to

infant volume (L), which is scaled to infant body weight (kg). Methylmercury ingested in breast milk is absorbed from the gastrointestinal tract directly to fetal plasma ($hour^{-1}$). Similar to the maternal model, exchange between infant plasma and RBCs is diffusion-limited (L/hour). The infant brain model is identical to the maternal model, with: (1) flow-limited transfer of methylmercury from infant plasma to brain plasma; (2) diffusion-limited transfer of methylmercury from brain plasma to brain tissue (L/day); (3) first-order conversion of methylmercury to inorganic mercury (day^{-1}); and (4) first-order loss of incorporated mercury (day^{-1}). The infant kidney model is identical to the maternal model with flow-limited exchange between methylmercury in plasma and the kidney. As in the maternal model, urinary excretion of methylmercury in the infant is represented as clearance from plasma (L/day). The default value for the clearance coefficient is zero, representing typical conditions in which methylmercury makes a negligible contribution to urinary mercury. Exchanges of methylmercury between the lumped other tissue compartment and plasma are flow-limited.

Elimination pathways for methylmercury from the infant include: (1) fecal excretion of unabsorbed or biliary methylmercury; (2) demethylation of methylmercury in the brain; (3) transfer of methylmercury to hair; and (4) transfer of methylmercury from plasma to urine (nominally set to zero). The infant hair model is identical to the maternal hair model. The start of infant hair growth is specified by the number of days following birth when hair growth begins, which is nominally set to the day of birth. Methylmercury enters hair from the slowly perfused tissue compartment (which includes skin). The transfer is assumed to be diffusion-limited and governed by a clearance coefficient (L/hour), the concentration of methylmercury in slowly perfused venous plasma and a hair/blood partition coefficient. Appearance of methylmercury in hair is subject to a time delay (nominal value 7 days), representing the time between exposure of the hair follicle and appearance of hair on the body surface. The model also includes a first-order elimination pathway for methylmercury in hair (L/hour), representing fugitive loss. The nominal value for the clearance rate is set equal to the clearance rate from tissue to hair.

The model was initially calibrated with data from studies conducted in rodents (Oskarsson et al. 1995; Sundberg et al. 1991); however, comparisons to observation made in these studies are not reported in Byczkowski and Lipscomb (2001). The model was evaluated by comparing predictions with observations from studies of mother-infant pairs following exposures to methylmercury (Amin-Zaki et al. 1976; Fujita and Takabatake 1977). The Amin-Zaki et al. (1976) study measured methylmercury in maternal hair, breast milk, and infant blood following an outbreak of poisonings in Iraq related to consumption of methylmercury in grain. The estimated intake was 0.12 mg methylmercury/kg/day for a period of 4 months during lactation. The model predicted the observed buildup and decline of

methylmercury in hair during and following the exposure period as well as the observed decline in breast milk and infant blood levels (Amin-Zaki et al. 1976). The model also predicted concentrations of total mercury in maternal blood, hair, and breast milk, and infant blood and hair, within 1 SD of observations in a group of 34 mother-infant pairs (Fujita and Takabatake 1977).

Ou et al. 2018 Model

Ou et al. (2018) extended the Byczkowski and Lipscomb (2001) model to include additional compartments in the fetal and infant models. The fetal and infant models were expanded to include compartments representing placenta, plasma, RBCs, brain, fat, kidney, liver, slowly and richly perfused tissues, and hair. Infant growth rates were derived from data on Chinese children. Tissue volumes of infants were assigned values based on Bjorkman (2004). Other compartments and exchanges are identical to Byczkowski and Lipscomb (2001) and Gearhart et al. (1995). Exchanges between plasma and all tissues are either flow- or diffusion-limited. Flow-limited exchanges are governed by tissue plasma flows (L/hour), the tissue-plasma partition coefficient, and the concentration gradient for methylmercury between plasma and tissue venous plasma. Diffusion-limited exchanges are governed by first-order plasma-tissue diffusion coefficients (L/hour), tissue-plasma concentration gradients, and tissue/plasma partition coefficients. Exchanges between plasma and all tissues except RBCs and the brain are flow-limited.

Elimination pathways for methylmercury from the maternal system include: (1) fecal excretion of unabsorbed or biliary methylmercury and inorganic mercury produced in the intestine; (2) demethylation of methylmercury in the brain and liver; (3) transfer of methylmercury to hair; (4) transfer of methylmercury from plasma to urine; (5) transfer of methylmercury to the placenta and fetus; and (6) transfer of methylmercury to breast milk. Conversion of methylmercury to mercury is simulated in the brain and liver with clearance coefficients (L/hour). Disposition of the inorganic mercury produced from demethylation is not simulated. Methylmercury enters hair from the slowly perfused tissue compartment (which includes skin). The transfer is assumed to be diffusion-limited and governed by a clearance coefficient (L/hour), concentration of methylmercury in slowly perfused venous plasma, and a hair/blood partition coefficient. The model also includes a first-order elimination pathway for methylmercury in hair (L/hour), representing loss from hair to the environment. Methylmercury lost from hair is lost from the systemic distribution.

The lactation model simulates transfer of methylmercury into breast milk, transfer to the nursing infant, and biokinetics of methylmercury in the infant. Transfer of methylmercury into breast milk begins on the day of conception. Transfer to breast milk is flow-limited, governed by plasma flow to breast tissue, a breast/plasma partition coefficient. The plasma flow to breast tissue was assigned a value that was 7% of cardiac output. The breast/plasma partition coefficient varied with time during lactation, reflecting time-dependency of breast milk protein content. Production of breast milk is an exponential function of infant body weight. Milk consumption by the infant is dependent on age.

The model was evaluated with data on methylmercury levels in infant hair, maternal hair, cord blood, and maternal venous blood collected from 40 pregnancies (Ou et al. 2018). The maternal model was assigned inputs to agree with measured levels of methylmercury in maternal hair and venous blood. These inputs were then used to simulate the pregnancy and lactation periods. Predicted methylmercury levels in breast milk and infant hair were compared to observations. The model predicted observations made during the first 3 months of lactation. At later times during lactation (days 90–400) predictions diverged from observations to a greater extent.

Pope and Rand 2021 Model

Pope and Rand (2021) developed a PBPK model for simulating the kinetics of methylmercury in humans. The structure of the model was similar to the Gearhart et al. (1995; Clewell et al. 1999) model without the maternal-fetal transfer compartments. The PBPK model includes compartments for blood (with plasma and RBC compartments), brain, fat, intestine, kidney, liver, hair, and lumped compartments representing all other rapidly and slowly perfused tissues. The model simulates demethylation of methylmercury in the intestine and liver as elimination pathways; disposition of the inorganic mercury produced from demethylation is not simulated. Exchanges between plasma and all tissues are flow-limited governed by tissue plasma flows (L/hour), the tissue-plasma partition coefficient, and the concentration gradient for methylmercury between plasma and tissue venous plasma. Within blood, exchanges between RBCs and plasma are first order and governed by rate coefficients ($hour^{-1}$). Transfers between the intestinal lumen and intestinal tissue are also governed by first-order rate coefficients ($hour^{-1}$). Transfers to bile, feces, and hair are governed by first-order clearance coefficients (L/hour). Demethylation activity is assigned to the intestinal lumen and liver, the latter representing all other sites of demethylation. The rate of demethylation is first-order, with the rate coefficients in the liver being 0.0125 of the rate in the intestinal lumen.

The model was calibrated by adjusting methylmercury transfer coefficients to observations of hair mercury elimination kinetics measured in two adult subjects who repeatedly ingested fish meals (Caito et al. 2018). The parameters that were adjusted included the rate coefficient for demethylation in the intestinal lumen, rate coefficients for exchange of methylmercury between intestinal lumen and intestinal tissue, and clearance coefficients for biliary transfer, fecal excretion, and transfer from plasma to hair. The model was independently calibrated to observations made in two subjects. The calibrated model predicted hair mercury elimination half-times of 40.1 days in a female subject and 51.8 days in a male subject. The corresponding half-times derived from the observations made on the same subjects were 45 and 44 days, respectively (Caito et al. 2018).

The calibrated model was then used to simulate blood methylmercury concentrations corresponding to various exposure scenarios. The model predicted blood methylmercury elimination half-times of 46.9 days in an adult man, 38.9 days in an adult female, and 31.5 days in a child. A simulation of elimination of methylmercury during a 50-day period following a single oral dose administered to an adult female predicted that 73% would be demethylated in the intestinal lumen, 13% would be eliminated in hair, 9% would be demethylated in other tissues, and 6% would be eliminated in feces. The contribution of hair as an elimination pathway for methylmercury was predicted to be higher (18%) in children.

Young et al. 2001 Model

Young et al. (2001) developed a PBPK model for simulating the kinetics of methylmercury in humans and 11 other animal species (cat, cow, goat, guinea pig, hamster, monkey, mouse, pig, rabbit, rat, and sheep). The methylmercury model provides methylmercury parameter values and species-specific physiological parameters for a generic model for simulating maternal and fetal kinetics of a parent chemical and metabolite in humans and rats (Luecke et al. 1994, 1997). The generic model includes 24 maternal tissue compartments and 17 fetal tissue compartments. The Young et al. (2001) model includes only the maternal compartments. Transfers between plasma and tissues are governed by tissue plasma flow; the concentration difference between tissue plasma and plasma, where the tissue plasma concentrations are calculated as the ratio of the tissue concentration and tissue/plasma concentration equilibrium ratios (referred to as binding constants); and a diffusion constant that represents the fraction of arterial-plasma concentration equilibrium achieved in the tissue. Transfers are flow-limited if the diffusion constant is 1 and diffusion-limited if the constant is <1. Methylmercury parameters for the various animal species are not reported in Young et al. (2001); however, diffusion-limit transfers of both

methylmercury and inorganic mercury are discussed. Demethylation of methylmercury to inorganic mercury is assumed to occur in the liver and is governed by a first-order rate coefficient ($time^{-1}$). The excretion pathways for methylmercury and inorganic mercury are not described in Young et al. (2001), although based on Luecke et al. (1994), the model simulates transfer from the liver to the gastrointestinal tract (biliary) and transfer from the kidney to elimination. Young et al. (2001) refer to elimination rates constants for the liver and kidney and note that the methylmercury model does not simulate reabsorption of mercury transferred to the gastrointestinal tract, as it was not needed to predict observations of blood and tissue mercury kinetics. Young et al. (2001) do not discuss transfer to hair or demethylation in the gastrointestinal tract.

Models were fit to observations of blood and tissue mercury levels by applying allometric scaling derived from regression analysis of body weight and scaled parameter values estimated in mice, rats, monkeys, and humans. Values for other species were interpolated. The allometrically scaled parameters included the demethylation rate constant, elimination rate constants for methylmercury and inorganic mercury, and binding tissue/blood coefficients for methylmercury and inorganic mercury in the brain, kidney, and liver. In some cases, rates for specific species were not included in deriving allometric scaling factors if the species was considered to be an outlier (e.g., tissue/blood coefficients for the brain, kidney, and liver in rats). Comparisons of predicted and observed blood and tissue levels of methylmercury and inorganic mercury are presented in Figures 1 through 11 of Young et al. (2001); quantitative estimates of goodness of fit were not reported. Based on the Figures 1 through 11 of Young et al. (2001), the model predicted the temporal patterns of blood and tissue methylmercury, inorganic mercury, and total mercury (depending on data available from the study) in all species evaluated. Data from the studies of the various animal species are described in Young et al. (2001) and included humans (Sherlock et al. 1984), cats (Charbonneau et al. 1976; Hollins et al. 1975), cows (Ansari et al. 1973; Sell and Davison 1975), goats (Sell and Davison 1975), guinea pigs (Iverson et al. 1973), hamsters (Omata et al. 1986), pigs (Gyrd-Hansen 1981), rabbits (Petersson et al. 1991), and sheep (Kostyniak 1983).

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to mercury compounds are discussed in Section 5.7, Populations with Potentially High Exposures.

Age. Children and older adults (≥65 years of age) are likely to have increased susceptibility to mercury compared to younger adults as it is generally accepted that developing and aging systems are more susceptible than mature, but not yet declining, systems. As reviewed in Section 3.1.2 (Distribution), mercury that crosses the placenta is distributed to the fetus, and nursing neonates may also be exposed to mercury in breast milk. Epidemiological studies show that umbilical cord BHg and maternal mercury biomarkers measured during gestation or at parturition (reflective of neonatal mercury exposure) are associated with adverse health outcomes during childhood, including decrements in neurological function (reviewed in Chapter 2). Outbreaks of severe neurodevelopmental effects occurred in association with maternal ingestion of methylmercury in seafood (congenital Minamata disease) and from ingestion of wheat contaminated with a methylmercury fungicide (Iraq outbreak). The vulnerability of the developing nervous system to mercury is supported with abundant evidence of animal studies (reviewed in Chapter 2). Differences in elimination kinetics may also contribute to differences in susceptibility of children and adults (Pope and Rand 2021).

Regarding older adults, it is well-established that physiological functions (e.g., renal, neurological) decline with age. Thus, populations with age-related compromises in physiological function would be anticipated to be more susceptible to mercury than younger populations.

Nutritional Status. As discussed in Section 3.4 (Interactions with other Chemicals), interactions of mercury with selenium, selenocysteine, and selenoenzymes are thought to be important mechanisms by which inorganic mercuric and methylmercury exert cellular toxicity (see Section 2.21 General Mechanisms of Action). These interactions provide mechanisms for possible associations between susceptibility to mercury toxicity and selenium nutritional status. Mercury can displace copper and zinc from binding sites on metallothionein (and other metalloproteins) and induce the synthesis of

metallothionine (see Section 2.21 General Mechanisms of Action). These interactions provide mechanisms for possible associations between susceptibility to mercury toxicity and copper and zinc nutritional status.

Pre-existing Conditions, Diseases, and Exposure to Other Substances. Epidemiological and animal studies have identified neurological and renal systems as the most sensitive targets for all forms of mercury. Therefore, it is assumed that any condition or disease that compromises physiological function of these organ systems could increase susceptibility to mercury toxicity. Examples of underlying conditions include individuals with compromised renal function (e.g., glomerular nephritis) and atypical neurological function (e.g., cerebral palsy). Studies in laboratory animals have also identified cardiovascular, hematological, immunological, reproductive, and developmental effect as targets for mercury; thus, underlying diseases or compromised function of these systems may increase susceptibility to mercury toxicity. Increased sensitivity to mercury may also occur due to use of alcohol, tobacco, or any other substance that causes deficits in physiological function. Available information on toxic actions provides support for possible synergism between co-exposure to PCBs and methylmercury in disrupting regulation of brain levels of dopamine that may influence neurological function and development (ATSDR 2004). Mercury induces the synthesis of metallothionine (see Section 2.21 General Mechanisms of Action). This may provide mechanisms for potential toxicologic interactions between mercury and other metals that bind to and induce synthesis of metallothionine such as cadmium and lead.

Genetic Polymorphisms. Numerous genetic polymorphisms that may alter susceptibility to mercury through altered toxicokinetics (e.g., absorption, distribution, and retention of mercury) or toxicodynamics (e.g., effects) have been identified. The most well-studied polymorphisms are glutathione-associated genes and genes associated with mercury transport and elimination. Several other polymorphisms that may alter susceptibility to mercury have been identified, although little data are available. Unless otherwise indicated, information below was obtained from reviews by Andreoli and Sprovieri (2017), Basu et al. (2014), and Gundacker et al. (2010).

Glutamate cysteine ligase (GCL) and glutathione S-transferases (GST). Glutathione is an intracellular scavenger of oxidants and electrophiles, and glutathione conjugation is an important detoxification pathway for mercury. GCL is an enzyme involved in glutathione synthesis, it is encoded by two polymorphic genes (GCLC, GCLM), while glutathione transferases, which catalyze glutathione conjugation, are encoded by several other genes (GSTM1, GSTT1, GSTA1, GSTP1). Genetic alterations in glutathione-related genes could result in altered detoxification and elimination of mercury. Studies in

humans indicate that some GCL and GST genetic variants are associated with increased biomarkers of mercury exposure (blood, plasma, or hair mercury levels), while others are associated with decreased biomarkers of mercury exposure. For example, the half-time for decrease in urinary mercury following a decrease in exposure to Hg^0 vapor varied with genotype of GCLM-588; 77 days for the CC genotype and 34 days for the CT/TT genotype (Harari et al. 2012). Specific findings included increased risk of low birth weight in mercury-exposed mothers with GSTT1 and/or GSTM1 deletions, increased retention of mercury in the umbilical cord with a minor GCLC allele, and increased risk of myocardial infarction in mercury-exposed individuals with a specific GCLM variant.

L Amino Acid Transporters (LAT). LAT1 and LAT2, encoded by human polymorphic genes, SLC7A5 and SLC7A8, respectively, actively transport mercury across cell membranes. Genetic alterations in SLC7 genes could result in altered uptake of mercury. However, no significant differences in blood mercury levels were observed in individuals with different SLC7A5 phenotypes (Parajuli et al. 2018).

Organic anion transporters (OAT). Members of the OAT family are responsible for proximal tubular uptake of mercury in the kidney. Limited genetic and functional diversity of the gene encoding OAT1 (SLC22A6) indicate that it may not contribute substantially to interindividual differences in renal elimination of mercury. In contrast, the gene encoding OAT3 (SLC22A8) shows a number of functional variants, some of which show reduced or complete loss of function, while others have no apparent effect on function. Studies in humans indicate that some OAT1 and OAT3 genetic variants are associated with decreased blood, plasma, or hair biomarkers of inorganic mercury exposure.

Metallothionein (MT). MT proteins bind to and sequester mercury. Genetic alterations in MT genes could result in altered distribution and retention. A functional polymorphism of MT4 was associated with increased hair mercury levels in medical students, while polymorphisms of MT1 and MT2 had no apparent effect on mercury levels. However, other human studies show that some MT1 and MT2 genetic variants are associated with increased biomarkers of mercury exposure, while others are associated with decreased biomarkers of mercury exposure. Significant associations have been reported between MT1 and MT2 variants and altered neurobehavior or cognitive performance in mercury-exposed children.

Selenoprotein. Selenoproteins bind to and sequester mercury as well as provide an antioxidant function. They are encoded by the polymorphic SEP and GPX genes. Genetic alterations in these genes could result in altered distribution and retention. A SEPP1 variant in humans has been associated with lower levels of biomarkers of methylmercury exposure, but with increased levels of biomarkers of inorganic

mercury exposure. SEPHS2 and GPX3 variants in humans have been associated with increased levels of biomarkers of mercury exposure (Parajuli et al. 2018).

ATP binding cassette (ABC) transporters. ABC transporters, also known as multidrug resistance-associated proteins (MRPs) are involved in mercury elimination via active transport across biological membranes. Genetic alterations in ABC genes could result in altered elimination of mercury. Studies in humans indicate that some MRP2 genetic variants are associated with increased levels of biomarkers (blood, plasma, or hair mercury levels) of inorganic mercury exposure, while others are associated with decreased levels of biomarkers of inorganic mercury exposure. Significant associations have been reported between an ABCC1 variant and altered mental and psychomotor development in mercury-exposed infants.

Other polymorphisms.

- Epidemiological studies show increased risk of mercury-associated cognitive or neurobehavioral effects in children and/or adults with one or more genetic variants of the following genes: apolipoprotein E (APOE), brain-derived neurotrophic factor (BDNF), catechol-O-methyltransferase (COMT), CPOX, paraoxonase1 (PON1), progesterone receptor (PGR), serotonin-transporter-linked polymorphic region (5-HTTLPR or SLC6A4), and transferrin (TF). Several of these polymorphisms showed synergistic effects when two or more were present.
- A limited number of epidemiological studies reported potential associations between genetic variants and increased risk of mercury-associated cardiovascular effects (e.g., hypertension, coronary artery disease, cardiac events), including metalloproteinase (MMP-2, MMP-9) and nitric oxide synthase (NOS).
- Certain genetic variants of heat shock protein 70 (HSPA1A, HSPA1B) in former workers with occupational exposure to mercury vapor were associated with increased risk of chronic mercury intoxication (CMI) diagnosis (Chernyak and Merinova 2017). CMI is characterized by a range of cognitive, personality, and sensorimotor disorders.
- Variants of genes involved in the folate pathway (CBS, MTRR) have been associated with increased levels of biomarkers of mercury exposure, while variants of genes involved in mediation of oxidative stress (NOS, TXNRD2) have been associated with decreased levels of biomarkers of mercury exposure (Parajuli et al. 2018).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to mercury compounds are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for mercury compounds from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by mercury compounds are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Humans are exposed to a mixture of methylmercury and inorganic mercury (primarily mercuric and elemental) in their local environments, with either being more or less pronounced under certain circumstances (e.g., occupational exposure to Hg^0 vapor, consumption of methylmercury in fish). Exposure to mercury that leads to absorption of mercury in any form can be detected from measurement of total mercury (inorganic plus organic) in blood or urine. A change in exposure to either form of mercury will be reflected in a change in blood or urine total mercury (Awata et al. 2017; Birch et al. 2014; Jain 2017; Kim et al. 2017; Mahaffey et al. 2009; Nielsen et al. 2014; Razzaghi et al. 2014; Yin et al. 2016). Measurements of total mercury in blood and urine can be considered biomarkers of total exposure to all forms of mercury and do not provide information to confidently estimate the magnitude of exposures specific to methylmercury, inorganic mercury compounds, or elemental mercury. Mercurialentis, a clinically distinct discoloration of the anterior capsule of the lens observable via slit-lamp examination, is also a diagnostic biomarker of mercury exposure (Byrns and Penning 2017; El-Sherbeeny et al. 2006). However, as this is a qualitative biomarker (exposure levels cannot be estimated), it is not further discussed below.

As discussed below, biomarkers that are more strongly correlated to methylmercury exposure are methylmercury concentration in whole blood, or total mercury concentration in RBCs or hair; these are more significant depots for accumulation of methylmercury than inorganic mercury. Biomarkers that are more strongly correlated to exposure to inorganic forms of mercury are inorganic mercury in blood (or plasma) and inorganic mercury or total mercury in urine. Berglund et al. (2005) found that approximately 5% of the methylmercury in hair was converted to inorganic mercury during sample processing. Additionally, demethylation after absorption contributes inorganic mercury to blood and urine; this complicates distinguishing exposures to inorganic forms of mercury from exposures to methylmercury based solely on measurements of total mercury in blood or urine.

Biomarkers of Exposure to Inorganic Mercury

Urine. Mercuric inorganic mercury is the dominant species of mercury excreted in urine (see Section 3.1.4, Excretion) and reflects the contributions of inorganic mercury intake (inhalation, ingestion) and inorganic mercury formed from demethylation of absorbed methylated mercury (Sherman et al. 2013). In populations in which the main source of exposure was to inorganic mercury, urinary mercury has been shown to correlate with inorganic mercury exposure. Measurement of total mercury in urine has

been used as a biomarker for exposure to Hg^0 vapor. Studies of exposed production and processing workers and dentists have shown that urinary mercury correlates with Hg^0 concentrations in air (Barregard 1993; Ehrenberg et al. 1991; Nordhagen et al. 1994; Roels et al. 1987). Tsuji et al. (2003) found that urinary inorganic mercury was also correlated with Hg^0 vapor exposures in unexposed workers and in populations from the general public, in which Hg^0 vapor exposures were considerably lower than in exposed workers. Urinary total mercury and inorganic mercury levels have also been shown to correlate with number of Hg^0 amalgam dental surface restorations (Berglund et al. 2005; Jarosinska et al. 2008; Maserejian et al. 2008; Vahter et al. 2000; Woods et al. 2007; Yin et al. 2013). Urinary total mercury was found to correlate with kidney mercury concentrations measured in kidney donors (Akerstrom et al. 2017).

Urinary mercury can be measured as a rate of urinary excretion of mercury (µg/day) based on a timed sample with a measured urine volume, or as a concentration (µg/L) based on a timed to untimed sample, with or without adjustments for urine creatinine concentration or specific gravity (Araki et al. 1986; Barber and Wallis 1986). The creatinine and specific gravity adjustments are intended to standardize a measured concentration for variations in urine volume, which by itself can result in concentration or dilution of urinary mercury (Diamond 1988; Lee et al. 1996; MacPherson et al. 2018; Martin et al. 1996; Trachtenberg et al. 2010). Lee et al. (1996) found similar correlations ($r>0.8$) between Hg^0 vapor concentrations in air and the various urine metrics in mercury workers who had worked for >2 years, including mercury excretion rate and mercury concentration with or without adjustment for creatinine concentration or specific gravity. Urinary mercury concentrations (µg/L) decrease with decreasing eGFR (Jin et al. 2018).

Urinary porphyrins have been studied for utility as biomarkers of mercury body burden (Geier et al. 2011; Woods et al. 2005, 2009). Mercury can inhibit various enzymes in the heme synthesis pathway, leading to increased urinary excretion of pentacarboxyporphyrin, precoproporphyrin, and coproporphyrin (Geier et al. 2011). Urinary excretion of porphyrins had been shown to correlate with urinary excretion of mercury in humans and rats (Pingree et al. 2001; Woods et al. 2005). Urinary excretion of porphyrins in children was shown to correlate with the number of mercury amalgam restorations (Geier et al. 2011). Clinical testing of urinary porphyrins is typically performed to diagnose porphyria; a disruption of heme metabolism.

Blood. Mercury in blood is predominantly a mixture of methylmercury and inorganic mercury. The geometric means of total mercury (range 0.678–0.703 µg/L) and methylmercury (range 0.431–

0.489 µg/L) estimated for the U.S. population based on data from NHANES for the period 2011–2016 suggested that methylmercury comprised approximately 61–70% of blood total mercury (CDC 2019). The bulk of the remaining fraction (30–39%) is likely to be inorganic mercury; however, the geometric mean concentration of inorganic mercury was below the limit of detection (0.27 µg/L). Based on data reported in NHANES (2011–2012), the number of Hg^0 amalgam dental surface restorations and amount of fish consumed were significant variables in explaining blood total mercury, inorganic mercury, and methylmercury concentrations (Yin et al. 2016). In a clinical study (28 adult subjects), blood inorganic mercury, but not blood organic mercury, was found to correlate with number of Hg^0 amalgam dental surface restorations; however, blood organic mercury, but not blood inorganic mercury, correlated with fish consumption (Berglund et al. 2005).

Biomarkers of Exposure to Methylmercury. Exposure to methylmercury can be detected from measurements of methylmercury in blood and measurements of total mercury in hair and nails. The concentration of total mercury in blood is not considered to be a specific metric for methylmercury exposure because exposure to inorganic mercury will contribute to blood mercury. However, blood total mercury can be used as a metric for methylmercury exposure in populations in which methylmercury is the dominant source of exposure to mercury. Measurement of total mercury in RBCs can also serve as a metric of exposure to methylmercury, because most of the methylmercury in whole blood resides in RBCs. A high RBC/plasma ratio (>10) for total mercury is indicative of methylmercury exposure. For the same reason, measurements of total mercury in plasma are less useful as exposure metrics of methylmercury, since most of the mercury in plasma is inorganic mercury, regardless of the contributions of methylmercury or inorganic mercury to total mercury exposure. Measurement of urine total mercury is not considered to be a useful biomarker for exposure to methylmercury, because mercury excreted in urine is predominantly inorganic following exposure to methylmercury or inorganic mercury.

Blood. The concentration of methylmercury in whole blood and RBCs has been shown to correlate with methylmercury consumption (Airaksinen et al. 2011; Berglund et al. 2005). Following absorption of methylmercury, methylmercury is the dominant mercury species in blood, with most of the methylmercury associated with RBCs (see Section 3.1.2, Distribution). It follows that, in populations in which methylmercury is the dominant source of mercury intake, total mercury in blood will be dominated by methylmercury and the blood total mercury concentration will reflect methylmercury intake. This would not apply to populations in which the dominant form of exposure is to elemental mercury or other forms of inorganic mercury. Total blood mercury should be interpreted as a biomarker of exposure to

methylmercury only if other information is available that supports methylmercury being the dominant form of exposure in the population.

In populations where fish are a major contributor to the diet, total mercury concentrations in blood correlate with fish intake (Grandjean et al. 1992). Numerous studies have found that blood (or RBC) total mercury concentrations correlate with dietary fish or marine mammal consumption, a metric for methylmercury intake (Airaksinen et al. 2011; Awata et al. 2017; Kioumourtzoglou et al. 2016; Nielsen et al. 2014; Razzaghi et al. 2014). In populations in which fish is a major contributor to the diet, methylmercury accounts for nearly all of the mercury in umbilical cord blood and, as a result, methylmercury and total mercury concentrations in cord blood are correlated (Sakamoto et al. 2007).

Measurement of total mercury in plasma is not widely used as a biomarker for exposure to methylmercury. The reason for this is that plasma methylmercury typically makes a relatively small contribution to total mercury in blood. However, within the plasma compartment, methylmercury and inorganic mercury are in a ratio close to one (Berglund et al. 2005; Carneiro et al. 2014).

Hair. The concentration of total mercury in hair is correlated with blood methylmercury concentration (Berglund et al. 2005; Budtz-Jorgensen et al. 2004; Liberda et al. 2014; Morrissette et al. 2004; Phelps et al. 1980). Hair total mercury concentrations correlate with dietary consumption of mercury from fish and marine mammals (Berglund et al. 2005; Castano et al. 2015; Johnsson et al. 2005; Tian et al. 2011; Yaginuma-Sakurai et al. 2012). The correlation between blood and hair mercury in association with methylmercury consumption was demonstrated in a clinical study that measured the time-course for changes in total mercury in blood and new-grown hair during and following consumption of methylmercury in fish (Yaginuma-Sakurai et al. 2012). This study measured total mercury in blood and new-grown hair (repeatedly sampled close to the scalp) of 27 adults who consumed methylmercury in fish (3.4 µg methylmercury/kg/week) for a period of 14 weeks with continued measurements for a 15-week period following cessation of the exposure. Concentrations of total mercury in blood and new-grown hair increased during exposure and decreased following exposure with similar half-times for blood (57±18 [SD] days) and hair (64±22 days). Hair/blood ratios (µg/kg hair per µg/L blood) remained relatively constant during the study. The median ratio at the start of exposure was 354 (5^{th}–95^{th} percentile range: 267–475) and just prior to cessation of exposure, the median ratio was 321 (5^{th}–95^{th} percentile range: 264–451). The mean hair mercury half-time was estimated to be 44 days (95% CI 41, 48) based on longitudinal measurements of mercury in hair of 37 adults following a period of fish meals (Caito et al. 2018).

The correlation between total mercury in hair and blood methylmercury derives from several factors. Methylmercury is accumulated in hair to a much greater extent than is inorganic mercury (Shi et al. 1990; Yasutake and Hachiya 2006). Based on studies conducted in rats, the mercuric chloride dose would have to be approximately 400 times the dose of methylmercury to achieve the same hair mercury level (Yasutake and Hachiya 2006). The Rothenberg et al. (2016a) study found that the dominant form of mercury in hair was methylmercury (65% of total). In populations in which methylmercury is the dominant form of exposure, the methylmercury contribution has been found to be higher (e.g., >80%; Akagi et al. 1995; Cernichiari et al. 2007; George et al. 2010; Harada et al. 1998; Marinho et al. 2014). A portion of the inorganic mercury in human hair has been attributed, in part, to demethylation that occurs in processing the hair sample for analysis, absorbed inorganic mercury, and demethylation of methylmercury within the hair follicle. Berglund et al. (2005) found that approximately 5% of the methylmercury in hair was converted to inorganic mercury during sample processing.

The relationship between hair mercury and blood mercury has been modeled as a linear relationship with estimated slopes (µg/kg hair per µg/L blood) that have large inter-study variability, ranging from 140 to 370 with estimated means across studies of approximately 250 (Clarkson and Magos 2006; Clarkson et al. 1988). The hair/blood concentration ratio has been measured in numerous studies and shows high inter-individual variability, with population means ranging from 100 to 400 (Albert et al. 2010; Budtz-Jorgensen et al. 2004; Clarkson et al. 1988; Liberda et al. 2014;Yaginuma-Sakurai et al. 2012). The World Health Organization and United Nations (WHO 1990, 2004) recommend a hair/blood ratio of 250 for interconverting hair and blood mercury concentrations.

Mercury in hair is retained until the hair strand is shed. As a result, the mercury content of a hair reflects the history of blood methylmercury levels. Since methylmercury enters hair during keratinization in the hair follicle, and hair grows from the hair follicle outward, analysis of hair strand segments can provide a basis for reconstructing a temporal history of blood methylmercury concentrations, providing that the ratio of concentrations (hair/blood) and rate of hair growth are known (Boischio et al. 2000; Caito et al. 2018; Cox et al. 1989; Sakamoto et al. 2008, 2016). Maternal hair mercury and neonatal hair mercury are correlated, reflecting transfer of maternal methylmercury to the newborn during gestation and nursing (Castano et al. 2015; Gundacker et al. 2010; Marques et al. 2013a; Ramirez et al. 2000).

Several sources of error can affect measurements of total mercury and methylmercury in hair. External contamination of hair with mercury can result in an overestimate of mercury incorporated into hair. Hair

waving and permanents can decrease hair mercury levels (Dakeishi et al. 2005; Yamaguchi et al. 1975; Yamamoto and Suzuki 1978; Yasutake et al. 2003).

Nails. Similar to hair, nails are composed largely of keratin, which provides abundant sulfhydryl ligands for formation of S-conjugates with methylmercury (Baden et al. 1973; Baswan et al. 2017; Gupchup and Zatz 1999). Methylmercury has been identified in human nails (Krystek et al. 2012). A study of total mercury and inorganic mercury in human nails found that the inorganic mercury fraction ranged from 10 to 16%; the corresponding range of organic mercury (total mercury minus inorganic mercury) was 85 to 90% (Suzuki et al. 1989). The total mercury concentration of fingernails and toenails correlate with total mercury in hair and methylmercury in blood (Alfthan 1997; Bjorkman et al. 2007; Hinners et al. 2012; Ohno et al. 2007; Sakamoto et al. 2015). The total mercury concentration in hair has also been shown to correlate with dietary mercury consumption and dietary fish consumption (Ohno et al. 2007; Rees et al. 2007; Yoshizawa et al. 2002).

3.3.2 Biomarkers of Effect

No specific biomarkers of effect have been identified for any category of mercury compounds. Effects of mercury are not unique to mercury; thus, it is not possible to identify exposure without measurement of mercury biomarkers. For example, in workers with known exposure to elemental mercury, signs of neurological effects may suggest that exposure has occurred; however, clinical findings need to be coupled with biomarkers of exposure.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Dietary fish is an important source of exposure to methylmercury in most populations. As a result, dietary exposure to methylmercury will occur with exposures to other chemicals that bioaccumulate in fish. ATSDR (2004) assessed evidence for potential toxicity interactions between methylmercury, chlorinated dibenzodioxins (CDDs), hexachlorobenzene, *p,p'*-DDE, and PCBs, all of which are fish contaminants. Available information on toxic actions of the individual components provided support for possible synergism between PCBs and methylmercury in disrupting regulation of brain levels of dopamine that may influence neurological function and development (ATSDR 2004).

Oceanic fish and marine mammals are major sources of dietary intakes of both selenium and methylmercury. Interactions of mercury with selenium, selenocysteine, and selenoenzymes are thought to

be important mechanisms by which inorganic mercuric and methylmercury exert cellular toxicity (see Section 2.21 General Mechanisms of Action). These interactions provide mechanisms for potential toxicologic interactions between methylmercury and selenium (Ralston and Raymond 2018; Ralston et al. 2008).

Fish contain other nutrients that have been shown to be important modifiers of development. These include 3-omega LCPUFAs, iodine, and iron (Cheatham 2008; Choi et al. 2008a; Muldoon et al. 2014). Nutritional benefits of fish consumption are a source of negative confounding in epidemiological studies that assess potential associations between prenatal methylmercury exposure and neurodevelopmental outcomes (Choi et al. 2008a).

Mercury can displace copper and zinc from binding sites on metallothionein (and other metalloproteins) and induces the synthesis of metallothionine (see Section 2.21 General Mechanisms of Action). These interactions provide mechanisms for potential toxicologic interactions between mercury and other metals that bind to and induce synthesis of metallothionine such as cadmium, copper, lead, and zinc (Aschner et al. 2006; Wu et al. 2016; Yasutake and Nakamura 2011; Zalups and Cherian 1982).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of mercury compounds is located in Table 4-1. For this profile, mercury compounds are classified into three general categories: (1) elemental mercury; (2) inorganic mercury compounds (e.g., mercuric chloride); and (3) organic mercury compounds (e.g., methylmercury). An inorganic mercury compound is a compound of mercury that does not contain a chemical bond between mercury and carbon. Inorganic mercury salts are inorganic mercury compounds that can dissociate into a mercury cation (e.g., mercuric chloride, mercuric sulfide). Inorganic mercury compounds that are not salts include mercury oxides (e.g., mercuric oxide). Organic mercury compounds contain bonds between mercury and carbon (e.g., methylmercuric chloride, phenylmercuric acetate). Mercuric acetate has been included as an organic form of mercury. However, the bonds of the salt are not covalent and, in aqueous solution, the mercury behaves like an inorganic form.

Table 4-1. Chemical Identity of Selected Inorganic and Organic Mercury Compounds[a]

Characteristic	Elemental	Inorganic	Inorganic
Chemical name	Mercury	Mercuric (II) chloride	Mercuric (II) sulfide
Synonym(s) and registered trade name(s)	Colloidal mercury; liquid silver; mercury, metallic; quicksilver; metallic mercury[b]; hydrargyrum	Bichloride of mercury; mercury bichloride[d]; mercury chloride[d]; mercury dichloride; mercury perchloride; mercury (II) chloride; perchloride of mercury; corrosive sublimate[d]; corrosive mercury chloride; dichloromercury; Calochlor; Fungchex; TL 898	Etiops mineral[c]; mercury sulfide, black[d]; vermillion; Chinese red; C.I. Pigment Red 106; C.I. 77766[c]; quicksilver vermillion; Chinese vermillion; red mercury sulfide; artificial cinnabar; red mercury sulfuret[d]
Chemical formula	Hg[c]	$HgCl_2$[c]	HgS[c]
Chemical structure	Hg	Hg^{++} Cl^- Cl^-	Hg=S
CAS Registry Number	7439-97-6[c]	7487-94-7[c]	1344-48-5[c]

Table 4-1. Chemical Identity of Selected Inorganic and Organic Mercury Compounds[a]

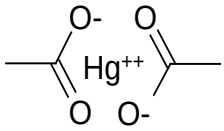
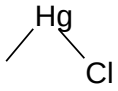
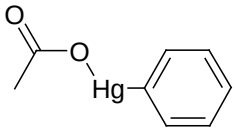
Characteristic	Inorganic	Inorganic	Organic
Chemical name	Mercurous (I) chloride	Mercuric (II) acetate[e]	Methylmercury
Synonym(s) and registered trade name(s)	Calomel; mild mercury chloride; mercury monochloride; mercury protochloride; mercury subchloride; calogree; cyclosan[c]; mercury chloride[d]; Calogreen; Calomel Calotab; Cylosan	Acetic acid, mercury (2+ salt); bis(acetyloxy) mercury; diacetocymercury; mercury diacetate; mercury (II) acetate; mercury (2+) acetate; mercury acetate[d]	Methylmercury cation; methylmercury II; mercury(1+), methyl; methylmercury ion; methylmercury(II) cation; monomethylmercury cation
Chemical formula	Hg_2Cl_2[b]	$HgC_4H_6O_4$[b]	CH_3Hg
Chemical structure	Cl–Hg–Hg–Cl		
CAS Registry Number	10112-91-1	1600-27-7	22967-92-6

Table 4-1. Chemical Identity of Selected Inorganic and Organic Mercury Compounds[a]

Characteristic	Organic	Organic	Organic
Chemical name	Methylmercuric chloride	Dimethyl mercury	Phenylmercuric acetate
Synonym(s) and registered trade name(s)	Chloromethylmercury; monomethyl mercury chloride; methylmercury chloride; methylmercury monochloride[b]; Caspan	Mercury, dimethyl; methyl mercury[c]	(Acetato)phenylmercury; acetoxyphenylmercury; phenylmercury acetate[c]; acetophenylmercucy; mercury (II) acetate, phenyl-; mercury, (acetato)phenyl-; phenylmercury acetate; phenylmercuriactetate; PMA; PMAC; Pmacetate; Cerasan Slaked Lime; Gollitox; liquiphene; Mersolite; Tag Fungicide; Tag HL-331; Nylmerate; Scutl; Riogen; PMAS
Chemical formula	CH_3HgCl[f]	C_2H_6Hg[c]	$C_8H_8HgO_2$[c]
Chemical structure			
CAS Registry Number	115-09-3	593-74-8[c]	62-38-4[c]

[a]All information obtained from NLM (2020), except where noted.
[b]RTECS 1997.
[c]Budavari 1989.
[d]Lewis 1993.
[e]Although organic moieties are associated with the mercury atom, the mercury-carbon bonds are ionic, not covalent, in nature; in aqueous solution, Hg^{2+} is released. Therefore, based on chemical properties, mercuric acetate is classified as an inorganic compound for this profile. Due to the presence of carbon in the acetate moiety, mercuric acetate could also be classified as an organic compound.
[f]ASTER 1997.

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of mercury compounds is located in Table 4-2. Mercury has seven naturally occurring isotopes, with the most common being mercury-202 (Gonzalez-Raymat et al. 2017). The fate and properties of mercury are greatly dependent upon its oxidation state which are mainly: elemental mercury Hg^0, mercurous Hg^+ (I), and mercuric Hg^{2+} (II).

Table 4-2. Physical and Chemical Properties of Selected Inorganic and Organic Mercury Compounds[a]

	Elemental	Inorganic		
Property	Mercury	Mercuric (II) chloride	Mercuric (II) sulfide	Mercurous (I) chloride
Molecular weight	200.59	271.52	232.68	472.09
Color	Silver-white (liquid metal); tin-white (solid mercury)	White	Black or grayish-black (mercuric sulfide, black); bright scarlet-red blackens on exposure to light (mercury sulfide, red)	White
Physical state	Heavy, mobile, liquid metal; solid mercury is a ductile, malleable mass that may be cut with a knife	Crystals, granules, or powder; rhombic crystalline solid[b]	Heavy amorphous powder, also occurs as black cubic crystals (mercury sulfide, black); powder, lumps, hexagonal crystals (mercury sulfide, red)	Heavy powder; rhombic crystals or crystallin powder[c]
Melting point	-38.87°C	277°C	Transition temperature (red to black) 386°C; sublimes at 446°C (mercuric sulfide, black)[c]; sublimes at 583°C (mercuric sulfide, red)	Sublimes at 400–500°C without melting; 302°C[c]
Boiling point	357.72°C	302°C	502°C (predicted)[d]	384°C[c]
Density (g/cm^3)	13.534 at 25°C	5.4 at 25°C	7.55–7.70 (mercuric sulfide, black); 8.06–8.12 g/cc (mercuric sulfide, red)[c]	7.15 g/cc; 6.993 g/cc[c]
Odor	Odorless[b]	Odorless[c]	Odorless	Odorless
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Selected Inorganic and Organic Mercury Compounds[a]

	Elemental	Inorganic		
Property	Mercury	Mercuric (II) chloride	Mercuric (II) sulfide	Mercurous (I) chloride
Solubility:				
Water	0.28 µmoles/L at 25°C	69 g/L at 20°C[e]	Insoluble (mercuric sulfide, black), soluble in aqua regia with separation of sulfur, in warm hydriodic acid with evolution of hydrogen sulfide (mercuric sulfide, red)	$2x10^{-4}$ g/100 mL at 25°C
Organic solvents	Soluble in H_2SO_4 upon boiling in lipids; readily soluble in HCl[c]; soluble in 2.7 mg/L pentane[b]	1 g/3.8 mL alcohol, 1 g/200 mL C_6H_6, 22 mL ether, 12 mL glycerol, 40 mL CH_3COOH, acetone, CH_3OH, ethyl acetate; 33 g/100 cc alcohol at 25°C, slightly soluble in carbon disulfide, pyridine[b]	Insoluble in alcohol, dilute mineral acids	Insoluble in alcohol, ether
Partition coefficients:				
Log K_{ow}	5.95[f]	No data	1.53 (predicted)[d]	-0.550 (predicted)[d]
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	$2x10^3$ mmHg at 25°C	1 mmHg at 136.2°C	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	Not flammable[b]	No data	No data	No data
Flashpoint	Not flammable[b]	Not flammable[b]	No data	No data
Flammability limits	Not flammable[b]	Not flammable[b]	No data	No data
Conversion factors	1 ppm=8.18 mg/m^3 1 mg/m^3=0.122 ppm	No data	No data	No data
Explosive limits	Non-combustible[b]	Non-combustible[b]	No data	No data
Valence states	+1, +2	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Selected Inorganic and Organic Mercury Compounds[a]

	Inorganic	Organic			
Property	Mercuric (II) acetate	Methylmercury	Methylmercuric chloride[g]	Dimethyl mercury	Phenylmercuric acetate
Molecular weight	318.70	216.63	251.1[h]	230.66	366.75
Color	White[c]	White (chloride salt)[e]	White[i]	Colorless	White to cream[c]
Physical state	Crystals or crystalline powder; solid at 25°C and 1 atm[b]	Crystalline solid (chloride salt)[e]	Crystals[i]	Liquid	Small lustrous prisms; crystalline powder, small prisms or leaflets[b]
Melting point	178–180°C	-60.5°C (predicted)[d]	170°C[h]	-56.6°C (predicted)[d]	149°C; 148–150°C[c]
Boiling point	118°C (predicted)[d]	83.0°C (predicted)[d]	117°C (predicted)[d]	92°C	291°C (predicted)[d]
Density (g/cm^3)	3.28	4.06 g/mL at 25°C (chloride salt)[e]	4.06 g/mL at 25°C[i]	3.1874 g/mL at 20°C	No data
Odor	Slight acetic odor	Disagreeable odor[e]	No data	No data	Odorless[j]
Odor threshold:					
Water	No data	No data	No data	No data	No data
Air	No data	No data	No data	No data	No data
Solubility:					
Water	1 g in 2.5 mL cold; 1 mL boiling water; 25 g/100 mL at 10°C, 100 g/100 mL at 100°C[b]	0.145 mol/L (predicted)[d]	<0.1 mg/mL at 21°C[i]	Insoluble $1.00x10^3$ mg/L[h]	Soluble in about 600 parts water; 1 g/180 mL[b]
Organic solvents	Soluble in alcohol, acetic acid[b]	No data	DMSO ≥100 mg/mL at 27°C, 95% C_2H_5OH 10–50 mg/mL at 27°C; acetone ≥100 mg/mL at 27°C[i]	Easily soluble in ether, alcohol	Soluble in alcohol, benzene, acetone; 6.8 mL $CHCl_3$, 200 mL ether[b]
Partition coefficients:					
Log K_{ow}	-0.662 (predicted)[d]	0.08 (predicted)[d]	0.390 (predicted)[d]	2.28[b]	0.71[b]
Log K_{oc}	No data	No data	No data	2.73[h]	1.72[h]

Table 4-2. Physical and Chemical Properties of Selected Inorganic and Organic Mercury Compounds[a]

	Inorganic	Organic			
Property	Mercuric (II) acetate	Methylmercury	Methylmercuric chloride[g]	Dimethyl mercury	Phenylmercuric acetate
Vapor pressure	13.9–15.6 mmHg at 25°C (predicted)[d]	0.0085 mmHg at 25°C (chloride salt)[e]	0.0085 mmHg at 25°C[i]	62.3 mmHg at 25°C[j]	1.20×10^{-4} mmHg at 25°C[b]
Henry's law constant at 25°C	1.00×10^{-7} (predicted)[d]	No data	No data	No data	1.22×10^{-8} atm m^3/mol[b]
Autoignition temperature	No data	No data	Probably nonflammable[i]	Easily inflammable	No data
Flashpoint	Not flammable[b]	No data	Probably nonflammable[i]	Easily inflammable	No data
Flammability limits	Not flammable[b]	No data	Probably nonflammable[i]	Easily inflammable	No data
Conversion factors	No data	No data	1 ppm=10.27 mg/m^3 1 mg/m^3=0.097413 ppm	1 ppm=9.43 mg/m^3 1 mg/m^3=0.106 ppm	No data
Explosive limits	Noncombustible[b]	No data	No data	No data	Probably combustible[i]
Valence state	+2	+2	+2	+2	+2

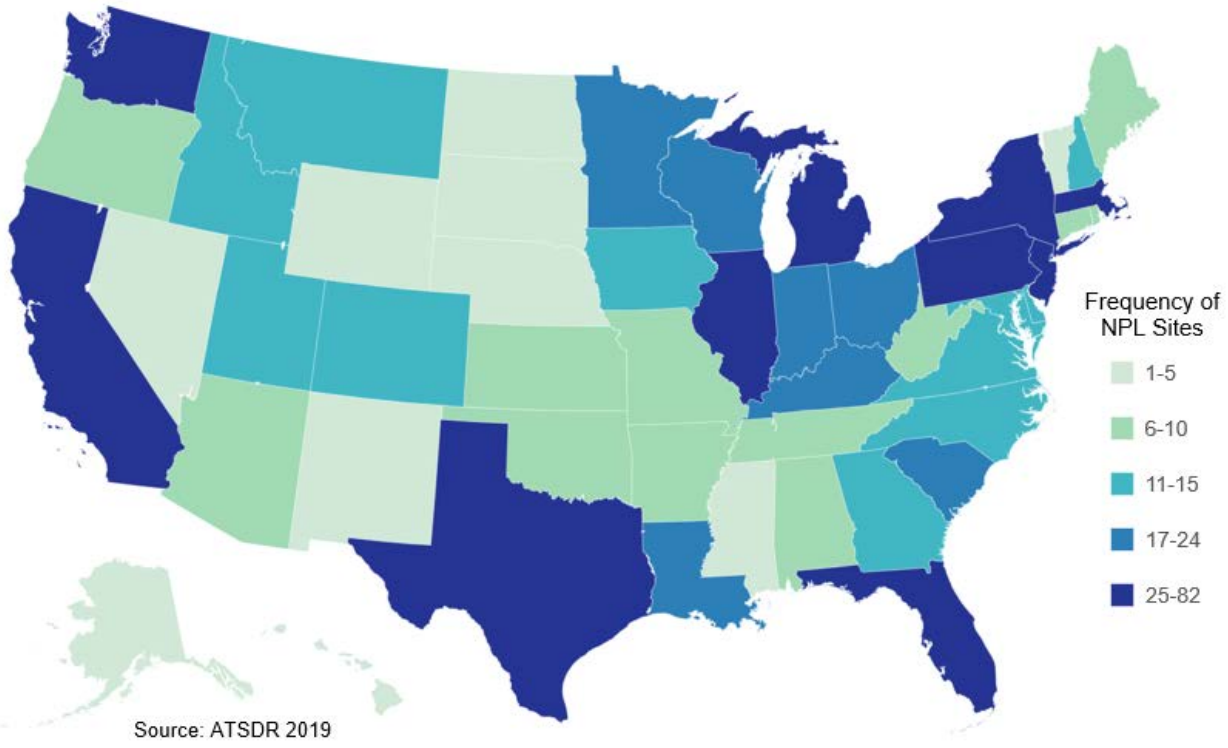
[a]All information obtained from Budavari (1989) except where noted.
[b]NLM 2020.
[c]Lewis 1993.
[d]EPA 2021a, 2021b, 2021c, 2021d, 2021e.
[e]Grandjean and Yorifuji 2012.
[f]Stein et al. 1996.
[g]Commonly occurring form of methyl mercury; proprietary names include bis-methylmercuric sulfate (cerewet), methylmercury cyanoguianidine or methylmercury dicyanodiamide (agrosol, morsodren, panogen, panospray), methylmercury nitrile (chipcote), and methylmercury proprionate (metasol MP).
[h]ASTER 1997.
[i]NTP 1997.
[j]Long and Cattanach 1961.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Mercury or mercury compounds have been identified in at least 838 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which mercury has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 828 are located within the United States, 1 is located in Guam, 2 are located in the Virgin Islands, and 7 are located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with Mercury or Mercury Compound Contamination



- The general population is primarily exposed to mercury through the ingestion of foods.
- The general population may also be exposed to mercury by inhalation of ambient air. Exposure from ingestion of drinking water is a minor exposure pathway. Mercury released from mercury amalgam restorations can also contribute to mercury exposure.
- Occupational exposure for persons working with mercury or mercury compounds, such as mercury recycling and reprocessing facilities or dental offices where mercury is used in dental amalgams, may occur through inhalation or dermal contact.

- Most mercury in the atmosphere is in the gaseous elemental form, which can remain suspended in air for long periods of time and is subject to long-range atmospheric transport. When released or deposited to land or water, mercury can be transformed to methylated forms by anaerobic microorganisms. Methylmercury is highly bioaccumulative and biomagnifies in the food chain.

Mercury occurs naturally as a mineral and is distributed throughout the environment by both natural and anthropogenic processes. The natural global bio-geochemical cycling of mercury is characterized by degassing of the element from soils and surface waters, followed by atmospheric transport, deposition of mercury back to land, vegetation and surface water, and sorption of the compound to soil or sediment particulates. Mercury deposited on land and open water is, in part, revolatilized back into the atmosphere. This emission, deposition, and revolatilization creates difficulties in tracing the movement of mercury to its sources. Major anthropogenic sources of mercury releases to the environment include mining and smelting; industrial processes involving the use of mercury, including chloralkali production facilities; combustion of fossil fuels, primarily coal; production of cement; and medical and municipal waste incinerators and industrial/commercial boilers. Natural sources include volcanic activity, wildfires that release sequestered mercury from biomass, and weathering of mercury-containing rocks.

The element has three valence states and is found in the environment in the metallic form and in the form of various inorganic and organic complexes. The major features of the bio-geochemical cycle of mercury include degassing of mineral mercury from the lithosphere and hydrosphere, long-range transport in the atmosphere, wet and dry deposition to land and surface water, sorption to soil and sediment particulates, revolatilization from land and surface water, and bioaccumulation in both terrestrial and aquatic food chains.

Potential sources of general population exposure to mercury include inhalation of mercury vapors in ambient air, ingestion of drinking water and foodstuffs contaminated with mercury, and exposure to mercury through dental and medical treatments. Dietary intake is the most important source of nonoccupational exposure to mercury, with fish and other seafood products being the dominant source of mercury in the diet. Most of the mercury consumed in fish or other seafood is the highly absorbable methylmercury form. Consumption of rice can also make a substantial contribution to dietary mercury intake. Intake of elemental mercury from dental amalgams is another important contributing source to the total mercury body burden in humans in the general population. This is expected to decline as use of dental amalgams is being phased-out in many countries.

Mercury is present in a variety of human tissues. Mercury has also been detected in urine, human breast milk, nails, hair, and placenta in individuals in the general population. Inhalation of mercury vapor in workplace atmospheres is the main route of occupational exposure to the compound. Mercury has a long history of use in industrial processes and as a therapeutic agent (Clarkson and Magos 2006). Occupational exposure to mercury has occurred in a variety of industries that process or use the element (e.g., felting, chloralkali processing, fluorescent lamp production, gold mining and processing, lithium-6 purification, dentistry applications of mercury amalgam, mercury battery production, natural gas production, recycling, and thermometer production).

Members of the general public with potentially high exposures include individuals who live in proximity to former mercury mining or production sites, secondary production (recycling) facilities, municipal or medical incinerators, or coal-fired power plants. Other populations at risk of exposure include recreational and subsistence fishers who routinely consume meals of fish that may be contaminated; subsistence hunters who routinely consume the meat and organ tissues of marine mammals; individuals with a large number of dental amalgams; fetuses by maternal-fetal transfer and breastfed infants through maternal-breast milk transfer; medical exposure (e.g., ethylmercury used as a preservative in vaccines); occupational sources; individuals who use consumer products containing mercury (e.g., traditional or herbal remedies, or cosmetics, including skin lightening creams); and individuals where intentional (religious or cultural use) or unintentional mercury spills have occurred. Historically, mercury compounds were also used as pharmaceutical agents (e.g., antibiotics, antiseptics, diuretics) (Clarkson and Magos 2006).

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Mercury is a naturally occurring element that is usually found as mercuric sulfide (cinnabar), an insoluble, stable compound. It occurs in the earth's crust at levels averaging 0.5 ppm, but the actual concentration varies considerably depending on location (Budavari 1989; Sidle 1993). Mercury is mined using both open pit (10% of production) and underground mining techniques (90%) (Drake 1981).

Mercury ores are processed inexpensively to produce metallic mercury. Due to the low boiling point of elemental mercury, mercury can be refined by heating the ore and condensing the vapor to form metallic mercury. This method is 95% efficient and yields mercury that is 99.9% pure. The methods used to

refine mercury ores are uncomplicated. Smaller refineries use simple firing and condensing equipment, while larger operations use continuous rotary kilns or mechanically feeding and discharging multiple-hearth furnaces (DOI 1985).

According to the U.S. Geological Survey (USGS), mercury has not been produced as a principal mineral commodity in the United States since 1992; however, it is recovered as a byproduct from processing gold-silver ore at mines located in Nevada (USGS 2020). Metals in the gold ores are extracted with an aqueous cyanide solution, with typical mercury recoveries of between 10 and 20% (DOI 1993; USGS 1997). In addition, mercury can be recovered from batteries, compact and traditional fluorescent lamps, dental amalgam, medical devices, old thermostats, and mercury-contaminated soils. It was estimated that in 2019, <40 metric tons of mercury were consumed domestically in the United States (USGS 2020). The USGS reported that, in 2019, eight facilities operated by six companies in the United States accounted for the majority of secondary mercury produced and were authorized by the U.S. Department of Energy to temporarily store mercury. Typically, mercury-containing products such as automobile convenience switches, barometers, mercury containing lightbulbs, computers, dental amalgams, medical devices, and thermostats are retrieved by smaller companies and transported to the refining establishments for mercury reclamation. Due to the continued phase-out of compact and traditional fluorescent lighting for light-emitting-diode (LED) lighting, mercury recycling has increased.

Annual global mine production of mercury was estimated to be around 4,000 metric tons in 2019 (USGS 2020). China is the overwhelming producer of mined mercury (~3,500 metric tons in 2019). Other nations with mine production of mercury include: Argentina, Kyrgyzstan, Mexico, Norway, Peru, and Tajikistan (USGS 2020). Artisanal goldmining is practiced in many countries. In artisanal mining, gold is extracted from a substrate (e.g., pulverized ore, sediment, soil) by mixing the substrate with elemental mercury to form mercury-gold amalgam. The amalgam is washed, sedimented, and roasted to vaporize the elemental mercury out of the amalgam. This process can result in direct exposures of mine workers, gold shop merchants, and nearby households to mercury vapor and can release mercury to the environment where it can be converted to methylmercury (Counter et al. 1998; Diringer et al. 2015; Moody et al. 2020; Ramirez et al. 2000; Salazar-Camacho et al. 2021)

Tables 5-1 and 5-2 list the facilities in each state that process or recycle mercury and mercury compounds, respectively. Data from the TRI is intended to meet the requirements of the Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313 for mercury and the mercury compounds category.

If a facility processes or imports mercury or mercury containing compounds, it is required to report these data to the TRI and this meets the definition of the reporting category, Produce.

Table 5-1. Facilities that Produce, Process, or Use Mercury

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	1	0	99	1, 5, 12
AL	7	0	999	1, 5, 12, 13, 14
AR	4	0	99	1, 5, 12, 13, 14
AZ	8	0	9,999	1, 4, 5, 6, 8, 12, 13, 14
CA	31	0	99,999	1, 2, 5, 7, 8, 9, 10, 11, 12, 13, 14
CO	6	0	99	1, 5, 8, 12, 13, 14
CT	3	0	999	8, 14
DC	1	0	99	7
DE	1	1,000	9,999	8, 9
FL	6	0	9,999	1, 4, 5, 8, 9, 12, 13, 14
GA	6	0	999	1, 2, 8, 12, 13, 14
HI	1	0	99	1, 5
IA	5	0	9,999	1, 5, 7, 8, 12, 13, 14
ID	3	0	999	1, 5, 12, 13, 14
IL	19	0	9,999	1, 5, 6, 8, 12, 13, 14
IN	8	0	9,999	1, 2, 5, 6, 8, 12, 13, 14
KS	4	0	999	1, 2, 5, 8, 12, 13, 14
KY	9	0	99,999	1, 5, 8, 10, 12, 13, 14
LA	14	0	9,999,999	1, 2, 3, 5, 12, 13, 14
MA	7	0	9,999	1, 5, 8, 11, 12, 13, 14
MD	2	0	99	14
ME	2	0	99	12, 14
MI	5	0	9,999	1, 5, 8, 9, 13, 14
MN	6	0	9,999	1, 5, 8, 12, 13, 14
MO	2	0	99	1, 5, 14
MP	1	0	99	1, 13
MS	3	0	99	1, 5, 9, 12, 14
MT	2	0	99	1, 10, 13, 14
NC	4	0	999	8, 12, 14
NE	9	0	999	1, 3, 4, 5, 9, 12, 13, 14
NJ	1	0	99	12
NM	1	10,000	99,999	1, 5, 12
NV	9	0	9,999,999	1, 8, 9, 12, 13, 14
NY	6	0	9,999	1, 11, 12, 13, 14

Table 5-1. Facilities that Produce, Process, or Use Mercury

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
OH	20	0	9,999,999	1, 2, 3, 5, 7, 8, 9, 10, 12, 13, 14
OK	4	0	99	1, 2, 5, 8, 9, 12, 13, 14
OR	2	0	999	12, 14
PA	17	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14
RI	1	0	99	12, 14
SC	3	0	99	1, 5, 8, 12, 14
SD	1	0	99	1, 5, 14
TN	7	0	9,999,999	1, 2, 3, 5, 9, 12, 13, 14
TX	44	0	99,999	1, 2, 4, 5, 7, 8, 9, 11, 12, 13, 14
UT	5	0	99	1, 5, 12, 14
VA	4	0	9,999	1, 5, 7, 12, 14
VT	1	0	99	8
WA	1	100	999	14
WI	8	0	999,999	1, 3, 5, 7, 9, 12, 14
WV	10	0	9,999	1, 5, 12, 13, 14
WY	5	0	9,999	1, 2, 5, 8, 9, 12, 13, 14

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI19 2020 (Data are from 2019)

Table 5-2. Facilities that Produce, Process, or Use Mercury Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	14	0	999,999	1, 2, 5, 7, 9, 12, 13, 14
AL	34	0	99,999	1, 3, 4, 5, 6, 8, 12, 13, 14
AR	18	0	99,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
AZ	21	0	99,999	1, 2, 3, 4, 5, 8, 9, 12, 13, 14
CA	70	0	99,999	1, 2, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	19	0	9,999,999	1, 4, 5, 6, 7, 8, 9, 12, 13, 14
CT	2	0	999	1, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
DC	1	0	99	14

Table 5-2. Facilities that Produce, Process, or Use Mercury Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
DE	3	0	99	1, 2, 3, 5, 7, 12, 13, 14
FL	33	0	99,999	1, 2, 3, 4, 5, 8, 9, 11, 12, 13, 14
GA	21	0	999	1, 2, 3, 4, 5, 8, 12, 13, 14
GU	1	0	99	7, 9
HI	7	0	99	1, 2, 5, 9, 12, 13, 14
IA	26	0	9,999	1, 3, 4, 5, 7, 9, 12, 13, 14
ID	11	0	9,999	1, 5, 7, 8, 11, 12, 13, 14
IL	38	0	9,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14
IN	38	0	9,999	1, 2, 3, 4, 5, 7, 9, 11, 12, 13, 14
KS	21	0	9,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
KY	23	0	9,999	1, 2, 3, 4, 5, 8, 9, 10, 12, 13, 14
LA	46	0	99,999	1, 2, 3, 4, 5, 9, 10, 11, 12, 13, 14
MA	1	100	999	9
MD	13	0	999	1, 3, 4, 5, 9, 12, 13, 14
ME	3	0	999	1, 5, 12, 14
MI	30	0	99,999	1, 4, 5, 7, 8, 9, 12, 13, 14
MN	16	0	99,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
MO	29	0	9,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
MP	1	0	99	7, 9
MS	11	0	999	1, 2, 3, 4, 5, 8, 12, 13, 14
MT	15	0	99	1, 2, 3, 4, 5, 6, 9, 12, 13, 14
NC	33	0	999,999	1, 2, 3, 5, 7, 8, 9, 12, 13, 14
ND	12	0	999,999	1, 4, 5, 9, 12, 13, 14
NE	10	0	9,999	1, 2, 3, 5, 7, 9, 12, 13, 14
NH	2	0	99	1, 2, 3, 5, 9, 12, 13, 14
NJ	15	0	9,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14
NM	9	0	999	1, 3, 4, 5, 9, 12, 13, 14
NV	39	0	49,999,999	1, 2, 3, 5, 9, 12, 13, 14
NY	13	0	9,999	1, 5, 6, 8, 12, 13, 14
OH	39	0	9,999	1, 2, 3, 4, 5, 7, 9, 11, 12, 13, 14
OK	24	0	99,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14
OR	9	0	99	1, 5, 8, 12, 13, 14
PA	51	0	99,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14
PR	5	0	99	1, 3, 5, 11, 12, 13, 14
RI	2	0	999	7, 14
SC	25	0	999,999	1, 3, 4, 5, 6, 7, 8, 10, 12, 13, 14
SD	3	0	99,999	1, 5, 9, 12, 13, 14
TN	26	0	9,999	1, 2, 5, 8, 9, 10, 11, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Mercury Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
TX	83	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
UT	23	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14
VA	17	0	999	1, 3, 4, 5, 6, 7, 9, 10, 12, 13, 14
WA	23	0	999	1, 2, 3, 5, 7, 8, 9, 10, 12, 13, 14
WI	28	0	9,999	1, 3, 4, 5, 7, 8, 9, 12, 13, 14
WV	19	0	999,999	1, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
WY	13	0	99,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI19 2020 (Data are from 2019)

5.2.2 Import/Export

Until 1989, the United States was a net importer of mercury. After that, market values of mercury fluctuated and consumption diminished, leading to a decreased need for imported mercury (DOI 1985; Drake 1981). U.S. imports of mercury fell sharply between 1987 and 1990 (DOI 1990, 1993). The import volumes were: 636 metric tons in 1987, 329 metric tons in 1988, 131 metric tons in 1989, and 15 metric tons in 1990. However, imports of mercury began increasing after 1990: 56 metric tons in 1991, 92 metric tons in 1992, 40 metric tons in 1993, 129 metric tons in 1994, and 277 metric tons in 1995 (USGS 1997). Most recent data show low import volume as compared to the 1990s. In 2015, 2016, 2017, 2018, and 2019, mercury imports were reported as 26, 24, 20, 6, and 10 metric tons, respectively (USGS 2020). According to USGS (2020) for the period 2016−2018, imports were from Canada (39%), France (32%), Switzerland (13%), China (8%), and other countries (8%) (USGS 2020).

Exports of elemental mercury were effectively eliminated on January 1, 2013, as a result of the Mercury Export Ban passed by Congress in 2008 (DeVito and Brooks 2013). In addition, beginning on January 1, 2020, exports of five mercury compounds have also been banned (Mercury (I) chloride or calomel; mercury (II) oxide; mercury (II) sulfate; mercury (II) nitrate; and cinnabar or mercury sulphide) (EPA

2020b). In 2008, 2009, 2010, 2011, and 2012, U.S. exports of mercury were 732, 753, 459, 132, and 110 metric tons, respectively (USGS 2013).

5.2.3 Use

Mercury has many applications in industry due to its unique properties, such as its fluidity, its uniform volume expansion over the entire liquid temperature range, its high surface tension, and its ability to alloy with other metals. However, domestic consumption of mercury has shown a downward trend since the early 1970s. In 1995, consumption was 463 metric tons, down 10% from 1994. In 2019, consumption was estimated as <40 metric tons (USGS 2020). The most important domestic end users of mercury in 2019 were those involved in the production of chlorine-caustic soda (chloralkali), dental products, electronics, and fluorescent-lighting manufacturing industries (USGS 2020). In 2020, the use of mercury in the production of chloralkali was decreased when one of the two operating facilities in the United States converted to a non-mercury process. Many past uses of mercury, such as in automobile convenience switches, alkaline batteries, paints and pigments, fungicides and pesticides, thermometers and other scientific and medical devices, have been discontinued, although these historical uses still represent a significant emission source (CDC 2015). For example, it has been estimated that 150–200 tons of mercury are still contained in old automobiles in the United States and up to 10 tons of mercury per year may be released from shredded vehicles (DeVito and Brooks 2013). Another historical use of note is the former use of mercury in the making of felt hats starting during the industrial revolution through the early 20th century (Beauchamp et al. 2021; Byrns and Penning 2017). Hatters using this process were often exposed to high levels of mercury, which resulted in a characteristic neurological syndrome referred to “Mad Hatter’s Disease” (see Section 2.16).

Electrical Applications. Mercury was a critical element in alkaline batteries; however, mercury use in batteries has been discontinued in the United States, with a few exceptions. The Mercury-Containing and Rechargeable Battery Management Act of 1996 began the phase out of mercury in batteries in the United States. Common AAA, AA, C, and D alkaline batteries no longer contain mercury. The total amount of mercury sold in batteries has declined from 5,585 pounds in 2001 to 1,203 pounds in 2013 (IMERC 2015). Currently, the only types of batteries in the United States that contain mercury are specialty button cell batteries and mercuric oxide batteries used for military and medical applications that that require a high-energy density and a flat voltage curve (IMERC 2015). The EPA estimated that, in 2018, approximately 8,915 pounds of mercury were used to produce switches, relays, and sensors in the United States and an additional 1,637 pounds of mercury were used in lighting lamps and bulbs (EPA 2020b).

Medical Applications. Although many medical and laboratory uses of mercury are being phased out, mercury has been used domestically in laboratories and in a number of medical devices such as gastrointestinal dilators, manometers, sphygmomanometers, and thermometers (DeVito and Brooks 2013). It is also widely used in dental amalgam fillings, which contain approximately 50% metallic mercury, 35% silver, 9% tin, 6% copper, and trace amounts of zinc. The EPA reported that, in 2018, approximately 9,287 pounds of elemental mercury were used to produce dental amalgam in the United States (EPA 2020b). Thimerosal is a mercury-containing compound that prevents the growth of bacteria and fungus and is still used as a preservative for flu vaccines in multi-dose vials to keep the vaccine free from contamination (CDC 2011). It is no longer used in childhood vaccines. The last children's vaccines that used thimerosal as a preservative expired in 2003 (CDC 2020). In 2018, it was estimated that approximately 290 pounds of mercury were used in vaccine usage in the United States (EPA 2020b).

Chemical/Mining Applications. Mercury is a catalyst in reactions to form polymers, such as vinyl chloride and urethane foams. The preparation of chlorine and caustic soda (NaOH) from brines also uses mercury as a catalyst. In this process, mercury is used as a moving cathode to separate sodium and chlorine (Rieber and Harris 1994). This mercury can be recycled with 95% efficiency (Drake 1981). Consumption occurs as mercury is lost in wastewater treatment, recaptured, reprocessed, and sent to landfills (Rieber and Harris 1994).

5.2.4 Disposal

Mercury is an element; thus, its chemical structure cannot be further broken down. In its elemental form, mercury is highly toxic when its vapors are inhaled. Therefore, incineration of mercury is not recommended as a disposal method. Mercury-containing waste products include waste effluents from chloralkali plants and discarded mercury-containing mechanical and electrical devices (DOI 1985). Under current federal guidelines, mercury and its compounds are considered hazardous substances, and various regulations are in effect to control the emission of mercury into the environment (especially organic compounds) (DOI 1985). Emissions from mercury ore processing facilities and mercury cell chloralkali plants are limited to 2.3 kg/day/facility. Emissions of mercury from the incineration or drying of wastewater sludges is limited to 3.2 kg/day/facility (EPA 1975a, 1975b). In addition, dumping wastes containing more than trace amounts of mercury is prohibited.

Recycling of mercury-containing compounds is an important method of disposal. Recycling (retorting) is a treatment for five categories of mercury wastes including: (D009) characteristic mercury; (K106) chlor-alkali waste; (P065) mercury fulminate; (P092) phenylmercuric acetate; and (U151) elemental mercury. From 1987 to 1991, annual production of mercury from old scrap averaged nearly 180 metric tons, equivalent to 16% of the average reported consumption during that period (DOI 1993). Virtually all mercury can be reclaimed from mercury cell chloralkali plants, electrical apparatuses, and control instruments when plants are dismantled or scrapped (DOI 1985). Increased recycling would decrease the mercury load from waste sites and treatment plants. As environmental concerns increase with respect to the disposal of mercury, the recovery by recycling and industrial processes will become a more significant source of domestic supply (DOI 1985).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

Mercury is released to the environment by both natural processes (e.g., volcanic activity, wildfires that release sequestered mercury from biomass, and weathering of mercury-containing rocks) and anthropogenic sources. Pyle and Mather (2003) analyzed data from active volcanoes and estimated that annual mercury emissions from volcanic activity was approximately 700 Mg/year (700 metric tons/year), which accounts for roughly 20–40% of all natural emissions. Studies of 11 western U.S. states between 2000 and 2013 estimated that the average annual emission of mercury due to wildfires in these states was 3,100±1,900 kg/year (3.1 metric tons/year) (Webster et al. 2016).

Anthropogenic releases have historically been primarily to the atmosphere; however, in the United States, these levels have been decreasing as regulations and engineering controls on point source and fugitive emissions limit the amount of mercury released to air. On-site land disposal now accounts for the majority of all of the releases of mercury from facilities that are required to report to the TRI (EPA 2020a). Streets et al. (2017) performed a comprehensive temporal review of worldwide anthropogenic emission sources of mercury and estimated that a cumulative total of 1,540 Gigagrams (1,540,000 metric tons) of mercury have been released to the environment from human activity, the bulk of which (24%) occurred from silver mining and smelting. The cumulative anthropogenic emission budget of mercury to the environment is shown in Table 5-3.

Table 5-3. Cumulative Worldwide Man-made Releases of Mercury to Air, Land, and Water Until 2010

Emission source	Amount released to air (Gg)	Amount released to land/water (Gg)	Total amount (Gg)
Copper smelting	4.91	12.6	17.5
Zinc smelting	10.5	25.3	35.8
Lead smelting	6.04	8.57	14.6
Iron making	1.2	1.45	2.65
Steel making	0.41	2.41	2.82
Mercury production	91.7	321	413
Gold, large-scale production	21	114	135
Gold, artisanal	34.4	51.6	86
Silver production	146	219	365
Cement production	3.29	3.47	6.76
Caustic soda production	8.80	63.6	72.4
Coal combustion	26.4	11.4	37.8
Oil combustion	0.77	0	0.77
Municipal waste incineration	34.6	0	34.6
Other waste burning	27.8	0	27.8
Electrical and measuring equipment	5.52	97.7	179
Chemicals manufacturing	47.5	131	179
Dental	1.06	5.69	6.75
Total Gg (metric tons)	472 (472,000)	1,070 (1,070,000)	1,540 (1,540,000)

Source: Adapted with permission from Streets et al. 2017. Copyright (2017) American Chemical Society.

5.3.1 Air

Estimated releases of 4,409 pounds (~2 metric tons) of elemental mercury to the atmosphere from 329 facilities reporting to TRI domestic manufacturing and processing facilities in 2019, accounted for about 3.3% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). Another 31,119 pounds (~14 metric tons) of mercury compounds released to the atmosphere from 1,063 facilities reporting to TRI domestic manufacturing and processing facilities in 2019, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). These releases are summarized in Tables 5-4 and 5-5.

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Elemental Mercury[a]

		Reported amounts released in pounds (metric tons) per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	1	10	0	0	28	0	10	28	38
AL	7	653	0	0	7	0	657	3	660
AR	4	45	0	0	191	0	236	0	236
AZ	8	33	0	0	64	111	76	132	208
CA	31	335	8	0	30,026	10	29,605	774	30,379
CO	6	51	0	0	14	1	64	1	65
CT	3	1	0	0	0	7	1	7	8
DC	1	0	0	0	0	0	0	0	0
DE	1	1	0	0	0	0	1	0	1
FL	6	76	0	0	125	0	176	25	201
GA	6	3	0	0	16	110	3	126	129
HI	1	14	0	0	0	0	14	0	14
IA	5	293	0	7	0	12,458	300	12,458	12,758
ID	3	1	0	0	230	0	231	0	231
IL	19	16	2	0	3,114	0	3,089	43	3,132
IN	8	50	4	0	186	7	224	23	247
KS	4	37	0	0	522	96	38	106	144
KY	9	12	1	0	6,139	268	916	293	1,208
LA	14	236	187	0	1,791	14	7,896	56	7,952
MA	7	0	0	0	9	6	0	8	8
MD	2	1	0	0	1	0	1	1	2

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Elemental Mercury[a]

		Reported amounts released in pounds (metric tons) per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
ME	2	0	0	0	0	0	0	0	0
MI	5	72	0	0	1	270	79	270	349
MN	6	6	0	0	35	0	7	35	42
MO	2	13	0	0	25	0	32	6	39
MP	1	45	0	14	12,217	0	45	0	45
MS	3	5	0	0	2	0	5	2	7
MT	2	1	0	0	116	0	1	0	1
NC	4	0	0	0	2	0	0	1	1
NE	8	91	0	0	2,336	108	208	132	339
NJ	1	3	0	0	0	0	3	0	3
NM	1	1	0	0	1,401	12	1	112	113
NV	9	28	0	0	104	0	2,353	91	2,444
NY	6	14	7	0	2	26	1,314	35	1,349
OH	20	1,337	13	0	1,362	187	4,535	468	5,003
OK	4	11	0	0	416	0	13	8	21
OR	2	3	0	0	0	418	418	418	836
PA	17	97	589	0	99	35,307	1,091	35,405	36,497
RI	1	0	0	0	1	0	0	1	1
SC	3	27	0	0	5	0	34	1	35
SD	1	30	0	0	80	0	31	0	31
TN	7	32	10	0	8,712	62	42	8,774	8,817
TX	44	231	6	0	90	54	12,503	109	12,612
UT	5	95	0	0	6	1	175	7	182
VA	4	3	0	0	0	0	3	0	3
VT	1	0	0	0	2,411	0	0	0	0
WA	1	0	0	0	398	0	0	0	0
WI	8	21	0	0	2,804	1,973	21	2,259	2,280
WV	10	18	0	0	956	0	3,057	328	3,385

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Elemental Mercury[a]

		Reported amounts released in pounds (metric tons) per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WY	5	357	0	1	140	0	887	9	896
Total	329	4,409 (2)	831 (0.4)	22 (0.01)	76,181 (35)	51,507 (23)	70,395 (32)	62,555 (28)	132,950 (60)

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI19 2020 (Data are from 2019)

Table 5-5. Releases to the Environment from Facilities that Produce, Process, or Use Mercury Compounds[a]

		Reported amounts released in pounds (metric tons) per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	14	80	0	0	431,368	202	431,438	213	431,650
AL	34	1,383	13	0	14,861	62	15,413	904	16,318
AR	17	1,589	10	0	84,508	1	86,061	47	86,108
AZ	20	521	1	0	42,329	2	42,834	18	42,852
CA	65	665	44	0	20,920	230	21,416	443	21,859
CO	19	440	3	0	3,350	34	3,645	182	3,827
CT	2	0	0	0	0	0	0	0	0
DC	1	4	0	0	0	0	4	0	4
DE	3	105	1	0	22	1	128	1	129
FL	33	729	976	1	13,999	17	15,567	154	15,722
GA	21	295	27	0	339	2	553	110	663

Table 5-5. Releases to the Environment from Facilities that Produce, Process, or Use Mercury Compounds[a]

		Reported amounts released in pounds (metric tons) per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
GU	1	0	0	0	0	0	0	0	0
HI	7	31	2	5	17	1	38	18	56
IA	26	226	8	0	1,298	75	935	672	1,607
ID	11	1,023	2	0	2,917	0	3,941	1	3,942
IL	36	1,045	34	0	3,014	6,213	3,645	6,661	10,306
IN	37	2,050	14	0	2,683	200	4,496	451	4,947
KS	21	203	7	0	559	19,679	677	19,771	20,448
KY	23	1,069	8	0	2,783	182	3,768	273	4,041
LA	43	394	13	4	1,468	19	1,846	52	1,898
MA	1	0	0	0	0	0	0	0	0
MD	13	137	5	0	517	28	206	480	686
ME	3	32	0	0	22	0	43	11	54
MI	29	338	13	0	38,686	17	7,094	31,960	39,054
MN	16	196	1	0	890	5	915	177	1,092
MO	28	1,071	6	1	1,106	2,094	2,157	2,121	4,278
MP	1	0	0	0	0	0	0	0	0
MS	11	412	199	22	428	42	701	402	1,104
MT	14	192	1	18	1,091	14	1,268	48	1,316
NC	33	1,200	9	0	36,820	44	3,014	35,058	38,072
ND	11	1,017	6	0	1,269	34	2,180	146	2,326
NE	10	240	2	0	24,378	97	18,707	6,011	24,718
NH	2	3	0	0	110	0	3	110	113
NJ	15	29	52	0	405	707	33	1,160	1,194
NM	9	58	0	2	846	630	906	630	1,536
NV	34	2,935	0	0	4,019,290	330,653	4,007,357	345,523	4,352,879
NY	13	96	0	0	1,723	30	1,818	32	1,850
OH	39	987	17	120	2,759	247	3,530	601	4,130
OK	23	350	4	0	2,095	378	2,240	587	2,827
OR	9	64	4	0	1,958	1	222	1,804	2,027
PA	51	1,676	12	0	4,211	178	3,768	2,310	6,078
PR	5	122	2	0	16	0	125	16	141
RI	2	1	0	0	0	0	1	0	1
SC	25	1,351	12	0	204	115	1,525	157	1,682
SD	3	22	0	0	7,045	0	7,067	0	7,067
TN	26	749	451	0	1,585	36	2,775	46	2,821
TX	83	3,521	235	99	69,103	6,569	70,343	9,183	79,526

Table 5-5. Releases to the Environment from Facilities that Produce, Process, or Use Mercury Compounds[a]

		Reported amounts released in pounds (metric tons) per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
UT	21	675	382	0	87,268	1	80,213	8,114	88,327
VA	17	380	5	0	350	8	713	30	743
WA	23	315	3	0	324	133	583	191	774
WI	27	238	3	0	1,629	2,316	901	3,285	4,186
WV	19	503	17	0	5,296	76	4,694	1,197	5,891
WY	13	356	0	0	767	11	881	254	1,134
Total	1,063	31,119 (14)	2,602 (1)	271 (0.1)	4,938,627 (2,240)	371,384 (168)	4,862,388 (2,206)	481,615 (218)	5,344,003 (2,424)

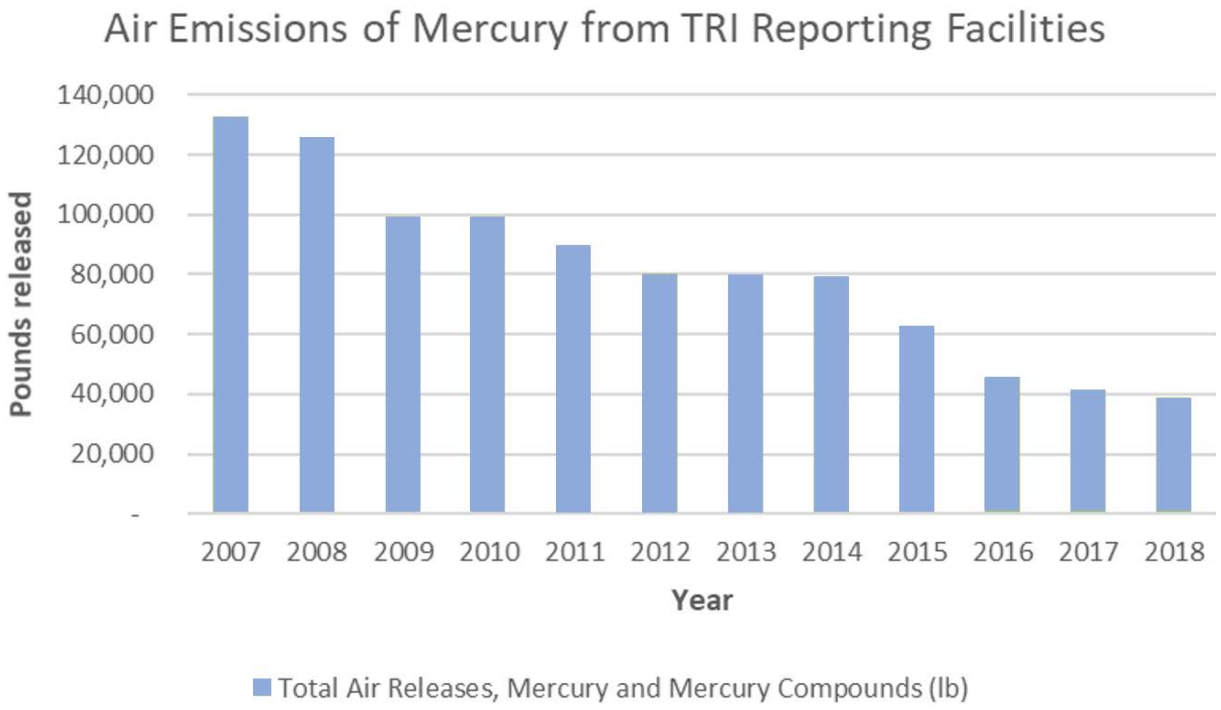
[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI19 2020 (Data are from 2019)

In the United States, atmospheric releases of mercury have been declining for the last 2 decades as fugitive and stack source emissions have been reduced. Figure 5-2 shows the atmospheric emissions of facilities required to report to the TRI from 2007 to 2018 (EPA 2020a).

Figure 5-2. Temporal Atmospheric Emissions of Mercury from Facilities Required to Report to the Toxics Release Inventory



Source EPA 2020a

The bulk of these emissions (>90%) arise from stack emissions rather than fugitive emissions. Releases of mercury and mercury compounds to air decreased by 71% from 2007 to 2018, with electric utility providers having a decline in mercury air emissions of approximately 90% during this period (EPA 2020b).

The United Nations Global Mercury Assessment for 2018 estimated that the global inventory of mercury emissions to the atmosphere from anthropogenic sources in 2015 was approximately 2,220 metric tons (UNEP 2018). Artisanal and small-scale gold mining is the greatest emission source, representing approximately 38% of the total followed by stationary combustion of coal from power plants (13.1%), cement production (10.5%), and non-ferrous metal production, principally aluminum, copper, lead, and zinc (10.3%). Anthropogenic emissions by sector source type are illustrated in Table 5-6. Globally, the greatest amount of atmospheric emissions of mercury are estimated to come from Asia (49%, of which 39% is from East and South-east Asia), followed by South America (18%), and Sub-Saharan Africa (16%). Mercury emissions from cremation, which contributed 0.17% of the total global anthropogenic mercury emissions in 2019 (UNEP 2018), are expected to increase as global cremations increase (Tibau and Grube 2019).

Table 5-6. Global Anthropogenic Emissions of Mercury to the Atmosphere by Sector

Sector	Mercury emissions (range), metric tons	Percentage of total amount
Artisanal and small scale gold mining	838 (675–1,000)	37.7
Stationary combustion of coal from power plants	292 (255–346)	13.1
Cement production (raw materials and fuel, excluding coal)	233 (117–782)	10.5
Non-ferrous metal production (principally aluminum, copper, lead, and zinc)	228 (154–338)	10.3
Waste	147 (120–223)	6.6
Stationary combustion of coal (industrial)	126 (106–146)	5.67
Large-scale gold production	84.5 (72.3–97.4)	3.8
Vinyl-chloride monomer (mercury catalyst)	58.2 (28.0–88.8)	2.6
Stationary combustion of coal (domestic/residential, transportation)	55.8 (36.7–69.4)	2.51
Biomass burning (domestic, industrial, and power plant)	51.9 (44.3–62.1)	2.33
Pig iron and steel production (primary)	29.8 (19.1–76.0)	1.34
Chloralkali production (mercury process)	15.1 (12.2–18.3)	0.68
Waste incineration (controlled burning)	15.0 (8.9–32.3)	0.67
Oil refining	14.4 (11.5–17.2)	0.65
Mercury production	13.8 (7.9–19.7)	0.62
Secondary steel production	10.1 (7.65–18.1)	0.46
Cremation	3.77 (3.51–4.02)	0.17
Stationary combustion of oil (domestic/residential, transportation)	2.70 (2.33–3.21)	0.12
Stationary combustion of oil (power plants)	2.45 (2.17–2.84)	0.11
Stationary combustion of oil (industrial)	1.40 (1.18–1.69)	0.06
Stationary combustion of gas (power plants)	0.349 (0.285–0.435)	0.02
Stationary combustion of gas (domestic/residential, transportation)	0.165 (0.13–0.22)	0.01
Stationary combustion of gas (industrial)	0.123 (0.10–0.15)	0.01
Total	2,220 (2,000, 3,820)	100

Source: UNEP 2018

5.3.2 Water

Estimated releases of 378 pounds (~0.4 metric tons) of elemental mercury to water from 329 facilities reporting to TRI domestic manufacturing and processing facilities in 2019, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). Another 2,691 pounds (~1.2 metric tons) of mercury compounds that were released to the water from 1,063 facilities reporting to TRI domestic manufacturing and processing facilities in 2019, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). These releases are summarized in Tables 5-4 and 5-5.

Natural weathering of mercury-bearing minerals in igneous rocks can contribute substantially to environmental mercury. An analysis conducted in 1972 estimated that this source directly released about 800 metric tons of mercury per year to surface waters of the earth (Gavis and Ferguson 1972). Atmospheric deposition of elemental mercury from both natural and anthropogenic sources has been identified as an indirect source of mercury to surface waters (WHO 1991). Mercury associated with soils can be directly washed into surface waters during rain events. Surface runoff is an important mechanism for transporting mercury from soil into surface waters, particularly for soils with high humic content (Meili 1991). Mercury may also be released to surface waters in effluents from industrial processes (Dean et al. 1972; EPA 1971; UNEP 2018).

Atmospheric deposition is a significant source of mercury emissions to water bodies. Gaseous elemental mercury can remain suspended in the atmosphere for many months and is susceptible to long-range atmospheric transport. While the United States and Canada have reduced mercury emissions significantly over the last several decades, anthropogenic emissions arising from outside of North America continue to deposit mercury into the Great Lakes Basin. The International Joint Commission (IJC) reported that Environment Canada estimates that 95% of anthropogenic deposition in Canada arises from foreign sources (IJC 2015). Cohen et al. (2016) developed a model to estimate atmospheric deposition of mercury to the Great Lakes and calculated that the United States contributed the most anthropogenic emissions (25%), followed by China (6%). Canada's deposition of mercury to the Great Lakes in 2005 was estimated to approximately 2%, while 15% was attributed to India, Russia, and Mexico. All other nations combined were estimated to contribute a little over 4% of the total atmospheric deposition of mercury to the Great Lakes. The rest of the deposition arose from oceanic natural emissions and re-emissions of previously deposited mercury (32%), terrestrial natural emissions and re-emissions (17%), biomass burning (5.1%), and geogenic emissions such as those coming from volcanoes (6.4%).

The Mercury Deposition Network (MDN) provides long-term temporal records of total mercury deposition in precipitation across the United States and Canada. Annual deposition data from the MDN are provided in Table 5-7 for select years for the previous 2 decades.

Table 5-7. Mercury Deposition Data from the Mercury Deposition Network for North America

Year	Deposition (μg/m^2)
1998	10.56
2005	9.08
2010	8.96
2015	8.91
2018	8.78

Source: MDN 2020

According to the United Nations Global Mercury Assessment, anthropogenic global mercury emissions to waters from artisanal and small-scale gold mining was approximately 1,220 metric tons in 2015 (UNEP 2018). The majority of releases occurred in South America (53%), East and Southeast Asia (36%), and Sub-Saharan Africa (8%). Additionally, another 580 metric tons of mercury were released to water from other anthropogenic activities, primarily waste treatment, ore mining and processing, and from the energy sector.

5.3.3 Soil

Estimated releases of 76,181 pounds (~34.6 metric tons) of elemental mercury to soil from 329 facilities reporting to TRI domestic manufacturing and processing facilities in 2019, accounted for about 57% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). Another 4,938,627 pounds (~2,240.8 metric tons) of mercury compounds released to soil from 1,063 facilities reporting to TRI domestic manufacturing and processing facilities in 2019, accounted for over 90% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). These releases are summarized in Tables 5-4 and 5-5.

Atmospheric deposition of mercury from both natural and anthropogenic sources has been identified as an indirect source of mercury to soil and sediments (MDN 2020; Sato and Sada 1992; WHO 1990, 1991). Since vapor-phase mercury is subject to long-range transport, it can be deposited to remote areas such as

the Arctic. Atmospheric deposition of mercury in the Arctic was estimated as 133±9 metric tons per year in 1990 and decreased to 119±10 metric tons in 2005 (Goodsite et al. 2013). Risch et al. (2017) compiled data from the National Atmospheric Deposition Program for years 2007–2014 and determined that the annual deposition flux rate in deciduous-coniferous forests in 16 states in the eastern United States was approximately 11.7 μg/m^2-year (range 2.2–23.4 μg/m^2-year). Mercury is released to cultivated soils through the direct application of inorganic and organic fertilizers (e.g., sewage sludge and compost), and lime (Andersson 1979). The use of biosolids as a nutrient for agricultural soils has the potential to release mercury to soils. Lomonte et al. (2010) studied the levels of mercury in biosolids from a wastewater treatment plant in Melbourne, Australia and found concentrations between 3.5 and 8.4 mg/kg.

Additional anthropogenic releases of mercury to soil are expected as a result of the disposal of industrial and domestic solid waste products (e.g., thermometers, electrical switches, and batteries) to landfills (see Table 5-8). Another source of mercury releases to soil is the disposal of municipal incinerator ash in landfills (Mumma et al. 1990). In 1987, nationwide concentrations of mercury present in the ash from municipal waste incineration ranged from 0.03 to 25 ppm (Mumma et al. 1990). Such releases may exhibit a seasonal variability. For example, fly ash collected prior to Christmas in December of 1989 contained significantly less mercury (6.5 ppm) than ash collected after Christmas in January of 1990 (45–58 ppm), possibly as a result of the increased use and disposal of batteries containing mercury in toys and other equipment used during this season (Mumma et al. 1991). Emission sources include stack emissions, ashes collected at the stack, ashes from electrostatic precipitators, and slags (Morselli et al. 1992). An analysis of mercury concentrations in soil, refuse combustibles, and bottom and fly ash from incinerators showed increasing concentrations of 0, 2, 4, and 100 mg/kg (ppm), respectively (Goldin et al. 1992).

Table 5-8. Estimated Discards of Mercury in Products in Municipal Solid Waste[a]

	Amount in tons (metric tons)[b]						
Products	1970	1975	1980	1985	1989	1995	2000
Batteries							
Alkaline	4.1	38.4	158.2	352.3	419.4	41.6	0.0
Mercuric oxide	301.9	287.8	266.8	235.2	196.6	131.5	98.5[c]
Others	4.8	4.7	4.5	4.5	5.2	3.5	0.0
Subtotal batteries	310.8	330.9	429.5	592.0	621.2	176.6	98.5
Electric lighting							
Fluorescent lamps	18.9	21.5	1.1	0.7	0.8	1.0	11.6[d]
High intensity lamps	0.2	0.3	23.2	27.9	26.0	14.7	1.2
Subtotal lighting	19.1	21.8	24.3	28.6	26.7	15.7	12.6

Table 5-8. Estimated Discards of Mercury in Products in Municipal Solid Waste[a]

Paint residues	30.2	37.3	26.7	31.4	18.2	2.3	0.5
Fever thermometers	12.2	23.2	25.7	32.5	16.3	16.9	16.8
Thermostats	5.3	6.8	7.0	9.5	11.2	8.1	10.3
Pigments	32.3	27.5	23.0	25.2	10.0	3.0	1.5
Dental uses	9.3	9.7	7.1	6.2	4.0	2.9	2.3
Special paper coating	0.1	0.6	1.2	1.8	1.0	0.0	0.0
Mercury light switches	0.4	0.4	0.4	0.4	0.4	1.9	1.9
Film pack batteries	2.1	2.3	2.6	2.8	0.0	0.0	0.0
Subtotal other sources	91.8	107.8	83.7	109.8	61.1	35.1	33.3
Total discards	421.7 (382.6)	460.5 (417.8)	537.5 (487.6)	730.4 (662.6)	709.0 (643.2)	227.4 (206.3)	144.4 (131.0)

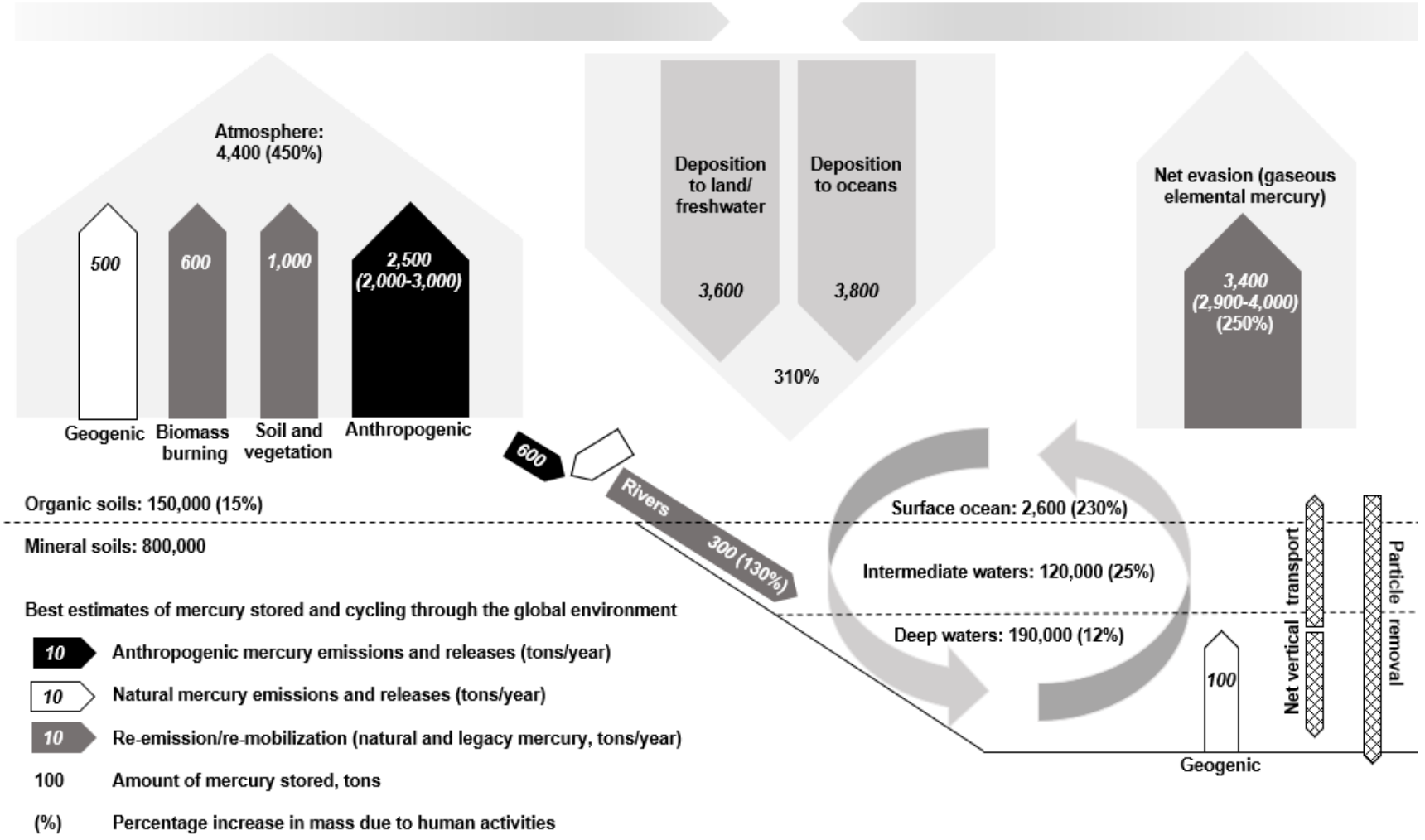
[a]EPA (1992a) (except fluorescent lamps estimates).
[b]Discards before recovery; 1 ton equals 2,000 pounds.
[c]The estimates for the years 1995–2000 do not reflect state, federal, or battery manufacturers' efforts to reduce the mercury content of batteries. Since 1992, several states have restricted mercury use in batteries and/or banned the sale of mercuric oxide batteries. Federal legislation to restrict mercury use in batteries is pending. The battery industry has eliminated mercury as an intentional additive in alkaline batteries, except in button cells.
[d]The estimated contribution of mercury from fluorescent lamps disposal to municipal solid waste was calculated based on industry estimates of a 4% growth rate in sales in conjunction with a 53% decrease in mercury content between 1989 and 1995, and a further 34% decrease in mercury content by the year 2000 (to 15 mg mercury per 4-foot fluorescent lamp) (National Electric Manufacturers Association 1995).

Source: EPA 1996

5.4 ENVIRONMENTAL FATE

The natural global bio-geochemical cycling of mercury is characterized by degassing of the element from soils and surface waters, followed by atmospheric transport, deposition of mercury back to land and surface waters, and sorption of the compound to soil or sediment particulates. Figure 5-3 summarizes the approximate global contributions of natural and anthropogenic sources to the mercury cycle (UNEP 2018). Mercury deposited on land and open water is, in part, revolatilized back into the atmosphere. This emission, deposition, and revolatilization creates difficulties in tracing the movement of mercury to its sources (WHO 1990). Particulate-bound mercury can be converted to insoluble mercury sulfide and precipitated or bioconverted into more volatile or soluble forms that re-enter the atmosphere or are bioaccumulated in aquatic and terrestrial food chains (EPA 1984).

Figure 5-3. Global Mercury Budget: Impact of Human Activities on the Mercury Cycle and the Resulting Increase in Mercury Accumulated in Soils and Oceans



Source: UNEP (2018)

5.4.1 Transport and Partitioning

Air. Mercury has three valence states. The specific state and form of the compound found in an environmental medium is dependent upon a number of factors, including the redox potential and pH of the medium. The most reduced form is metallic or elemental mercury, which is a liquid at ambient temperatures, but readily vaporizes. Over 95% of the mercury found in the atmosphere is gaseous mercury (Hg^0), the form involved in long-range (global) transport of the element. Residence time in the atmosphere has been estimated to range from 6 days (Andren and Nriagu 1979) to 2 years (EPA 1984). Approximately 5% of atmospheric mercury is associated with particulates, which have a shorter atmospheric residence time, are removed by dry or wet deposition, and may show a regional or local distribution pattern (Nater and Grigal 1992). Atmospheric inputs may be more significant in areas where other sources of contamination, such as contaminated rivers, are less important or nonexistent (Kelly et al. 1991). Although local sources are important, a 72-hour travel time trajectory for mercury indicates that some mercury found in rain may originate from sources up to 2,500 km (1,550 miles) away (Glass et al. 1991). Over the last 140 years, the atmospheric mercury concentrations have increased by a factor of 3.7, or approximately 2% per year (Swain et al. 1992).

Metallic mercury released in vapor form to the atmosphere can be transported long distances before it is converted to other forms of mercury, and wet and dry deposition processes return it to land and water surfaces. Dry deposition may account for approximately 70% of the total atmospheric deposition of mercury during the summer, although on an annual basis, wet and dry deposition may be of equal importance (Lindberg et al. 1991). Up to 22% of the annual input of mercury to Lake Erie is from dry deposition of mercury-containing atmospheric particles or from precipitation (Kelly et al. 1991). Wet deposition is the primary method of removal of mercury from the atmosphere (approximately 66%) (Fitzgerald et al. 1991; Lindqvist et al. 1991) and may account for virtually all of the mercury content in remote lakes that do not receive inputs from other sources (e.g., industrial effluents) (Hurley et al. 1991; Swain et al. 1992). Most inert mercury (Hg+2) in precipitation is bound to aerosol particulates, which are relatively immobile when deposited on soil or water (Meili et al. 1991). Mercury is also present in the atmosphere to a limited extent in unidentified soluble forms associated with particulate matter. In addition to wet and dry deposition processes, mercury may also be removed from the atmosphere by sorption of the vapor form to soil or water surfaces (EPA 1984).

Water. In soils and surface waters, mercury can exist in the mercuric (Hg^{+2}) and mercurous (Hg^{+1}) states as a number of complex ions with varying water solubilities. Mercuric mercury, present as complexes

and chelates with ligands, is probably the predominant form of mercury present in surface waters. The transport and partitioning of mercury in surface waters and soils are influenced by the particular form of the compound. More than 97% of the dissolved gaseous mercury found in water consists of elemental mercury (Vandal et al. 1991). Volatile forms (e.g., metallic mercury and dimethylmercury) are expected to evaporate to the atmosphere, whereas solid forms partition to particulates in the soil or water column and are transported downward in the water column to the sediments (Hurley et al. 1991). Vaporization of mercury from soils may be controlled by temperature, with emissions from contaminated soils being greater in warmer weather when soil microbial reduction of Hg^{+2} to the more volatile elemental mercury is greatest (Lindberg et al. 1991). Vapor-phase mercury volatilized from surface waters has been measured (Schroeder and Fanaki 1988); however, the dominant process controlling the distribution of mercury compounds in the environment appears to be the sorption of nonvolatile forms to soil and sediment particulates, with little resuspension from the sediments back into the water column (Bryan and Langston 1992). Cossa et al. (1988) found that 70% of the dissolved mercury in St. Lawrence River water was associated with organic matter. The study authors reported that the removal mechanism was flocculation of organic mercury colloids in freshwater. Methylmercury and other mercury fractions are strongly bound to organic matter in water and may be transported in runoff water from contaminated lakes to other surface waters and soils (Lee and Iverfeldt 1991). Small amounts (2–4 ng/L [ppt]) of mercury are able to move from contaminated groundwater into overlying lakes, with concentrations reaching a maximum near the sediment/water interface; however, since most of the mercury in the groundwater is derived from atmospheric sources, this low range of values indicates that most of the mercury deposited on soil (92–96% of the 10.3 µg/m^2/year of mercury deposited) is absorbed to the soil and does not leach down into the groundwater (Krabbenhoft and Babiarz 1992).

Sediment and Soil. The sorption process has been found to be related to the organic matter content of the soil or sediment. Mercury is strongly sorbed to humic materials and sesquioxides in soil at a pH >4 (Blume and Brummer 1991) and to the surface layer of peat (Lodenius and Autio 1989). Mercury has been shown to volatilize from the surface of more acidic soils (i.e., soil pH <3.0) (Warren and Dudas 1992). Adsorption of mercury in soil is decreased with increasing pH and/or chloride ion concentrations (Schuster 1991). Mercury is sorbed to soil with high iron and aluminum content up to a maximum loading capacity of 15 g/kg (15,000 ppm) (Ahmad and Qureshi 1989). Inorganic mercury sorbed to particulate material is not readily desorbed. Thus, freshwater and marine sediments are important repositories for inorganic forms of the element, and leaching is a relatively insignificant transport process in soils. However, surface runoff is an important mechanism for moving mercury from soil to water, particularly for soils with high humic content (Meili 1991). Mobilization of sorbed mercury from

particulates can occur through chemical or biological reduction to elemental mercury and bioconversion to volatile organic forms (Andersson 1979; EPA 1979, 1984). Metallic mercury may move through the top 3–4 cm of dry soil at atmospheric pressure; however, it is unlikely that further penetration would occur (Eichholz et al. 1988). Bachand et al. (2019) demonstrated that addition of coagulants, such as polyaluminum chloride and ferric sulfate, to soils contaminated with mercury reduced the transfer into aquatic systems by sequestering mercury into insoluble particulate forms resulting in enhanced settling of particles.

The volatilization and leaching of various forms of mercury (elemental, mercuric sulfide, mercuric oxide, and mercurous oxide) from soils or wastes were examined using the headspace method for volatilization and the Resource and Conservation Recovery Act (RCRA) leaching protocols for leaching through soil to determine if the leachates exceeded the RCRA limit of 200 µg/L (ppb) (Willett et al. 1992). With the exception of mercuric sulfide, the other forms of mercury increased in concentrations in the headspace vapor and in the leachate as the soil concentrations increased, although the elemental mercury concentrations never exceeded the RCRA limit, indicating that it was relatively nonleachable. Mercuric sulfide also did not exceed the background level for the leachate and was consistently <0.001 mg/m^3 for the vapor concentrations, indicating that it was also nonleachable and did not readily volatilize. This study also showed that concentrations of mercury in leachate could not be correlated with the concentration of mercury in the soil or in the headspace vapors (Willett et al. 1992). Mercuric sulfide has been found to strongly adsorb to soil, and even with weathering, any mercury released from the mercuric sulfide is readsorbed by the soil (Harsh and Doner 1981).

Other Media. Mercury emitted to the atmosphere is primarily in an inorganic form and it remains primarily in the inorganic form when deposition occurs to water bodies. However, in water and sediments, inorganic mercury can be transformed into methylmercury, which is very prone to bioaccumulate and biomagnify as it moves through the food chain (Riisgard and Hansen 1990; UNEP 2018). In a study of bioaccumulation of mercury in aquatic organisms, it was shown that fish had lower methylmercury bioaccumulation factors in sites with high organic carbon, especially sites with large coastal wetlands and large variability in dissolved organic carbon levels in the water column (Taylor et al. 2018b). Methylmercury in surface waters is rapidly accumulated by aquatic organisms; concentrations in carnivorous fish (e.g., pike, shark, and swordfish) at the top of both freshwater and marine food chains are biomagnified on the order of 10,000–100,000 times the concentrations found in ambient waters (EPA 1979, 1984; WHO 1990, 1991). The range in experimentally determined bioconcentration factor (BCF) values is shown in Table 5-9. The bioaccumulation potential for methylmercury in fish is influenced by

the pH of the water, with a greater bioaccumulation seen in waters with lower pH (BDI 2011; Ponce and Bloom 1991). Mercury concentrations in fish have also been negatively correlated with other water quality factors, such as alkalinity and dissolved oxygen content (Ontario Ministry of the Environment 1991). Biogeochemical and ecological mechanisms are responsible for the transfer of mercury from near-shore contaminated sediments to higher trophic levels in offshore environments. Anoxic conditions in estuaries favor the production of methylmercury; however, sediments high in total organic carbon and iron sulfides tend to reduce the bioavailability of mercury in these areas. Trophic relay or bioadvection of methylmercury from sediments in contaminated estuaries to offshore pelagic organisms may occur through predator-prey relationships or the movement of juvenile species to deeper waters (Chen et al. 2009).

Table 5-9. Bioconcentration of Various Mercury Compounds by Freshwater and Saltwater Organisms

Species	Tissue	Chemical	Duration (days)	Bioconcentration factor[a]
Freshwater species				
Mercury (II)				
Rainbow trout *Salmo gairdneri*	Whole body	Mercuric chloride	60	1,800
Fathead minnow *Pimphales promelas*	Whole body	Mercuric chloride	287	4,994[b]
Organomercury compounds				
Rainbow trout *S. gairdneri*	Whole body	Methylmercuric chloride	60	11,000
Rainbow trout *S. gairdneri*	Whole body	Methylmercuric chloride	75	85,700
Brook trout *Salvelinus fontinalis*	Muscle	Methylmercuric chloride	273	11,000–33,000
Brook trout *S. fontinalis*	Whole body	Methylmercuric chloride	273	10,000–23,000
Brook trout *S. fontinalis*	Muscle and whole body	Methylmercuric chloride	756	12,000
Fathead minnow *P. promelas*	Whole body	Methylmercuric chloride	336	44,130–81,570
Saltwater species				
Mercury (II)				
Eastern oyster (adult) *Crassostrea virginica*	Soft parts	Mercuric chloride	73	10,000
American lobster (adult) *Homarus americanus*	Soft parts	Mercuric chloride	30	129

Table 5-9. Bioconcentration of Various Mercury Compounds by Freshwater and Saltwater Organisms

Organomercury compounds				
Eastern oyster (adult) *C. virginica*	Soft parts	Methylmercuric chloride	74	40,000
Eastern oyster (adult) *C. virginica*	Soft parts	Phenylmercuric chloride	74	40,000

[a]Results are based on the concentration of mercury, not the concentration of the mercury compound to which the animal was exposed.
[b]From concentrations that caused adverse effects in a life-cycle test.

Source: ASTER 1997

Mercury levels in freshwater fish have been shown to be elevated in areas impacted by gold mining operations (Diringer et al. 2015; Salazar-Camacho et al. 2021). A study of fish impacted by gold mining in the Atrato River Basin, Columbia identified a correlation between total mercury levels with fish length and trophic level, indicating that mercury was biomagnifying in the ecosystem. The median total mercury level in all carnivorous fish (n=533) was 225.4±344.3 µg/kg and the median level in all non-carnivorous fish (n=289) was 82.4±91.3 µg/kg. Total mercury concentrations (median±SD) in the fish categorized by trophic level are shown in Table 5-10.

Table 5-10. Mercury Concentrations Found in Fish

Species	Total mercury median (±SD) µg/kg	Trophic level
Doncella *Ageneiosus pardalis*	678.5±344.9	3.8
Moncholo *Hoplias malabaricus*	401.4±278.5	4.5
Caga *Trachelyopterus fisheri*	374.3±250.0	3.5
Bagre sapo *Pseudopimelodus schultzi*	432.7±897.0	3.7
Agujeta *Ctenolucius beani*	270.9±289.1	4
Majarra Negra *Caquetaia umbrifera*	218.5±221.1	3.8
Mayupa *Sternopygus macrurus*	177.0±452.2	3.2
Mojarra Amarilla *Caquetaia kraussii*	218.0±200.6	3.4
Liso *Rhamdia quelen*	145.8±211.6	3.9

Table 5-10. Mercury Concentrations Found in Fish

Species	Total mercury median (±SD) µg/kg	Trophic level
Sardina colirroja *Astyanax fasciatus*	117.2±113.7	3
Charre *Pimelodus punctatus*	100.5±66.9	3.3
Cocobolo *Andinoacara pulcher*	116.7±59.7	3.3
Dentón *Leporinus muyscorum*	116.7±68.0	2.2
Bocachico *Prochilodus magdalenae*	93.1±113.2	2.1
Guacuco *Hypostomus hondae*	56.0±55.5	2
Viejita *Cyphocharax magdalenae*	32.0±53.2	2

Source: Salazar-Camacho et al. 2021

Ruus et al. (2015) analyzed different species in the Kongsfjorden food web system in Norway and found that tissue concentrations of methylmercury increased with increasing trophic level and were highly correlated with total mercury levels. The highest levels of total mercury and methylmercury were observed in birds (95–1,108 ng/g), which were at the highest trophic level in the food web, and the lowest levels were found in zooplankton (4.7–7.5 ng/g), the lowest trophic level in the foodweb.

Biomagnification factors for methylmercury in the food webs of Lake Ontario were lowest for the transfer of methylmercury from mysids to amphipods (1.1), plankton to amphipods (1.8), and plankton to mysids (2.4); intermediate for the transfer from mysids to fish (5.1) and amphipods to fish (6.5); and highest for the transfer from plankton to fish (10.4) (Evans et al. 1991). The biomagnification of methylmercury from water through several trophic levels is compared to the biomagnification of inorganic mercury in Table 5-11. Watras and Bloom (1992) reported that biomagnification of methylmercury in Little Rock Lake seems to be the result of two processes: the higher affinity of inorganic mercury in lower trophic level organisms and the high affinity of methylmercury in fish. Fish appear to accumulate methylmercury from both food sources and the water column. However, Hall et al. (1997) found that food was the predominant source of mercury uptake in fish. The BCF of methylmercury in fish in Little Rock Lake was $3x10^6$ (Porcella 1994). Mason et al. (1995) also compared bioaccumulation of inorganic mercury and methylmercury and found that passive uptake of the mercury complexes ($HgCl_2$ and CH_3HgCl) results in high concentrations of both the inorganic and methylated mercury in phytoplankton. However, differences in partitioning within phytoplankton cells between inorganic mercury (which is principally

membrane-bound) and methylmercury (which accumulated in the cytoplasm) led to a greater assimilation of methylmercury during zooplankton grazing.

Table 5-11. Comparison of the Biomagnification of Methylmercury and Inorganic Mercury in a Freshwater Food Chain (Little Rock Lake)

Medium or trophic level	Methylmercury	Inorganic mercury	Percent methylmercury
Water	1	10	10
Phytoplankton	10^5	$10^{5.7}$	15
Zooplankton	$10^{5.5}$	$10^{5.9}$	30
Fish	$10^{6.5}$	10^5	95

Source: Watras and Bloom 1992

Rumbold et al. (2018) studied biomagnification of mercury in two different locations along the Florida Keys using 50 different species of fish to determine whether the high biodiversity in coral reefs in these complex food webs reduces the biomagnification potential in these regions. It was determined that the Trophic Magnification Slopes (TMS) were very similar for the two sites and that these TMS were also within the ranges of slopes reported for food webs in other ecosystems; therefore, biomagnification of mercury in fish muscle tissue was not reduced in this complex ecosystem. In a similar study conducted along the coast of the Florida Keys, Thera and Rumbold (2014) assessed the trophic biomagnification factor of mercury using 57 species of invertebrates. They concluded that the levels of mercury increased by a factor of 5 with each unit increase in trophic level.

Most of the discrimination between inorganic and methylmercury thus occurs during trophic transfer, while the major enrichment factor is between water and the phytoplankton. This also has been reported for the diatom, *Thalassiosura weissflogii*, in a marine food chain (Mason et al. 1996). Methylmercury was accumulated in the cell cytoplasm, and its assimilation by copepods was 4 times more efficient than the assimilation of inorganic mercury. Bioaccumulation has been demonstrated for predator fish in both freshwater and marine systems and in marine mammals.

Aquatic macrophytes have been found to bioconcentrate methylmercury in almost direct proportion to the mercury concentration in the water (Ribeyre et al. 1991). Mortimer (1985) reported BCFs for several species of submerged aquatic plants exposed to inorganic mercury in laboratory aquaria of 3,300, 1.3, 0.9, and 1.3 for *Utricularia*, *Ceratophyllum*, *Najas*, and *Nitella*, respectively. The concentration factors used by this author was based on µg g^{-1} dry weight in the plant/µg mL^{-1} water day^{-1}.

The potential for bioaccumulation in terrestrial food chains is demonstrated by the uptake of mercury by the edible mushroom, *Pleurotus ostreatus*, grown on compost and containing mercury at concentrations of up to 0.2 mg/kg (ppm). The bioaccumulation factors reported ranged from 65 to 140, indicating that there are potential risks to human health if these mushrooms are eaten in large quantities (Bressa et al. 1988). Elevated concentrations of mercury in 149 samples of mushrooms representing 11 different species were reported by Kalac et al. (1991). The study authors collected mushrooms within 6 km of a lead smelter in Czechoslovakia in operation since 1786. Mercury was accumulated by *Lepista nuda* and *Lepiota rhacodes* at 11.9 mg/kg (ppm) and 6.5 mg/kg (ppm) (dry weight), respectively. The mean concentration of other species ranged from 0.3 to 2.4 mg/kg (ppm). Concentrations of mercury in most of the mushroom species collected in that location were higher than in mushrooms collected in other parts of the country.

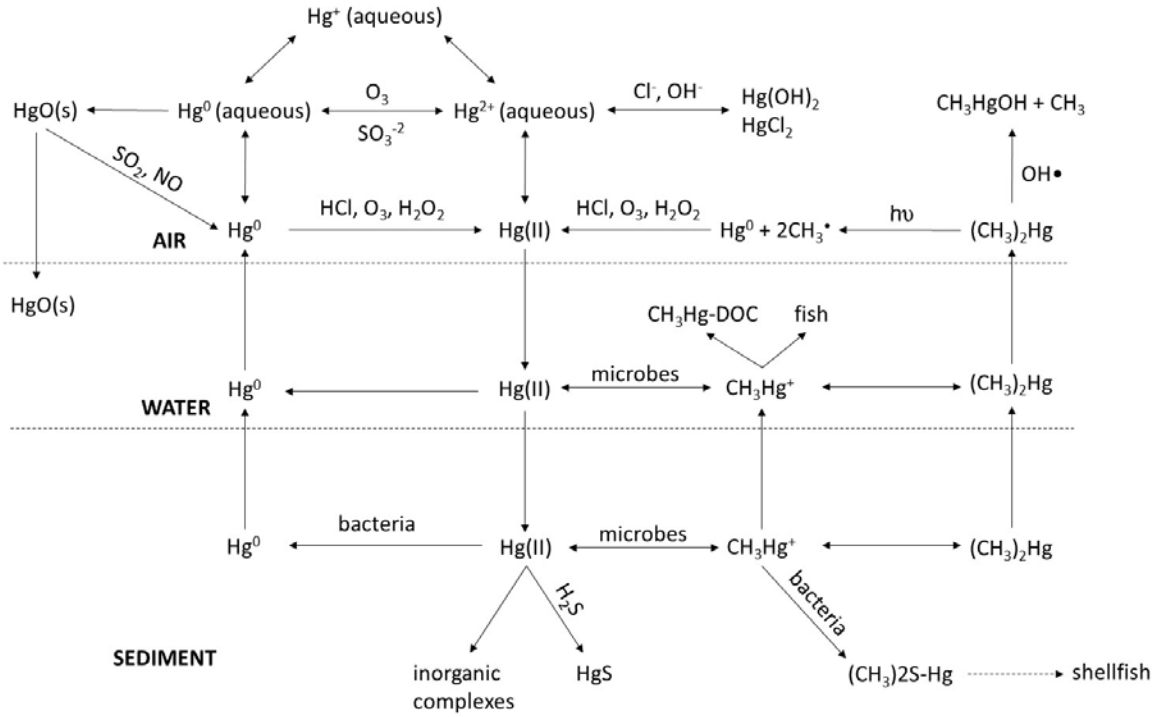
Data from higher plants indicate that virtually no mercury is taken up from the soil into the shoots of plants such as peas, although mercury concentrations in the roots may be significantly elevated and reflect the mercury concentrations of the surrounding soil (Lindqvist et al. 1991). In a study by Granato et al. (1995), municipal solid waste sludge mercury concentrations from the Metropolitan Water Reclamation District of Greater Chicago were found to range from 1.1 to 8.5 mg/kg (ppm), with a mean concentration of 3.3 mg/kg (ppm). From 1971 to 1995, sludge applications were made to a Fulton County, Illinois sludge utilization site. About 80–100% of the mercury applied to the soils in sewage sludge since 1971 still resided in the top 15 cm of soil. The study authors reported that sewage sludge applications did not increase plant tissue mercury concentrations in corn or wheat raised on the sludge utilization site.

Earthworms, *Lumbricus sp.*, bioaccumulate mercury under laboratory and field conditions in amounts that are dependent on soil concentrations and exposure duration (Cocking et al. 1994). Maximum mercury tissue concentrations in laboratory cultures were only 20% of the 10–14.8 µg/g (ppm) (dry weight) observed in individual worms collected from contaminated soils (21 µg/g) on the South River flood plain at Waynesboro, Virginia. Bioconcentration occurred under field conditions in uncontaminated control soil (0.2 µg Hg/g); however, total tissue mercury concentrations (0.4–0.8 µg/g dry weight) were only 1–5% of those for earthworms collected on contaminated soils. Uptake by the earthworms appeared to be enhanced in slightly acidic soils (pH 5.9–6.0) in laboratory cultures. Soil and earthworm tissue mercury contents were positively correlated under both field and laboratory conditions. Predation of earthworms contaminated with mercury could pass the contamination to such predators as moles and ground-feeding birds, such as robins (Cocking et al. 1994).

5.4.2 Transformation and Degradation

Mercury is transformed in the environment by biotic and abiotic oxidation and reduction, bioconversion of inorganic and organic forms, and photolysis of organomercurials. Inorganic mercury can be methylated by microorganisms indigenous to soils, fresh water, and salt water (Blanc et al. 2018). This process is mediated by various microbial populations under both aerobic and anaerobic conditions. The most probable mechanism for this reaction involves the nonenzymatic methylation of mercuric mercury ions by methyl cobalamin compounds produced as a result of bacterial synthesis. Mercury forms stable complexes with organic compounds. Monoalkyl mercury compounds (e.g., methylmercuric chloride) are relatively soluble; however, the solubility of methylmercury is decreased with increasing dissolved organic carbon content, indicating that it is bound by organic matter in water (Miskimmin 1991). Dialkyl mercury compounds (e.g., dimethyl-mercury) are relatively insoluble (EPA 1979, 1984). Dimethyl-mercury is volatile, although it makes up <3% of the dissolved gaseous mercury found in water (Andersson et al. 1990; Vandal et al. 1991). The major pathways for transformation of mercury and various mercury compounds in air, water, and soil are shown in Figure 5-4.

Figure 5-4. Transformation of Mercury in Air, Water, and Sediment



Dashed lines represent the boundary between environmental compartments.

Air. The primary form of atmospheric mercury, metallic mercury vapor (Hg^0), is oxidized by ozone to other forms (e.g., Hg^{+2}) and is removed from the atmosphere by precipitation (Brosset and Lord 1991). The oxidation/reduction of mercury with dissolved ozone, hydrogen peroxide, hypochlorite entities, or organoperoxy compounds or radicals may also occur in the atmosphere (Schroeder et al. 1991). The overall residence time of elemental mercury in the atmosphere has been estimated to be 6 days to 2 years, although in clouds, a fast oxidation reaction on the order of hours may occur between elemental mercury and ozone. Some mercury compounds, such as mercuric sulfide, are quite stable in the atmosphere as a result of their binding to particles in the aerosol phase (Lindqvist et al. 1991). Other mercury compounds, such as mercuric hydroxide ($Hg[OH]^2$), which may be found in the aqueous phase of the atmosphere (e.g., rain), are rapidly reduced to monovalent mercury in sunlight (Munthe and McElroy 1992). The main atmospheric transformation process for organomercurials appears to be photolysis (EPA 1984; Johnson and Braman 1974; Williston 1968).

Water. The most important transformation process in the environmental fate of mercury in surface waters is the methylation and demethylation cycle. The methylation of mercury in surface waters is largely driven by the presence of sulphate-reducing bacteria, and demethylation can occur through both abiotic and biotic means (Ouddane et al. 2015). The photochemical degradation of methylmercury is the most important process of the demethylation cycle at the surface or in shallow waters. Demethylation by biotic oxidation and reduction reactions are the dominant pathways at deeper depths and in sediments.

Any form of mercury entering surface waters can be microbially converted to methylmercury, given favorable conditions. The major factors that influence the rate of methylation are the abundance of anaerobic microorganisms that have the biochemistry to methylate mercury and the bioavailability of inorganic Hg(II) in these microorganisms (SERDP 2014). Sulfur-reducing bacteria are responsible for most of the mercury methylation in the environment (Gilmour and Henry 1991; Ouddane et al. 2015), with anaerobic conditions favoring their activity (Regnell and Tunlid 1991). Yeasts, such as *Candida albicans* and *Saccharomyces cerevisiae*, whose growth is favored by low pH conditions, are able to methylate mercury and are also able to reduce ionic mercury to elemental mercury (Yannai et al. 1991). Methyl cobalamin compounds produced by bacterial synthesis appear to be involved in the nonenzymatic methylation of inorganic mercury ions (Regnell and Tunlid 1991). The rate of methylmercury formation by this process is largely determined by the concentration of methyl cobalamin compounds, inorganic mercuric ions, and the oxygen concentration of the water, with the rate increasing as the conditions become anaerobic. Volatile elemental mercury may be formed through the demethylation of

methylmercury or the reduction of inorganic mercury, with anaerobic conditions again favoring the demethylation of the methylmercury (Barkay et al. 1989; EPA 1979; Regnell and Tunlid 1991). Increased dissolved organic carbon levels reduce methylation of mercury in the water column (Gilmour and Henry 1991), possibly as a result of the binding of free mercury ions to the dissolved organic carbon at low pH, thus reducing their availability for methylation, or the dissolved organic carbon may inhibit the methylating bacteria (Miskimmin et al. 1992). Alternatively, low pH favors the methylation of mercury in the water column, particularly in acid deposition lakes, while inhibiting its demethylation (Gilmour and Henry 1991). It has also been shown that the methylation rate is not affected by addition of sulfate in softwater lakes (Kerry et al. 1991). Even in polar marine systems, methylation of mercury can occur. Sea water and ice samples were collected in the East Antarctic sea and analyzed for total mercury and methylmercury (Gionfriddo et al. 2016). The marine nitrite-oxidizing bacterium, Nitrospina, was identified as the most likely source for microbially induced methylation of mercury in polar ice and water.

At a pH of 4–9 and a normal sulfide concentration, mercury will form mercuric sulfide. This compound is relatively insoluble in aqueous solution ($11x10^{-17}$ ppb), and it will therefore precipitate out and remove mercury ions from the water, reducing the availability of mercury to fish. Under acidic conditions, however, the activity of the sulfide ion decreases, thus inhibiting the formation of mercuric sulfide and favoring the formation of methylmercury (Bjornberg et al. 1988). Low pH and high mercury sediment concentrations favor the formation of methylmercury, which has greater bioavailability potential for aquatic organisms than inorganic mercury compounds. Methylmercury may be ingested by aquatic organisms lower in the food chain, such as yellow perch, which in turn are consumed by piscivorous fish higher in the food chain (Cope et al. 1990; Wiener et al. 1990). Mercury cycling occurs in freshwater lakes, with the concentrations and speciation of the mercury being dependent on limnological features and water stratification. Surface waters may be saturated with volatile elemental mercury, whereas sediments are the primary source of the mercury in surface waters. During the summer months, surface concentrations of methyl and elemental mercury decline as a result of evaporation, although they remain relatively constant in deeper waters (Bloom and Effler 1990).

Abiotic reduction of inorganic mercury to metallic mercury in aqueous systems can also occur, particularly in the presence of soluble humic substances (i.e., acidic waters containing humic and fulvic acids). This reduction process is enhanced by light, occurs under both aerobic and anaerobic conditions, and is inhibited by competition from chloride ions (Allard and Arsenie 1991).

Sediment and Soil. Mercury compounds in soils may undergo the same chemical and biological transformations described for surface waters. Mercuric mercury usually forms various complexes with chloride and hydroxide ions in soils; the specific complexes formed depend on the pH, salt content, and composition of the soil solution. Formation and degradation of organic mercurials in soils appear to be mediated by the same types of microbial processes occurring in surface waters and may also occur through abiotic processes (Andersson 1979). Elevated levels of chloride ions reduce methylation of mercury in river sediments, sludge, and soil (Olson et al. 1991), although increased levels of organic carbon and sulfate ions increase methylation in sediments (Gilmour and Henry 1991). In freshwater and estuarine ecosystems, the presence of chloride ions (0.02 M) may accelerate the release of mercury from sediments (Wang et al. 1991). Cesario et al. (2017) studied the methylation and demethylation kinetics of mercury in sediments, with and without salt-marsh plant vegetation, obtained from the Guadiana and Tagus Estuaries, Portugal. Methylation and demethylation rates varied between sediments of the estuaries depending upon the presence of vegetation and the macrophyte species present. The highest methylation rate constant was observed in *Sarcocornia fruticosa* vegetated sediments at the Castro Marim site in Guadiana (Km = 0.160 day^{-1},) and the lowest rate constant was observed in non-vegetated sediments at the Alcochete site in Tagus (Km = 0.009 day^{-1}). The role that vegetation plays in methylation cycling of mercury was studied by examining the seasonal variation of methylmercury production in three types of flooded agricultural wetlands (white rice, wild rice, and fallow fields), and two permanently flooded, non-agricultural managed wetland areas in the Yolo Bypass Wildlife Unit California (Windham-Myers et al. 2014). In addition to transport and transformation reactions that occur in air, water, soil and sediment, plant biomass also plays an indirect role in the methylation and demethylation cycle of mercury. Inorganic mercury may be taken up through plant roots in contaminated soils or deposited on leafy surfaces following atmospheric deposition, whereas methylmercury appears to be primarily taken up by plants via the root system (Windham-Myers et al. 2014). Thus, the transport of methylmercury into plants in wetland environments provides a temporary storage sink and reduces the levels in the surrounding aquatic environments. However, decomposition of plant tissue, deforestation, clearing of wetlands, and fires can release stored methylmercury to other environmental media. Methylmercury levels in rice leaves tended to increase from summer to fall during the growing season and were shown to correlate with root methylmercury levels. Degrading litter residue was shown to correlate with increased methylmercury production during the winter months in the wetlands.

The rates of mercury methylation and demethylation were studied in sediments obtained from the Deûle River, France (Ouddane et al. 2015). Sampling was conducted at two locations that were contaminated with mercury from previous industrial activity. At the first location, demethylation, rather than

methylation, was the dominant process. The study authors surmised that high levels of mercury found in this heavily contaminated site resulted in an increase in the rate of bacterial demethylation, either by reduction producing Hg^0 or oxidation yielding Hg^{2+} and CO_2. For the second site sampled, where total mercury levels were lower than the first site, the average net methylation potential was positive (methylation occurred at a greater rate than demethylation) even though there were sediments obtained at some depths where the rate of demethylation was greater than methylation.

In the late 1950s, unknown quantities of mercuric nitrate and elemental mercury were released into East Fork Poplar Creek from a government facility in Oak Ridge, Tennessee. Total mercury concentrations in the flood plain soil along the creek ranged from 0.5 to 3,000 ppm (Revis et al. 1989). The form of that mercury has been reported to be primarily mercuric sulfide (85–88%), with 6–9% present as elemental mercury (Revis et al. 1989, 1990). A very small amount was detected in the form of methylmercury (<0.02%). The reported presence of the mercuric sulfide suggests that the predominant biological reaction in soil for mercury is the reduction of Hg^{+2} to mercuric sulfide by sulfate-reducing bacteria under anaerobic conditions (Revis et al. 1989, 1990). Mercuric sulfide has very limited water solubility ($4.5x10^{-24}$ mol/L), and thus, in the absence of other solvents, is likely to have limited mobility in soil. Aerobic microorganisms can solubilize Hg^{+2} from mercuric sulfide by oxidizing the sulfide through sulfite to sulfate, with the Hg^{+2} being reduced to elemental mercury (Wood 1974). However, examination of the weathering of mercuric sulfide indicated that mercuric sulfide does not undergo significant weathering when bound to riverwash soil with a pH of 6.8, although degradation may be increased in the presence of chloride and iron (Harsh and Doner 1981).

Mercury, frequently present in mine tailings, was toxic to bacteria isolated from a marsh treatment system used to treat municipal wastewaters. The minimum concentration that inhibited the bacteria (as determined by intracellular ATP levels) was approximately 0.07±0.15 mg/L (ppm) (Desjardins et al. 1988).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to mercury depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of mercury in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical detection methods. In reviewing data on mercury levels monitored or estimated in

the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-12 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the ranges of concentrations detected worldwide in environmental media is presented in Table 5-13.

Table 5-12. Lowest Limit of Detection Based on Standards[a,b]

Media	Detection limit	Reference
Air	30 pg/m^3 (particulate); 45 pg/m^3 (vapor)	EPA 1999a Method IO-5
Drinking water	0.2 ng/L	EPA 2002 Method 1631E
Surface water and groundwater	0.2 ng/L	EPA 2002 Method 1631E
Soil	4.8 µg/kg	Frentiu et al. 2013
Sediment	4.8 µg/kg	Frentiu et al. 2013
Whole blood	0.2–0.33 µg/L	CDC 2019

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.
[b]A review of analytical methods to detect mercury in environmental matrices has been published by Suvarapu and Baek (2017).

Table 5-13. Summary of Environmental Levels of Mercury Worldwide

Media	Low	High	For more information
Outdoor air (ng/m^3)	0.000161 (particulate)	174,000 (vapor)	Section 5.5.1
Indoor air (ng/m^3)	<3	1,500	Section 5.5.1
Surface water (ppb)	<0.002	0.09	Section 5.5.2
Ground water (ppb)	0.21	300	Section 5.5.2
Drinking water (ppb)	<0.025	300	Section 5.5.2
Food (ppm)	<0.01	0.509	Section 5.5.4
Soil (ppm)	0.063	141,000	Section 5.5.3

Detections of mercury in air, water, and soil at NPL sites are summarized in Table 5-14.

Table 5-14. Mercury Levels in Water, Soil, and Air at National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	2	3.50	16.3	316	188
Soil (ppb)	1,750	2,720	28.7	376	216
Air (ppbv)	0.334	0.382	61.2	25	17

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

The vast majority of mercury found in the atmosphere occurs in the form of Hg^0 (gaseous elemental mercury). Total gaseous mercury (TGM) represents the sum of all gaseous compounds and gaseous elemental mercury, and has been reported to have a global background concentration typically in the range of 1.5–2.0 ng/m^3, although levels can vary due to local sources (Gworek et al. 2017). Data on mercury air levels are available at the Air Quality System (AQS) database, which contains ambient air quality data collected by EPA, state, local, and tribal air pollution control agencies from monitors throughout the country. For 2019, the arithmetic mean vapor phase levels ranged from 1.11 to 2.22 ng/m^3, with a maximum level of 248 ng/m^3 reported in Milwaukee, Wisconsin (EPA 2019). The arithmetic mean mercury concentration of total suspended particulates (TSP) ranged from 0.009 to 0.0025 ng/m^3. The arithmetic mean mercury levels associated with PM_{10} (particulate matter 10-micron diameter or less) ranged from 0.00619 to 1.50 ng/m^3, while the arithmetic means for mercury associated with $PM_{2.5}$ were 0.000161–0.000317 ng/m^3.

The Atmospheric Mercury Network (AMN) and the Mercury Deposition Network operate monitoring sites to record temporal atmospheric concentrations of mercury and deposition rates in North America. The average gaseous elemental mercury concentrations from the AMN from 2008 to 2018 are shown in Table 5-15.

Table 5-15. Atmospheric Mercury Network (AMN) Average Gaseous Elemental Mercury Concentrations, 2008–2018

Year	Averaged gaseous elemental mercury level (ng/m^3)
2008	1.53
2009	1.48
2010	1.50
2011	1.47
2012	1.49
2013	1.50
2014	1.53
2015	1.47
2016	1.39
2017	1.39
2018	1.33

Source: NADP 2020

As mercury is subject to long-range transport, it has been detected in Arctic atmospheric samples. The median (±SD) concentrations of mercury at Alert, Canada in the fall, winter, spring, and summer were 1.49 (±0.11), 1.59 (±0.17), 1.24 (±0.53), and 1.80 (±0.35) ng/m^3, respectively (Kirk et al. 2012).

Several decades ago, ambient atmospheric levels of mercury could have been an order of magnitude higher than current expected background levels. In 1990, metallic mercury concentrations in the gas and aerosol phases of the atmosphere in Sweden were 2–6 and 0.01–0.1 ng/m^3, respectively (Brosset and Lord 1991). Higher levels (10–15 µg/m^3) have been detected near point emission sources, such as mercury mines, refineries, and agricultural fields treated with mercury fungicides. Atmospheric concentrations of mercury over lakes in Wisconsin averaged 2.0 ng/m^3 (Wiener et al. 1990). Mercury levels ranged from 6.3 to 16.0 ng/m^3 above the water surface of the mercury-contaminated Wabigoon River in Ontario (Schroeder and Fanaki 1988). The mean vapor concentration of mercury in air over a forested watershed (Walker Branch Watershed) in Tennessee was 5.5 ng/m^3 in 1988–1989, while the particle-associated aerosol mercury concentration was determined to be 0.03 ng/m^3, or approximately 0.5% of the total atmospheric mercury (Lindberg et al. 1991). Lindberg et al. (1994) measured mercury vapor at concentrations of 2–6 ng/m^3 and particulate mercury at 0.002–0.06 ng/m^3 at Walker Branch Watershed, Tennessee, from August 1991 to April 1992. Particulate mercury concentrations are greater in precipitation than in ambient air. In the St. Louis River estuary, mercury levels in precipitation averaged 22 ng/L (ppt), although ambient air levels averaged 3 ng/m^3 (Glass et al. 1990).

Total gaseous mercury was measured (1992–1993) as part of the Florida Atmospheric Mercury Study (FAMS) (Gill et al. 1995). Average total gaseous mercury concentrations for 3–6-day integrated samples ranged from 1.43 to 3.11 ng/m^3 (mean 1.64 ng/m^3). In the same study, Dvonch et al. (1995) reported that the mean concentrations of total gaseous mercury measured at two inland Florida sites were significantly higher (3.3 and 2.8 ng/m^3) than measurements at an Atlantic coastal site (1.8 ng/m^3). The mean concentrations of particle-phase mercury collected at the inland sites (51 and 49 pg/m^3) were 50% higher than those at the coastal site (34 pg/m^3). The mean mercury concentration in rain samples was 44 ng/L (ppt) (range 14–130 ng/L). Guentzel et al. (1995) also reported results of the FAMS from 1992 to 1994. Particle-phase measurements ranged from 2 to 18 pg/m^3 at all sites. Measurements of monomethylmercury in precipitation ranged from <0.005 to 0.020 ng/L (ppt).

Keeler et al. (1994) measured atmospheric mercury in the Great Lakes Basin. The study authors reported that vapor-phase mercury levels were 4 times higher in Chicago, Illinois, than in South Haven, Michigan (8.7 versus 2.0 ng/m^3). Furthermore, a diurnal pattern was observed in the vapor-phase mercury levels measured at the Chicago site. The average concentration (ng/m^3) was 3.3 times greater for the daytime samples (8 AM to 2 PM) than for the night samples (8 PM to 8 AM), and the average concentration for the afternoon samples (2 PM to 8 PM) was 2.1 times greater than the night samples (average, 3.7 ng/m^3). Particulate-phase mercury concentrations were also higher at the Chicago site than at the South Haven site (98 versus 19 pg/m^3). Burke et al. (1995) reported that the concentration of mercury in vapor-phase samples measured over Lake Champlain was consistent with other rural areas (mean 2.0 ng/m^3; range 1.2–4.2 ng/m^3), and the concentrations were consistent across all seasons. Particulate-phase mercury concentrations averaged 11 pg/m^3, with the highest concentrations detected during the winter.

In the past, mercury was a component of indoor and outdoor, water-based latex paints; however, in 1990, most uses of mercury for interior and exterior paints and coatings were voluntarily cancelled by the manufacturers (DeVito and Brooks 2013). Prior to this cancellation, mercury levels in homes and buildings that were recently painted could be much higher than background levels. Indoor air mercury concentrations were determined in 37 houses in Ohio that had been painted with latex paint (Beusterien et al. 1991). Of the 37 homes studied, 21 homes had been painted with interior latex paint containing mercury a median of 86 days earlier, while the 16 control homes had not been recently painted with mercury-containing latex paints. Paint samples from the exposed homes contained a median concentration of 210 mg/L mercury (ppm) (range 120–610 mg/L). The median air mercury concentration (0.3 µg/m^3) was found to be significantly higher ($p<0.0001$) in the exposed homes (range: not detectable to 1.5 µg/m^3) than in the unexposed homes (range: not detectable to 0.3 µg/m^3). Among the exposed

homes, there were seven in which paint containing <200 mg/L mercury had been applied. In these homes, the median air mercury concentration was 0.2 µg/m^3 (range: not detectable to 1 µg/m^3). Six exposed homes had air mercury concentrations >0.5 µg/m^3. The study authors reported that elemental mercury was the form of mercury released to the air and that potentially hazardous mercury exposure could occur in homes recently painted with paint containing <200 mg Hg/L (Beusterien et al. 1991). In an indoor exposure study of families of workers at a chloralkali plant in Charleston, Tennessee, mercury levels in the air of the workers' homes averaged 0.92 µg/m^3 (ATSDR 1990).

A monitoring program established at a facility at Oak Ridge National Laboratories found that the major sources of mercury release to the air were vaporization from soil, burning of coal for a steam plant, and fugitive exhaust from a former lithium isotope separation facility contaminated with mercury (DOI 1991). When the monitoring program began in 1986, ambient air mercury vapor concentrations at the facility ranged from 0.011 to 0.108 µg/m^3. These values decreased to 0.006–0.071 µg/m^3 by 1990, while background levels near the facility remained at 0.006 µg/m^3. The decrease in mercury vapor concentrations occurred primarily as a result of an 80% reduction in coal burning at the steam plant; however, periods of drought and activities such as moving contaminated soil for construction were found to increase the atmospheric mercury concentrations on a transient basis (DOI 1991). Turner and Bogle (1993) monitored ambient air for mercury around the same industrial complex site at Oak Ridge, Tennessee. Elemental mercury was used in large quantities at the nuclear weapons plant between 1950 and 1963 in a process similar to chloralkali production. Soil and water contamination had been found at the site. The results of weekly ambient monitoring for gaseous mercury from 1986 through 1990 showed that gaseous mercury levels were well below the National Emission Standard for Hazardous Air Pollutants (1.0 mg/m^3) with the exception of one station. Mean mercury levels at the control site ranged from 5 to 6 µg/m^3, while levels at the on-site stations ranged from 6–11, 11–143, 68–174, 71–109, and 4–46 µg/m^3, depending on the station. Mean particulate mercury levels were 0.00003 µg/m^3 at the control site, compared with mean concentrations at the on-site stations ranging from 0.00006 to 0.00024 µg/m^3 (Turner and Bogle 1993).

5.5.2 Water

Concentrations of mercury in rainwater and fresh snow are generally <200 ng/L (ppt) (EPA 1984). Rainwater collected in monitoring stations in the U.S Great Lakes region (2002–2008) found annual average mean concentrations at 37 sites to range from 5.6 to 13.6 ng/L and temporal trends for decreasing and increasing concentrations, depending on location (Risch et al. 2012). Fitzgerald et al. (1991)

measured total mercury in rainwater from May through August 1989 at Little Rock Lake, Wisconsin. The total mercury concentrations ranged from 3.2 to 15.2 ng/L (ppt). Mercury concentrations in precipitation collected in Minnesota during 1988 and 1989 averaged 18 ng/L (ppt) for an average annual mercury deposition of 15 µg/m^2 (Glass et al. 1991). Antarctic surface snow contained a mean mercury concentration of <1 pg/g (ppt) (Dick et al. 1990). In Ontario, Canada, mercury present in precipitation at an average concentration of 10 ng/L (ppt) accounted for more than half of the mercury inputs to surface waters compared with inputs from stream runoff, suggesting that atmospheric deposition is a significant source of mercury in surface waters (Mierle 1990). Lindberg et al. (1994) measured total mercury in rain collected at Walker Branch Watershed, Tennessee from August 1991 to April 1992. Rain concentrations of total mercury ranged from 7.57 ng/L (ppt) in February 1992 to 17.4 ng/L (ppt) in April 1992. Burke et al. (1995) reported that the average concentration of mercury in precipitation samples measured over Lake Champlain was 8.3 ng/L (ppt) for the sampling year, and the average amount of mercury deposited per precipitation event was 0.069 µg/m^2. The highest concentrations of mercury in precipitation samples occurred during spring and summer months. Guentzel et al. (1995) reported results of the Florida Atmospheric Monitoring Study from 1992 to 1994. The study authors found that the wet season in south Florida accounted for 80–90% of the annual rainfall mercury deposition. Depositional rates in south Florida are 30–50% higher than those in central Florida. Measurements of monomethylmercury in precipitation samples ranged from <0.005 to 0.020 ng/L (ppt).

The natural occurrence of mercury in the environment means that mercury is likely to occur in surface waters, even when anthropogenic sources of mercury are absent. Methylated mercury averaged 0.024 (±0.009 SD) ng/L in Canadian Arctic waters and 0.023 ng/L (±0.011 SD) in the Hudson Bay (Kirk et al. 2012). Freshwaters without known sources of mercury contamination generally contain <5 ng/L (ppt) of total mercury in aerobic surface waters (Gilmour and Henry 1991). The USGS conducted sampling from 2012 to 2015 at six locations of the Brownlee Reservoir, Boise, and Snake River in Idaho (MacCoy and Williams 2016). Mercury levels in the water ranged from 0.48 to 8.8 ng/L, with the highest concentration observed in the Brownlee Reservoir. Mercury levels in water-borne particulates in the St. Louis River estuary ranged from 18 to 500 ng/L (ppt) (Glass et al. 1990). Water samples from lakes and rivers in the Ottawa, Ontario, region of Canada had total mercury concentrations of 3.5–11.4 ng/L (ppt), with organic mercury constituting 22–37% of the total mercury (Schintu et al. 1989). Mercury was detected in water samples from Crab Orchard Lake, Illinois, at 70–281 ng/L (ppt) (Kohler et al. 1990). Total mercury concentrations in surface waters of California lakes and rivers ranged from 0.5 to 104.3 ng/L (ppt), with the dissolved particulate fraction being dominant (89%; 0.4–12 ng/L [ppt]) (Gill and Bruland 1990).

The baseline concentration of mercury in unpolluted marine waters is typically approximately 0.3 ng/L (Gonzalez-Raymat et al. 2017). In contrast, the New York Bight, an inshore coastal area near the industrialized areas of New York Harbor and northern New Jersey, contained dissolved mercury concentrations in the range of 10–90 ng/L (ppt) (Fowler 1990).

Near-surface groundwaters in remote areas of Wisconsin were found to contain approximately 2–4 ng/L (ppt) of mercury, of which only a maximum of 0.3 ng/L (ppt) was determined to be methylmercury, indicating that groundwater was not a source of methylmercury in the lake (Krabbenhoft and Babiarz 1992). Mercury was found at levels >0.5 µg/L (ppb) in 15–30% of wells tested in some groundwater surveys (EPA 1985). Drinking water is generally assumed to contain <0.025 µg/L (ppb) (EPA 1984). A chemical monitoring study of California's public drinking water from groundwater sources was conducted by Storm (1994). This author reported that mercury was analyzed in 6,856 samples, with 225 positive detections and 27 exceedances of the maximum contaminant level (0.002 mg/L [200 ppb]). The mean mercury concentration was 6.5 ppb (median, 0.62 ppb; range, 0.21 to 300 ppb).

5.5.3 Sediment and Soil

Mercury is a natural constituent of soils occurring at a concentration of approximately 80 µg/kg (0.080 ppm) (Gonzalez-Raymat et al. 2017). In a review of the mercury content of virgin and cultivated surface soils from a number of countries, it was found that the average concentrations ranged from 20 to 625 ng/g (0.020–0.625 ppm) (Andersson 1979). The highest concentrations were generally found in soils from urban locations and in organic, versus mineral, soils. The mercury content of most soils varies with depth, with the highest mercury concentrations generally found in the surface layers. Median total mercury and methylmercury levels in soil of a remote watershed in the Adirondack Mountains, New York (Fishing Brook) were 170–235 and 0.28–0.94 ng/g (0.170–0.235 and 0.00028–0.00094 ppm), respectively (Burns et al. 2014). The same authors also studied total mercury and methylmercury levels of a coastal watershed (McTier Creek) in South Carolina. Median total mercury and methylmercury levels in these soils were 40–106 and 0.20–1.50 ng/g (0.040–0.106 and 0.00020–0.0015 ppm), respectively. Mercury levels in surface sediment (upper 10 cm) sampled in 10 lakes or watersheds from the Upper Columbia River Watershed in 2012 ranged from 0.01 to 0.28 mg/kg (ppm) (Washington State Department of Ecology 2013). Total mercury levels in 36 samples of soil obtained from a heavily contaminated site near a chloralkali production facility in Romania ranged from 0.08 to 114 mg/kg (ppm), with a mean value of 13.1 mg/kg (ppm; Frentiu et al. 2013).

Granato et al. (1995) reported that municipal solid waste sludge mercury concentrations from the Metropolitan Water Reclamation District of Greater Chicago ranged from 1.1 to 8.5 mg/kg (ppm), with a mean concentration of 3.31 mg/kg (ppm). Sludge applications to a sludge utilization site in Fulton County, Illinois, significantly increased extractable soil mercury concentrations from 1971 to 1995. In addition, 80–100% of the mercury applied to the soils in sewage sludge since 1971 still resided in the top 15 cm of soil.

Mercury levels in sediment the Penobscot River, Maine were reported to range from approximately 400 to 1,400 ng/g (range 0.400–1.4 ppm) over a 35-km area, with some samples exceeding 3,000 ng/g (Bodaly 2018). It was estimated that this river received approximately 6–12 metric tons of mercury emitted from a nearby chloralkali plant that was operational from 1967 to 2000. Peat cores obtained from two micro-tidal marshes in the Sacramento-San Joaquin Delta of California were used to reconstruct mercury levels over an approximate 6,000-year period (Drexler et al. 2016). Pre-anthropogenic levels of mercury were estimated to range from approximately 6.9 to 71 ng/g (0.0069–0.071 ppm) and the first man-made sources of mercury introduced to this watershed occurred around 1425 AD. Mercury levels peaked at 990 ng/g around the time of the California gold rush (~1850) as mercury is used to separate gold from its ore by forming an amalgam.

Facemire et al. (1995) reported industrial contamination of soils and sediment in several states in the southeastern United States. The study authors reported soil concentrations up to 141,000 ppm associated with contamination in northeastern Louisiana from mercury-charged manometers used to measure pressure and delivery from natural gas wells. In Tennessee, a maximum mercury concentration of 1,100 ppm (associated with previous operations of the Oak Ridge nuclear facility) was found in wetland soils adjacent to the East Fork Poplar Creek. A pharmaceutical company's effluents enriched sediments in a localized area of Puerto Rico to 88 ppm mercury (Facemire et al. 1995). Rule and Iwashchenko (1998) reported that mean soil mercury concentrations of 1.06 ppm were collected within 2 km of a former chlor-alkali plant in Saltsville, Virginia, and that these concentrations were 17 times higher than regional background soil samples (0.063 ppm). The study authors further reported that soil organic content, topographic factors, wind patterns, and elevation were variables significantly related to mercury concentration as determined by regression analysis. Soil mercury levels decreasing with distance from the former plant were indicative of a point source distribution pattern. A man-made land soil type (Udorthent), which appears to be a byproduct of the chloralkali manufacturing process, was found

proximal to the former plant site and contained about 68 times (4.31 ppm) the regional background concentration.

The top 15 cm of sediments in Wisconsin lakes contained higher levels of mercury (0.09–0.24 µg/g [ppm]) than sediments at lower sediment levels (0.04–0.07 µg/g [ppm]). Because the lakes are not known to receive any direct deposition of mercury, it was postulated that the primary mercury source was atmospheric deposition (Rada et al. 1989). Mercury levels in surface sediments of the St. Louis River ranged from 18 to 500 ng/L (ppt) (Glass et al. 1990). Mercury was detected in sediment samples from Crab Orchard Lake in Illinois at concentrations >60 µg/L (ppb) (Kohler et al. 1990). Surficial sediment samples from several sites along the Upper Connecting Channels of the Great Lakes in 1985 had mercury concentrations ranging from below the detection limit to 55.80 µg/g (ppm) (mean concentrations ranged from 0.05 to 1.61 µg/g [ppm] at four sites) (Nichols et al. 1991). Mercury concentrations were correlated with particle size fractions and organic matter content (Mudroch and Hill 1989). Surface sediment samples from the Lake Roosevelt/Upper Columbia River in Washington State were found to contain up to 2.7 µg/g (ppm) mercury (Johnson et al. 1990). Mercury concentrations in sediments up to 28 cm in depth in lakes adjacent to coal-fired power plants near Houston, Texas ranged from 255 to 360 mg/kg (ppm) in the summer and from 190 to 279 mg/kg (ppm) in the winter (Wilson and Mitchell 1991).

Surface sediments taken from Canadian lakes receiving atmospheric input from smelters contained between 0.03 and 9.22 µg/g (ppm) mercury, with the highest values being found in lakes nearest the smelters. However, sediment concentrations were not correlated with mercury concentrations in fish from the lakes; the fish concentrations ranged from 0.003 to 0.88 µg/g (ppm), with the highest concentration found in fish from one of the least contaminated lakes (Harrison and Klaverkamp 1990).

Estuarine and coastal marine sediment samples analyzed for the National Oceanic and Atmospheric Administration's (NOAA) National Status and Trends Program between 1984 and 1987 showed that 38 of 175 sites contained mercury concentrations in excess of 0.41 µg/g (ppm) (dry weight) (O'Connor and Ehler 1991). In addition, mercury sediment concentrations at six sites exceeded the NOAA effects range median concentration of 1.3 ppm (dry weight), which is the concentration determined to be equivalent to the median (50^{th} percentile) for all sites monitored. These six sites included five sites in the Hudson River/Raritan Estuary, New York Bight, and Raritan Bay areas between New York and New Jersey (ranging from 1.6 to 3.3 ppm dry weight) and one site in the Oakland Estuary in California (2.3 ppm dry weight) (NOAA 1991). Sediments taken from coastal areas off British Columbia, Canada contained concentrations of mercury ranging from 0.05 to 0.20 µg/g (ppm), while mercury concentrations

in fish from these waters were only slightly higher; BCFs ranged from <1 to 14 (Harding and Goyette 1989).

5.5.4 Other Media

Foods. The U.S. Food and Drug Administration (FDA) conducted a Total Diet Study (April 1982 to April 1984) to determine dietary intakes of selected industrial chemicals (including mercury) from retail purchases of foods representative of the total diet of the U.S. population (Gunderson 1988). The data were collected as part of eight food collections, termed Market Basket Surveys collected in regional metropolitan areas during the 2-year study and involved individual analysis of 234 food items representing the diets of eight different population groups. Mercury was detected in 129 adult foods; seafood, the major contributing food group, accounted for 77% (3.01 of the 3.9 µg of mercury) of the total mercury intake for 25–30-year-old males (Gunderson 1988). Minyard and Roberts (1991) reported results of a survey conducted on food samples analyzed at 10 state food laboratories between 1988 and 1989. These laboratories conducted food regulatory programs and analyzed findings of pesticides and related chemical residues for 27,065 food samples. In 1988, these laboratories reported methylmercury residues in 13 (0.09%) of 13,980 samples, with 1 sample exceeding federal or state tolerances. Similarly, in 1989, methylmercury was detected in 25 (0.19%) of 13,085 samples, with 1 sample exceeding federal or state tolerances. A survey of 220 cans of tuna, conducted in 1991 by the FDA, found an average methylmercury content (expressed as mercury) of 0.17 mg/kg (range <0.10–0.75 mg/kg) (Yess 1993). Levels of methylmercury were higher in solid white tune (0.26 mg/kg) and chunk white tuna (0.31 mg/kg) than in chunk light tuna (0.10 mg/kg) or chunk tuna (0.10 mg/kg). Previously, the FDA had determined methylmercury concentrations in 42 samples of canned tuna between 1978 and 1990 (Yess 1993) to range from <0.01 to 0.67 mg/kg methylmercury (expressed as mercury), with an average concentration of 0.14 mg/kg. These earlier results are similar to those obtained in the 1991 survey (Yess 1993).

The most recent data from the Markey Basket Surveys are included in the FDA Total Diet Study for mercury in consumed food items. Data from the 2006–2013 Total Diet Study are shown in Table 5-16.

The use of fish meal as a food for poultry and other animals used for human consumption may result in increased mercury levels in these animals. In Germany, poultry and eggs were found to contain average mercury concentrations of 0.04 and 0.03 mg/kg, respectively. Cattle are able to demethylate mercury in the rumen and thus absorb less mercury; therefore, beef (meat) and cow's milk contained only 0.001–0.02 and 0.01 mg/kg of mercury, respectively (Hapke 1991). A survey of raw foods in Germany in 1986

found that grains, potatoes, vegetables, and fruits contained average mercury concentrations of 0.005–0.05 mg/kg (fresh weight); however, wild mushrooms contained up to 8.8 mg/kg of mercury. Cocoa beans, tea leaves, and coffee beans contained average mercury concentrations of 0.005, 0.025, and 0.04 mg/kg, respectively. In all cases where the mercury content was high, selenium was also found in measurable, but lower, concentrations (Weigert 1991).

Pedersen et al. (1994) conducted a monitoring study to assess the levels of trace metals, including mercury, in table wine, fortified wine, beer, soft drinks, and various juices. The study authors reported that in all samples tested, mercury concentrations were at or below the detection limit (6 µg/L).

Fish and Shellfish. Consumption of fish is a major contributor to methylmercury exposure in most populations (EFSA 2012; Kim et al. 2016b; Vejrup et al. 2016; You et al. 2014; Zhang et al. 2010). Mercury levels in Great Lakes aquatic organisms have generally been trending lower since the 1970s; however, since about 1990, they have leveled off or even increased slightly (Grieb et al. 2020; IJC 2015). The initial decrease was likely due to decreasing atmospheric deposition from North America; however, increasing emissions from other parts of the world and climate change, along with many other factors are likely responsible for recent changes (Grieb et al. 2020). The Great Lakes Commission (GLC) reported that fish mercury levels in the Great Lakes region are positively correlated with areas of high forest cover and wetlands because forested areas in these regions of the Great Lakes receive higher dry deposition of mercury and have other watershed features that worsen the impacts of mercury emissions and deposition (BDI 2011). The report also found that fish in waterbodies near agricultural areas tended to have lower mercury levels since increased algal biomass in the aquatic food web tends to reduce methylmercury levels. They also noted that mercury levels in predatory fish such as walleye and largemouth bass are 55 and 25% lower, respectively, in the Great Lakes as compared to inland lakes nearby, which likely occurs due to dissimilarities in the food web structure, land-water linkages, and methylating potential variations between the larger and smaller water bodies.

The USGS compiled data from state and federal programs to study the temporal mercury levels in fish in rivers and lakes in the United States from 1969 to 2005 (Chalmers et al. 2011). They observed that declining mercury levels in sediment cores during the 1970s and 1980s correlated with the period of downward mercury levels in fish. Overall, from 1969 to 2005 in 90 rivers and lakes, mercury concentrations had no temporal trends at 57% of the sites, decreasing mercury levels in fish at 32% of the

Table 5-16. Mercury Concentrations in Food from the FDA Total Diet Study 2006–2013

Food	Number of analyses	Number of non-detects	Number of trace	Mean (mg/kg)	SD (mg/kg)	Median (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	LOD (mg/kg)	LOQ (mg/kg)
Milk, whole, fluid	16	16	0	0	0	0	0	0	0.010	0.040
Milk, lowfat (2%), fluid	16	16	0	0	0	0	0	0	0.010	0.040
Turkey breast, oven-roasted	15	13	2	0.0001	0.0004	0	0	0.001	0.010	0.040
Liver (beef/calf), pan-cooked with oil	15	10	5	0.001	0.001	0	0	0.003	0.010	0.040
Fish sticks or patty, frozen, oven-cooked	15	6	8	0.004	0.004	0.005	0	0.012	0.010	0.040
Eggs, scrambled with oil	14	14	0	0	0	0	0	0	0.010	0.040
Eggs, boiled	16	15	1	0.0001	0.0003	0	0	0.001	0.010	0.040
Peanut butter, smooth/creamy	16	15	1	0.0002	0.0008	0	0	0.003	0.020	0.070
Rice, white, enriched, cooked	16	10	6	0.0004	0.0006	0	0	0.002	0.010	0.040
Oatmeal, plain, cooked	16	15	1	0.0001	0.0005	0	0	0.002	0.010	0.040
Bread, white, enriched	16	15	1	0.0001	0.0005	0	0	0.002	0.020	0.070
Fruit-flavored cereal, presweetened	16	12	4	0.0004	0.0008	0	0	0.002	0.020	0.070
Crisped rice cereal	16	8	8	0.001	0.002	0.001	0	0.004	0.020	0.070
Raisins	16	10	6	0.001	0.001	0	0	0.003	0.020	0.050
Avocado, raw	16	15	1	0.0001	0.0003	0	0	0.001	0.020	0.070
Orange juice, frozen concentrate, reconstituted	14	14	0	0	0	0	0	0	0.010	0.040
Apple juice, bottled	15	15	0	0	0	0	0	0	0.010	0.040
Prune juice, bottled	16	14	2	0.0001	0.0003	0	0	0.001	0.010	0.040
Spinach, fresh/frozen, boiled	16	11	5	0.0003	0.0005	0	0	0.001	0.010	0.040
Collards, fresh/frozen, boiled	16	9	7	0.001	0.001	0	0	0.002	0.010	0.040
Cauliflower, fresh/frozen, boiled	15	15	0	0	0	0	0	0	0.010	0.040
Tomato, raw	16	16	0	0	0	0	0	0	0.010	0.040
Ice cream, light, vanilla	16	16	0	0	0	0	0	0	0.010	0.040
Fruit drink, from powder	16	16	0	0	0	0	0	0	0.010	0.040

Table 5-16. Mercury Concentrations in Food from the FDA Total Diet Study 2006–2013

Food	Number of analyses	Number of non-detects	Number of trace	Mean (mg/kg)	SD (mg/kg)	Median (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	LOD (mg/kg)	LOQ (mg/kg)
Baby food, infant formula, milk-based, iron fortified ready to feed (formerly high iron)	16	16	0	0	0	0	0	0	0.010	0.040
Baby food, infant formula, milk-based, low iron, ready to feed	8	8	0	0	0	0	0	0	0.010	0.040
Baby food, chicken and broth/gravy	16	16	0	0	0	0	0	0	0.010	0.040
Baby food, vegetables and beef	16	16	0	0	0	0	0	0	0.010	0.040
Baby food, mixed vegetables	16	16	0	0	0	0	0	0	0.010	0.040
Baby food, pears	16	16	0	0	0	0	0	0	0.010	0.040
Baby food, juice, apple	16	16	0	0	0	0	0	0	0.010	0.040
Yogurt, lowfat, fruit-flavored	16	16	0	0	0	0	0	0	0.010	0.040
Chicken breast, oven-roasted (skin removed)	16	16	0	0	0	0	0	0	0.010	0.040
Chicken nuggets, fast-food	16	16	0	0	0	0	0	0	0.010	0.040
Shrimp, boiled	15	7	8	0.006	0.006	0.007	0	0.016	0.010	0.040
Mushrooms, raw	16	9	7	0.001	0.001	0	0	0.003	0.010	0.040
Tuna noodle casserole, homemade	16	3	9	0.016	0.017	0.011	0	0.067	0.010	0.040
Fish sandwich on bun, fast-food	15	8	7	0.002	0.003	0	0	0.009	0.010	0.040
Clam chowder, New England, canned, condensed, prepared with whole milk	16	12	4	0.0003	0.0004	0	0	0.001	0.010	0.040
Syrup, chocolate	15	13	2	0.0003	0.0008	0	0	0.003	0.010	0.040
Jelly, any flavor	16	15	1	0.0001	0.0003	0	0	0.001	0.010	0.040
Carbonated beverage, fruit-flavored, regular	15	15	0	0	0	0	0	0	0.010	0.040
Baby food, infant formula, soy-based, ready to feed	16	16	0	0	0	0	0	0	0.010	0.040
Baby food, bananas	16	16	0	0	0	0	0	0	0.010	0.040
Salmon, steaks/fillets, baked	16	0	10	0.021	0.009	0.021	0.006	0.039	0.010	0.040

Table 5-16. Mercury Concentrations in Food from the FDA Total Diet Study 2006–2013

Food	Number of analyses	Number of non-detects	Number of trace	Mean (mg/kg)	SD (mg/kg)	Median (mg/kg)	Minimum (mg/kg)	Maximum (mg/kg)	LOD (mg/kg)	LOQ (mg/kg)
Baby food, cereal, rice, dry, prepared with water	15	12	3	0.0003	0.0006	0	0	0.002	0.010	0.040
Baby food, cereal, rice with apples, dry, prepared with water	6	6	0	0	0	0	0	0	0.010	0.040
Chicken breast, fried, fast-food (with skin)	15	15	0	0	0	0	0	0	0.010	0.040
Chicken thigh, oven-roasted (skin removed)	15	15	0	0	0	0	0	0	0.010	0.040
Chicken leg, fried, fast-food (with skin)	15	15	0	0	0	0	0	0	0.010	0.040
Catfish, pan-cooked with oil	15	7	8	0.003	0.004	0.002	0	0.016	0.010	0.040
Tuna, canned in water, drained	15	0	1	0.136	0.114	0.118	0.035	0.509	0.010	0.040
Cranberry juice cocktail, canned/bottled	15	15	0	0	0	0	0	0	0.010	0.040
Beef with vegetables in sauce, from Chinese carry-out	15	12	3	0.0003	0.0006	0	0	0.002	0.010	0.040
Fried rice, meatless, from Chinese carry-out	15	8	7	0.001	0.001	0	0	0.002	0.010	0.040

FDA = U.S. Food and Drug Administration; LOD = limit of detection; LOQ = limit of quantification; SD = standard deviation

Source: FDA 2017a

sites, and increasing levels at 11% of the sites. Data from the late 1980s to 2005 showed increasing levels of mercury in fish in some southeastern states, while no trend or decreasing levels in upper midwestern states were observed. These data are summarized in Table 5-17.

Table 5-17. Trends in Mercury Concentrations Based on Fish Data Aggregated by State from 1988 to 2005[a]

State	Sites	Number	Species	Begin year	End year	Median mercury (mg/kg)	p-Value	Percent change	Trend
Southeastern United States									
Georgia	112	266	LMB	1991	2001	0.24	<0.001	7.43	Up
Georgia	56	105	CCF	1991	2001	0.10	0.063	6.76	None
Louisiana	324	1,049	LMB	1994	2005	0.39	<0.001	3.78	Up
Louisiana	113	168	CCF	1994	2004	0.10	0.007	11.2	Up
Louisiana	178	328	FD	1994	2004	0.37	0.013	6.23	Up
Louisiana	72	125	RS	1994	2004	0.16	0.075	11.4	None
Louisiana	158	383	WC	1994	2004	0.21	0.601	1.14	None
Louisiana	178	378	BC	1995	2004	0.24	0.686	0.83	None
Louisiana	**169**	**444**	**B**	**1994**	**2004**	**0.52**	**0.019**	**-3.26**	**Down**
Louisiana	*42*	*66*	*BMBU*	*1995*	*2004*	*0.28*	*0.045*	*-6.66*	*Down*
North Carolina	37	61	BG	1989	1999	0.10	0.771	0.76	None
South Carolina	**129**	**963**	**B**	**1993**	**2004**	**0.80**	**0.003**	**3.02**	**Up**
South Carolina	70	194	CCF	1994	2004	<0.25	0.277	-2.29	None
South Carolina	**188**	**1,556**	**LMB**	**1993**	**2004**	**0.38**	**<0.001**	**-3.13**	**Down**
Midwestern United States									
Iowa	31	34	LMB	1994	2005	0.13	0.947	0.25	None
Iowa	44	60	CC	1993	2005	0.10	0.005	-6.11	Down
Iowa	87	142	CCF	1988	2005	0.09	<0.001	-6.14	Down
Indiana	194	285	CC	1988	2004	0.17	0.856	-0.11	None
Indiana	56	74	CCF	1988	2004	0.14	0.316	-1.04	None
Indiana	75	91	LMB	1991	2004	0.19	0.999	0.00	None
Michigan	55	158	LMB	1988	1997	0.31	0.632	-0.75	None
Minnesota	43	81	CCF	1990	2000	0.21	0.364	1.80	None
Minnesota	78	157	CC	1990	2001	0.13	0.085	-2.16	None

Table 5-17. Trends in Mercury Concentrations Based on Fish Data Aggregated by State from 1988 to 2005[a]

State	Sites	Number	Species	Begin year	End year	Median mercury (mg/kg)	p-Value	Percent change	Trend
Minnesota	*53*	*142*	*NP*	*1988*	*2001*	*0.27*	*0.001*	*-4.86*	*Down*
Minnesota	75	202	W	1989	2001	0.23	0.036	-3.16	Down

[a]Trends above the U.S. Environmental Protection Agency (EPA) advisory guideline (0.3 µg/g methylmercury) are in bold text. Upward trends starting below and ending above EPA guideline are underlined. Downward trends starting above and ending below EPA guideline are in italics. Trends below EPA guideline are in regular text.

B = bowfin; BC = black crappie; BG = bluegill; BMBU = bigmouth buffalo; CC = common carp; CCF = channel catfish; FD = freshwater drum; LMB = largemouth bass; NP = northern pike; RS = redear sunfish; W = walleye; WC = white crappie

Source: Chalmers et al. 2011

From 2012 to 2015, the USGS collected and analyzed individual fillets of mountain whitefish (*Prosopium williamsoni*), rainbow trout (*Oncorhynchus mykiss*), smallmouth bass (*Micropterus dolomieu*), and channel catfish (*Ictalurus punctatus*) for mercury in the Brownlee Reservoir and Snake River in Idaho (MacCoy and Williams 2016). Mercury levels in rainbow trout were analyzed for one site (Eckert) and had a median concentration of 0.02 mg/kg. Median mercury levels in mountain whitefish were 0.18 mg/kg at the Eckert sampling location and ranged from 0.11 to 0.18 mg/kg at the Middleton site during the 3-year sampling period. Channel catfish collected at three locations had median mercury levels that ranged from 0.11 to 0.28 mg/kg for all three sites. Smallmouth Bass collected from the Brownlee Reservoir in 2013 had median levels of 0.32 mg/kg, which exceeded Idaho water-quality criterion.

Sampling was conducted for different species of fish from 2006 to 2012 in the lower Penobscot River and upper estuary in Maine (Kopec et al. 2019). This river was contaminated by mercury discharges from a chloralkali plant that was operational from 1967 to 2000. Mercury levels were shown to be greatest in fish and shellfish near the plant and downstream from the plant as opposed to upstream or more distant locations. In the most heavily contaminated locations near the chloralkali facility, mean total mercury concentrations in fish muscle adjusted for size or age were 0.521 (95% CI 0.480, 0.566) mg/kg wet weight in American eels, 0.321 (95% CI 0.261, 0.395) in mummichog, 0.121 (95% CI 0.104, 0.140) in rainbow smelt, 0.155 (95% CI 0.142, 0.169) in tomcod, 0.0552 (95% C: 0.0427, 0.0714) in winter flounder, and 0.328 (95% CI 0.259, 0.413) in American lobster tail, and 0.522 (95% CI 0.488, 0.557) mg/kg dw in blue mussel.

Rumbold et al. (2018) studied mercury levels in 50 species of fish at two locations off the coast of the Florida Keys. The first location, Tennessee Reef Lighthouse (TRL), is a bank reef with moderate cover of hard coral, soft-coral, sponge, and macroalgae on a sandy bottom and the second location was a slightly shallower water, Long Key Hard Bottom (LKH), characterized by exposed hard substrate with soft-coral, sponge, and macroalgal cover. These data are presented in Table 5-18.

Table 5-18. Mercury Levels in 50 Species of Fish Obtained at Two Sites Along the Florida Reef Tract from April 2012 to December 2013

Common name	Scientific name	Mean (ng/g)	SD (ng/g)	Maximum (ng/g)	CV (%)
Tennessee Reef Lighthouse					
Bermuda chub	*Kyphosus sectatrix*	78.64	44.87	135.6	57.1
Bicolor damsel	*Stegastes partitus*	26.60	2.96	29.55	11.1
Black grouper	*Mycteroperca bonaci*	347.2	85.95	445.2	24.8
Blue runner	*Caranx crysos*	40.95	NR	NR	NR
Blue stripe grunt	*Haemulon sciurus*	390.9	108.8	506.1	27.8
Blue tang	*Acanthurus coeruleus*	35.28	5.32	44.08	15.1
Brown chromis damsel	*Chromis multilineata*	113.0	NR	NR	NR
Doctorfish tang	*Acanthurus chirurgus*	52.97	7.58	60.98	14.3
French angelfish	*Pomacanthus paru*	43.42	22.11	65.53	50.9
Gray angelfish	*Pomacanthus arcuatus*	58.11	26.34	91.63	45.3
Graysby grouper	*Cephalopholis cruentata*	322.0	68.33	417.4	21.2
Great barracuda	*Sphyraena barracuda*	1,713.8	882.3	3,401.4	51.5
Hogfish	*Lachnolaimus maximus*	129.6	41.44	200.0	31.9
Knobbed porgy	*Calamus nodosus*	153.0	50.23	203.2	32.8
Porkfish	*Anisotremus virginicus*	1,555.1	1,970.9	6,842.3	126.7
Princess parrotfish	*Scarus taeniopterus*	66.84	NR	NR	NR
Red lionfish	*Pterois volitans*	174.9	44.75	225.8	1.7
Redband parrotfish	*Sparisoma aurofrenatum*	42.52	10.17	56.91	23.9
Rock Beauty angelfish	*Holacanthus tricolor*	20.53	1.52	22.04	7.4
Saucereye porgy	*Calamus*	114.6	NR	NR	NR
Schoolmaster snapper	*Lutjanus apodus*	143.1	NR	NR	NR
Scrawled filefish	*Aluterus scriptus*	76.79	6.24	82.57	8.1
Sergeant major damsel	*Abudefduf saxatilis*	57.19	NR	NR	NR
Spanish grunt	*Haemulon macrostomum*	505.9	25.55	531.5	5.0

Table 5-18. Mercury Levels in 50 Species of Fish Obtained at Two Sites Along the Florida Reef Tract from April 2012 to December 2013

Common name	Scientific name	Mean (ng/g)	SD (ng/g)	Maximum (ng/g)	CV (%)
Spanish hogfish	*Bodianus rufus*	300.8	95.90	392.1	31.9
Spotted goatfish	*Pseudupeneus maculatus*	102.2	48.03	184.1	46.9
Stoplight parrotfish	*Sparisoma viride*	30.22	3.33	32.58	11.0
Trumpetfish	*Aulostomus maculatus*	133.3	NR	NR	NR
White grunt	*Haemulon plumierii*	304.1	53.05	340.1	10.6
Yellowtail damsel	*Chrysiptera parasema*	35.91			
Yellowtail snapper	*Ocyurus chrysurus*	104.4	45.45	149.8	43.5
Long Key Hard Bottom					
Atlantic spadefish	*Chaetodipterus faber*	242.6	66.47	310.9	27.4
Bermuda chub	*Kyphosus sectatrix*	50.99	23.80	97.41	46.7
Black grouper	*Mycteroperca bonaci*	343.1	13.14	356.3	3.8
Blue runner	*Caranx crysos*	252.2	166.0	460.7	65.8
Blue stripe grunt	*Haemulon sciurus*	265.4	65.28	356.1	24.6
Blue tang	*Acanthurus coeruleus*	40.90	NR	NR	NR
Cocoa damsel	*Stegastes variabilis*	118.4	NR	NR	NR
Doctorfish tang	*Acanthurus chirurgus*	96.37	NR	NR	NR
French angelfish	*Pomacanthus paru*	53.31	NR	NR	NR
Gray angelfish	*Pomacanthus arcuatus*	17.49	0.16	17.65	0.9
Gray snapper	*Lutjanus griseus*	190.2	31.10	216.1	16.4
Graysby grouper	*Cephalopholis cruentata*	152.5	NR	NR	NR
Great barracuda	*Sphyraena barracuda*	3,317.5	NR	NR	NR
Hogfish	*Lachnolaimus maximus*	142.3	55.66	257.5	39.1
Horse-eye jack	*Caranx latus*	147.8	NR	NR	NR
Lane snapper	*Lutjanus synagris*	256.2	NR	NR	NR
Leatherjacket	*Oligoplites saurus*	747.7	43.99	791.7	5.9
Lookdown	*Selene vomer*	234.9	90.64	322.3	38.5
Mutton snapper	*Lutjanus analis*	196.9	NR	NR	NR
Ocean surgeon	*Acanthurus bahianus*	41.41	0.02	41.43	0.0
Pigfish	*Orthopristis chrysoptera*	857.5	NR	NR	NR
Planehead filefish	*Stephanolepis hispidus*	77.57	NR	NR	NR
Porkfish	*Anisotremus virginicus*	501.6	151.1	702.5	30.1
Red grouper	*Epinephelus morio*	197.8	24.77	232.8	12.5
Red lionfish	*Pterois volitans*	239.3	25.01	264.4	10.4
Rock hind grouper	*Epinephelus adscensionis*	144.0	9.35	153.4	6.5

Table 5-18. Mercury Levels in 50 Species of Fish Obtained at Two Sites Along the Florida Reef Tract from April 2012 to December 2013

Common name	Scientific name	Mean (ng/g)	SD (ng/g)	Maximum (ng/g)	CV (%)
White grunt	*Haemulon plumierii*	320.5	78.05	494.7	24.3
Yellow jack	*Carangoides bartholomaei*	236.4	129.6	366.0	54.8
Yellowtail snapper	*Ocyurus chrysurus*	142.5	38.52	223.2	27.0

CV = coefficient of variation (SD/mean); NR = not reported; SD = standard deviation for means based on ≥2 fish

Source: Rumbold et al. 2018

As part of the National Pesticide Monitoring Program (NPMP), the U.S. Fish and Wildlife Service collected freshwater fish during 1976–1977 from 98 monitoring stations nationwide and analyzed them for mercury and other heavy metals (May and McKinney 1981). As part of this program, duplicate composite samples of a bottom-dwelling species and several representative predatory species were collected. Bottom-dwelling species sampled included common carp, common sucker, and channel catfish or other catfish species. Predatory species sampled were rainbow, brown, brook, or lake trout at cold water stations; largemouth bass or other sunfish family members, such as crappie or bluegill, at warm water stations; and walleye or other perch family members at cool water stations. May and McKinney (1981) reported that the mean concentration of mercury was 0.153 mg/kg (wet weight basis) in the 1972 NPMP survey and that the mean concentration declined significantly to 0.112 mg/kg (range 0.01–0.84 mg/kg) in the 1976–1977 survey. This decline was presumably due to curtailed production, use, and emissions of mercury (Lowe et al. 1985). May and McKinney (1981) identified an arbitrary 85th percentile concentration of 0.19 mg/kg for mercury to identify monitoring stations having fish with higher than normal concentrations of mercury. Most of these stations were downstream of industrial sites (e.g., chloralkali operations, pulp and paper plants, or pre-1900 gold and silver mining operations), while others were located in areas with major mercury ore (cinnabar) deposits. In a follow-up NPMP study conducted from 1980 to 1981, Lowe et al. (1985) reported a geometric mean mercury concentration of 0.11 mg/kg (wet weight) (range 0.01–1.10 mg/kg). The study authors reported that the downward trend in mercury residues in fish reported by May and McKinney (1981) may have leveled off, since no significant difference in the geometric mean values was detected in the follow-up study conducted in 1984–1985 as part of the National Contaminant Biomonitoring Program (Lowe et al. 1985; Schmitt and Brumbaugh 1990). However, large variations in mercury uptake among the fish species sampled, as well as among size classes of fish within the same species, may mask actual trends.

From 1986 to 1989, the National Study of Chemical Residues in Fish (NSCRF) was conducted by the EPA to assess the concentrations of 60 toxic pollutants (including mercury) in the tissues of benthic and predatory gamefish nationwide (EPA 1992b). Benthic species were analyzed as whole-body samples, while game fish species were analyzed as fillet samples, and all concentrations were reported on a wet weight basis. Mercury was detected at 92% of the 374 sites surveyed nationwide at a mean concentration of 0.260 mg/kg (median concentration of 0.17 mg/kg and maximum concentration of 1.8 mg/kg), and at 2% of the sites, measured mercury concentrations exceeded 1 mg/kg. Most of the higher mercury concentrations in fish were collected in the Northeast. Ten of the sites in the top 10^{th} percentile for high mercury concentrations were near pulp and paper mills, four were near Superfund sites, and most of the remaining sites were near industrial areas. However, the mercury sources could not be identified at all of these sites. Five sites were considered to represent background conditions and six USGS National Stream Quality Accounting Network (NASQAN) sites were also among the sites in the top 10^{th} percentile (EPA 1992b).

A national survey conducted by the EPA solicited data on mercury concentrations in fish collected by the states as part of their fish contaminant monitoring programs (EPA 1999b). The EPA asked all states to submit mercury residue data collected from their fish sampling programs from 1990 through 1995 to assess whether there were geographic variations or trends in fish tissue concentrations of mercury. Thirty-nine states provided information on the levels of contamination in their fish. The study included the following: information on the tissue concentrations of mercury, including the number of fish sampled (by species); the mean mercury concentration; and the minimum, median, and maximum concentrations reported for each species by state. Residue information for the three most abundant species sampled in each state included such species as the largemouth and smallmouth bass; channel, flathead, and blue catfish; brown and yellow bullhead; rainbow and lake trout; carp; walleye; north pike; and white sucker.

A summary of the mean, minimum, and maximum tissue concentrations of mercury detected for two of the sampled species with the widest geographical distribution; the largemouth bass and the channel catfish are given in Tables 5-19 and 5-20, respectively. As Table 5-19 shows, the maximum mercury residues reported for the largemouth bass exceeded the FDA action level (1 ppm [1 mg/kg]) in 16 states that collected and analyzed tissue samples for this species. The highest maximum mercury concentration reported for this species was 8.94 mg/kg, reported by New Jersey. Table 5-20 shows the maximum mercury residue reported for another widely distributed species, the channel catfish. While the maximum mercury residues reported for this species are not consistently as high as those for the largemouth bass,

maximum residues in channel catfish from six states still exceeded the FDA action level (1 ppm [1 mg/kg]). Consumption of large amounts of feral fish containing these high mercury residues exposes high volume fish consuming populations (those that consume >100 g fish/day) to potentially greater risk of mercury exposure than members of the general population.

Table 5-19. Mercury Concentrations (mg/kg) for Largemouth Bass Collected in Various States Throughout the United States (1990–1995)

State	Number of fish	Minimum	Mean[a]	Maximum[b]
Alabama	914	0.100	0.393	**1.630**
Arizona	35	0.700	**1.369**	**2.620**
Arkansas	1,190	0.030	0.675	**3.170**
California	517	0.030	0.291	**1.800**
Connecticut	507	0.032	0.505	**2.645**
District of Columbia	11	0.037	0.153	0.458
Florida	2,000	0.020	0.645	**4.360**
Georgia	968	0.010	0.274	**2.286**
Illinois	305	0.010	0.018	0.880
Louisiana	452	0.001	0.391	**1.883**
Maine	137	0.071	0.634	**1.343**
Massachusetts	152	0.045	0.399	**1.100**
Mississippi	505	0.090	0.651	**2.630**
Missouri	106	0.002	0.257	0.608
Nebraska	182	0.080	0.343	0.920
New Hampshire	35	0.210	0.573	**1.400**
New Jersey	173	0.030	0.664	**8.940**
New York	53	0.050	0.462	0.950
North Carolina	1,569	0.020	0.532	**3.600**
Oregon	140	0.030	0.332	0.980
Pennsylvania	139	0.090	0.293	0.750
South Carolina	505	0.230	0.994	**3.330**
Tennessee	64	0.100	0.255	0.830
Texas	58	0.043	0.237	0.657
Vermont	1	0.150	0.802	**1.200**
Washington	20	0.024	0.137	0.350

[a]Weighted average of composite samples where the weight is the number of fish in each composite ($\Sigma(C_i \times N_i)/N_t$, where C_i and N_i are the concentrations and number of fish in each composite sample, respectively, and N_t is the total number of fish in all composites).
[b]Tissue concentrations shown in **bold type** exceed the U.S. Food and Drug Administration (FDA) action level of 1 ppm (1 mg/kg).

Source: EPA 1999b

Table 5-20. Mercury Concentrations (mg/kg) for Channel Catfish Collected in Various States Throughout the United States (1990–1995)

State	Number of fish	Minimum	Mean[a]	Maximum[b]
Alabama	702	0.100	0.214	0.660
Delaware	19	0.020	0.050	0.133
District of Columbia	17	0.055	0.091	0.240
Georgia	658	0.010	0.084	**1.1143**
Iowa	323	0.030	0.104	0.410
Kansas	56	0.029	0.125	0.314
Louisiana	76	0.001	0.111	0.732
Maryland	157	0.006	0.033	0.256
Michigan	964	0.014	0.047	0.710
Mississippi	157	0.040	0.272	2.100
Missouri	198	0.002	0.052	0.350
Nebraska	238	0.001	0.109	0.643
New Mexico	78	0.100	0.297	**1.800**
Ohio	574	0.018	0.118	1.040
Oklahoma	324	0.100	0.193	0.640
South Carolina	42	0.250	0.345	**1.610**
Tennessee	138	0.100	0.173	0.650
Texas	44	0.043	0.193	**1.186**
West Virginia	65	0.030	0.139	**1.583**

[a]Weighted average of composite samples where the weight is the number of fish in each composite ($\Sigma(C_i \times N_i)/N_t$, where C_i and N_i are the concentrations and number of fish in each composite sample, respectively, and N_t is the total number of fish in all composites).
[b]Tissue concentrations shown in **bold type** exceed the U.S. Food and Drug Administration (FDA) action level of 1 ppm (1 mg/kg).

Source: EPA 1999b

The Northeast states and Eastern Canadian provinces issued their own mercury study, including a comprehensive analysis of current mercury concentrations in a variety of fresh water sportfish species (NESCAUM 1998). This study involved a large number of fish sampling sites in each state, many of which were remote lake sites that did not receive point source discharges. Top level piscivores (i.e., predatory fish) such as walleye, chain pickerel, and large and smallmouth bass were typically found to exhibit some of the highest concentrations, with average tissue residues >0.5 mg/kg and maximum residues >2 mg/kg. One largemouth bass sample was found to contain 8.94 mg/kg of mercury, while one smallmouth bass sampled contained 5.0 mg/kg. A summary of the mean and minimum–maximum (range) of mercury concentrations in eight species of fish sampled is shown in Table 5-21. This study

also identified a relationship between elevated mercury levels in fish and certain water quality parameters, including low pH, high conductivity, and elevated levels of dissolved organic carbon.

Table 5-21. Combined Data on Mercury Concentrations in Selected Fish Species Sampled in the Northeast[a]

Species	Number of samples[b]	Mean mercury concentration	Minimum–maximum mercury[c] concentration range (mg/kg)
Largemouth bass	1,019	0.51	0–**8.94**
Smallmouth bass	738	0.53	0.08–**5.0**
Yellow perch	1,346	0.40	0–**3.15**
Eastern chain pickerel	157	0.63	0–**2.81**
Lake trout	877	0.32	0–**2.70**
Walleye[d]	257	0.77	0.10–**2.04**
Brown bullhead	421	0.20	0–**1.10**
Brook trout	200	0.26	0–0.98

[a]Northeastern states include Main, Vermont, New Hampshire, Massachusetts, Rhode Island, Connecticut, New York, and New Jersey.
[b]In some cases, states reported an average of values from a given location; thus, the number of samples indicated may not represent the number of individual fish sampled.
[c]Maximum tissue concentrations shown in **bold type** exceed the U.S. Food and Drug Administration action level of 1 mg/kg (1 ppm).
[d]Walleye data are from New York State only and may not be representative of walleye mercury concentrations in other parts of the northeast.

Source: NESCAUM 1998

Lake trout taken from Lake Ontario between 1977 and 1988 did show a progressive decline in mercury contamination from 0.24 mg/kg in 1977 to 0.12 mg/kg in 1988 (Borgmann and Whittle 1991). Samples of zooplankton taken from an Illinois lake in 1986 contained approximately 0.01 mg/kg mercury; however, fish that fed on the zooplankton had whole-body mercury concentrations ranging from 0.0116 mg/kg for inedible shad to 0.069 mg/kg for edible largemouth bass, indicating bioaccumulation was occurring up the aquatic food chain. Older fish generally had higher mercury concentrations (Kohler et al. 1990). Mercury concentrations in crayfish taken from 13 Ontario lakes with no known mercury inputs ranged from 0.02 to 0.64 mg/kg; the concentrations were positively correlated with organism weight and fish mercury concentrations (Allard and Stokes 1989). Brown trout taken from Lake Ontario contained between 0.18 and 0.21 mg/kg mercury in unskinned fillets and between 0.24 and 0.26 mg/kg mercury in skinned fillets, indicating that methylmercury is associated with the protein fraction of fish tissue (Gutenmann and Lisk 1990).

Methylmercury constitutes over 99% of the total mercury detected in fish muscle tissue, with no detection of inorganic or dimethylmercury (Bloom 1992; Grieb et al. 1990). Mercury levels were examined in aquatic organisms taken from the Calcasieu River/Lake Complex in Louisiana. The order of enrichment was as follows: shrimp (0.2 mg/kg) < mussel (0.3 mg/kg) < fish (0.4 mg/kg) = oyster (0.4 mg/kg) < zooplankton (1.4 mg/kg) (Ramelow et al. 1989). Average mercury concentrations for aquatic organisms collected from the Wabigoon/English/Winnipeg River system in Canada were as follows: 0.06–2.2 mg/kg for crayfish, 0.01–0.55 mg/kg for perch, and 0.04–1.2 mg/kg for pike. Methylmercury concentrations were found to increase with distance from the pollutant source, possibly as a result of the increased bioavailability of organic mercury produced by aquatic microorganisms, whereas inorganic mercury was the predominant form at the source (Parks et al. 1991).

Typical mercury concentrations in large carnivorous freshwater fish (e.g., pike) and large marine fish (e.g., swordfish, shark, and tuna) have been found to >1 mg/kg (EPA 1984; Fairey et al. 1997; FDA 1994; Hellou et al. 1992; Hueter et al. 1995), with mercury content again being positively correlated with the age of the fish (Gutenmann et al. 1992; Hueter et al. 1995). Methylmercury concentrations in muscle tissue of nine species of sharks were analyzed from four locations off Florida (Hueter et al. 1995). Muscle tissue methylmercury concentration averaged 0.88 mg/kg (wet weight) and ranged from 0.06 to 2.87 mg/kg, with 33.1% of the samples exceeding the FDA action level (1 ppm [1 mg/kg]). A positive correlation between methylmercury and shark body length (size) also was found, such that sharks larger than 200 cm in total length contained methylmercury concentrations >1 mg/kg. Sharks collected off the southern and southwestern coastal areas contained significantly higher concentrations than those caught in the northeast coastal region (Cape Canaveral and north).

Methylmercury concentrations were highest in the Caribbean reef shark (*Carcharhinus perezi*). The two most abundant shark species in the U.S. east coast commercial shark fishery, sandbar (*C. plumbeus*) and blacktip (*C. limbatus*) sharks, are of special concern with respect to human health. Although the mean concentration of methylmercury in the sandbar shark (0.77 mg/kg) was below the average for all sharks, sandbar shark tissues contained up to 2.87 ppm methylmercury, and 20.9% of the samples exceeded the FDA action level of 1 ppm (1 mg/kg). A total of 71.4% of the blacktip shark samples (mean, 1.3 mg/kg) exceeded the FDA action level. The study authors suggested that continued monitoring of methylmercury concentrations in various sharks species in the commercial marketplace is warranted. In a study of sportfish collected in San Francisco Bay, Fairey et al. (1997) reported that the highest concentrations of mercury were detected in leopard shark muscle tissue (1.26 mg/kg). Bluefin tuna caught in the Northwest Atlantic Ocean in 1990 contained mercury at a mean muscle concentration of 3.41 mg/kg dry weight

(Hellou et al. 1992). Arctic cod (*Arctogadus glacialis*) that were obtained during the spring season under ice layers in the Amundsen Gulf/Franklin Bay had average mercury levels of 0.37 mg/kg dry weight and were significantly higher than those collected from the shallow coastal shelf region of the Beaufort Sea, near the Mackenzie Delta, suggesting differences in regional food webs (Kirk et al. 2012).

As part of the NOAA Status and Trends Program conducted from 1984 to 1987, mercury concentrations were analyzed in four marine bivalve species in U.S. coastal waters (NOAA 1987). Mercury concentrations in bivalve tissues were 0.01–0.48 mg/kg dry weight in oysters (*Crassostrea virginica*), 0.28–0.41 mg/kg in the Hawaiian oyster (*Ostrea sandwichensis*), 0.05–0.47 mg/kg in the blue mussel (*Mytilus edulis*), and 0.04–0.26 mg/kg in the California mussel (*Mytilus californianus*). Oysters (*Crassostrea virginica*) collected around the Gulf of Mexico between 1986 and 1989 had mercury concentrations ranging from <0.01 to 0.72 mg/kg (mean 0.127 mg/kg) (Presley et al. 1990). Oysters taken from the Mississippi Sound in 1986 generally did not contain mercury at levels exceeding the detection limit (0.02 mg/kg), although two samples had detectable mercury levels of 0.66 and 6.6 mg/kg (Lytle and Lytle 1990).

Marine Mammals. Consumption of marine mammals can be an important source of exposure to methylmercury in populations that are high consumers of marine mammals (Grandjean et al. 1992). Mercury concentrations have been analyzed in various tissues (i.e., muscle, liver, kidneys) from several species of marine mammals, including beluga whales, narwhal, white-toothed dolphins, pilot whales, ringed seals, harp seals, and walruses in the western and eastern Canadian Arctic (Wagemann et al. 1995). The mean mercury concentration (mg/kg dry weight) in liver tissue was highest in pilot whales (78 mg/kg), harp seals (36 mg/kg), Eastern Arctic ringed seals (29 mg/kg), narwhal (25 mg/kg), and Eastern Arctic beluga (22 mg/kg), with lesser amounts in Arctic walrus (5 mg/kg) and dolphins (4 mg/kg). Of the three tissues analyzed, mercury was most concentrated in the liver, with successively lower concentrations in the kidney and muscle tissue. This pattern prevails in most marine mammals. The concentration of total mercury is greater by a factor of 3 in the liver than in the kidney, but can be significantly higher in some species (see Table 5-22). Mean tissue residues in ringed seals from the western Arctic had significantly higher concentrations of mercury than those from the eastern Arctic. The study authors reported higher mercury levels in sediment (0.068–0.243 mg/kg dry weight) and water (11–29 ng/L) from the western Arctic, as compared to sediment (0.040–0.060 mg/kg dry weight) and water (3.7 ng/L) from the eastern Arctic. These differences in sediment and water mercury levels may be responsible for some of the observed differences in mercury tissue concentrations in the seals.

Table 5-22. Total Mercury Concentrations in Tissues of Marine Mammals in Alaska and Canada (mg/kg, Wet Weight)

Species	Date collected (location)	Muscle concentration (n)	Liver concentration (n)	Source
Polar bear	1972 (West Alaska)	0.043±0.001 (16)	4.235±1.385 (25)	ADFG 1976
	1972 (North Alaska)	0.168±0.089 (30)	29.914±22.547 (38)	
Beluga whale	1977 (South Beaufort Sea)	2.12±0.15 (11)	30.62±20.53 (8)	Muir et al. 1992
Ringed seal	1972 (Southeast Beaufort Sea)	0.23±0.11 (13)	1.0±1.16 (13)	Smith and Armstrong 1975
	1972–1973 (Amundsen Gulf)	0.72±0.33 (83)	27.50±30.10 (83)	Smith and Armstrong 1975, 1978
	1976 (Barrow Strait)	0.91±0.38 (27)	16.14±13.84 (27)	Smith and Armstrong 1978
	1976 (Strathcona Sound)	0.08±0.07 (37)	0.32±0.080 (36)	
	1976 (North Baffin Island)	0.31±0.17 (33)	3.76±3.42 (33)	
Bearded seal	1973 (Amundsen Gulf)	0.53±0.35 (3)	143±170 (6)	Smith and Armstrong 1975, 1978
	1974 (East Hudson Bay)	0.09±0.04 (55)	26.18±26.13 (56)	Smith and Armstrong 1978

Mercury tissue concentrations were detected in 17 adult and 8 fetal pilot whales from two stranding episodes off Cape Cod, Massachusetts (Meador et al. 1993). Total mercury occurred in high concentrations in both the liver and kidney, and liver concentrations were significantly correlated with the animal's length. Methylmercury, as a percentage of total mercury, varied inversely with total mercury, indicating that demethylation was occurring. Mean adult mercury concentrations in mg/kg dry weight in liver and kidneys were 176 mg/kg (range 1.9–626 mg/kg dry weight) and 27.5 mg/kg (range 6.8–49.7 mg/kg dry weight), respectively. Mean fetal mercury concentrations in mg/kg dry weight in liver and kidneys were 2.3 mg/kg (range 0.9–5.4 mg/kg dry weight) and 1.9 mg/kg (range, 0.6–3.9 mg/kg dry weight), respectively. The mean methylmercury concentration in mg/kg dry weight in adult liver tissue was 8 mg/kg (range 5.6–10 mg/kg). Aguilar and Borrell (1995) studied mercury tissue levels (1970–1988) in harbor porpoises in the eastern North Atlantic. The study authors reported that in most tissues of harbor porpoises, the mercury was virtually all in the form of methylmercury; however, the fraction of organic mercury in the liver was much lower than in the rest of the body tissues. The study authors found that for a given tissue, the concentrations detected were extremely variable between localities and years. Mercury concentrations in harbor porpoises ranged from 0.62 to 70 mg/kg in liver and from 0.66 to

22 mg/kg in muscle. The mean mercury concentration in liver for the eastern harbor porpoise population was 11.2 mg/kg. Mercury tissue levels progressively increased with the age of the animal; no significant differences were found between the sexes (Aguilar and Borrell 1995).

Plants. Consumption of rice can also make a substantial contribution to dietary mercury intake and, in some populations, rice has been shown to be the dominant sources of dietary mercury intake (Zhang et al. 2010). Although data on mercury distribution among freshwater vascular plant parts is lacking for unpolluted systems, Mortimer (1985) reported that total mercury in the roots of five species of freshwater vascular plants in the polluted Ottawa River was 10–40% higher than in the shoots. Speciation may be important in determining the patterns of mercury uptake, translocation, and excretion in macrophytes. Shoots of *Elodea densa* more readily accumulated methylmercury than inorganic mercury, and also excreted more inorganic mercury than methylmercury (Czuba and Mortimer 1980). Significant translocation of inorganic mercury from shoots to roots occurred in *E. densa* (Czuba and Mortimer 1980). In this species, methylmercury and inorganic mercury moved in opposite directions, with methylmercury moving towards the young shoot apex and inorganic mercury moving towards lower (older) parts of the shoot (Czuba and Mortimer 1980). Dolar et al. (1971) noted the same methylmercury pattern in the water milfoil (*Myriophyllum spicatum*). Using solution culture experiments, the study authors showed that mercury accumulation was greater when plants were exposed to inorganic mercury ($HgCl_2$) than organic methylmercury (CH_3HgCl) and that mercury accumulation from the nutrient solution was rapid and approached maximum values in 2 hours. Organomercury compounds (methylmercury chloride, phenylmercuric acetate, phenylmercuric chloride, and phenylmercuric hydroxide) were more available than inorganic compounds (HgF_2 and $HgCl_2$) from lake sediments. The various organomercury and inorganic mercury compounds were added to sediment at concentrations of 0, 46, 230, and 460 mg/kg prior to rooting water milfoil. After 20 days, concentration of mercury in the plant tissues exposure to 46, 230, and 460 mg/kg of the inorganic mercury compounds in the sediment were 1.71–4.01, 4.81–6.03, and 6.61–10.2 mg/kg, respectively. In contrast, the concentrations of mercury in plant tissues exposed to 46, 230, and 460 mg/kg of the organic mercury compounds in the sediment were 2.40–7.15, 36–84.5, and 114.6–243.1 mg/kg, respectively. The control plants (no mercury compounds added to the sediments) contained 0.3 mg/kg mercury. It is clear from this experiment that organomercury compounds may accumulate significantly in the above-ground parts of some macrophytes. Mortimer (1985) found that although *E. densa* shoots had lower total mercury contents than roots, with 32% of the mercury in the shoots in the form of methylmercury, compared to only 10% in the roots.

Grasses sampled downwind of a municipal waste incinerator contained up to 0.20 µg/g (ppm) of mercury, with concentrations decreasing with increasing distance from the facility (Bache et al. 1991). Background mercury levels in vegetation were usually <0.1 mg/kg dry weight (Lindqvist et al. 1991); however, mushrooms collected 1 km from a lead smelter in Czechoslovakia contained between 0.3 and 12 mg/kg dry weight (Kalac et al. 1991).

Consumer and Medicinal Products. Various consumer and medicinal products may contain mercury or mercury compounds (e.g., skin lightening creams and soaps, herbal remedies, laxatives, tattooing dyes, fingerpaints, artists paints, and make-up paints), but all of these products originate from outside of the United States (Barr et al. 1973; DeVito and Brooks 2013; Dyall-Smith and Scurry 1990; Lauwerys et al. 1987; McKelvey et al. 2011; Rastogi 1992; Wendroff 1990). The EPA maintains a website that lists the consumer products that may contain mercury (https://www.epa.gov/mercury/mercury-consumer-products#list).

Barr et al. (1973) reported elevated mercury levels in the blood of women using skin lightening creams, although the mercury compound and concentrations in the skin cream were not determined. Dyall-Smith and Scurry (1990) reported that one skin lightening cosmetic cream contained 17.5% mercuric ammonium chloride. Lauwerys et al. (1987) reported a case of mercury poisoning in a 3-month-old infant whose mother frequently used a skin lightening cream and soap containing inorganic mercury during her pregnancy and during the 1-month lactation period following birth. However, the mercury concentration and specific mercury compound in the cream and soap were not determined. Al-Saleh and Al-Doush (1997) analyzed the inorganic mercury content of 38 skin lightening creams in Saudi Arabian markets. The creams were manufactured in a variety of countries, including India and Pakistan, other Arab countries, Thailand, Taiwan, Indonesia, England, and Germany. Almost 50% of the creams tested exceeded the tolerance limit of 1 ppm. The mean concentration of mercury in the 38 creams was 994 mg/kg, with a range of 0–5,650 mg/kg. It is not known whether any of these products are available in the United States.

Metallic mercury was also the source of two cases of mercury poisoning caused by the dermal application of an over-the-counter anti-lice product (Bourgeois et al. 1986). The more severely poisoned individual applied 30 g of ointment containing 9 g of metallic mercury (300,000 mg/kg) to his entire body. Wands et al. (1974) also reported the deaths of two individuals due to the excessive use of a laxative preparation containing mercurous chloride (calomel).

Metallic mercury has been used by Mexican-American and Asian populations in traditional remedies for chronic stomach disorders (Espinoza et al. 1995, 1996; Geffner and Sandler 1980; Trotter 1985). Perharic et al. (1994) reported cases of poisonings resulting from exposure to traditional remedies and food supplements reported to the National Poisons Unit in London, England. From 1989 to 1991, elemental mercury was implicated in several poisonings following exposure to traditional Asian medicines. In one case, the mercury concentration in the medicinal product taken orally was 540,000 mg/kg. The mercury was in its elemental or metallic form. Espinoza et al. (1995, 1996) reported that while examining imported Chinese herbal balls for the presence of products from endangered species, the study authors detected potentially toxic levels of arsenic and mercury in certain herbal ball preparations. Herbal balls are aromatic, malleable, earth-toned, roughly spherical, hand-rolled mixtures primarily composed of herbs and honey that are used to make medicinal teas. These herbal balls are used as a self-medication for a wide variety of conditions, including fever, rheumatism, apoplexy, and cataracts. Herbal balls similar to those analyzed are readily available in specialty markets throughout the United States. Mercury (probably mercury sulfide) was detected in eight of the nine herbal balls tested. The recommended adult dose for the herbal balls is two per day. Ingesting two herbal balls could theoretically provide a dose of up to 1,200 mg of mercury.

Samudralwar and Garg (1996) conducted trace metal analysis on a variety of plants used in Indian herbal remedies and other medicinal preparations. The study authors reported mercury concentrations of 0.139, 0.180, 0.027, 0.0125, 0.0117, and <0.010 mg/kg for Bowen's kale, Neem leaves, Gulvei leaves, Kanher bark, Vekhand root, and orange peel, respectively.

Hoet and Lison (1997) reported on an unusual non-occupational source of mercury exposure in a woman who used prescription nasal drops that contained 300 mg/L borate phenylmercury. The study authors reported that the woman, who had used the nasal drops over a long period of time, had high urinary levels of mercury (82 mg/kg), but that blood levels were not abnormal (5.5 µg/L).

Mercuric sulfide, or cinnabar, was reported to be used in tattooing dyes to produce a red pigmentation (Bagley et al. 1987; Biro and Klein 1967). An analysis of finger paints and make-up paints manufactured in Europe showed that they all contained <1 mg/kg mercury (Rastogi 1992). Rastogi and Pritzl (1996) conducted another study to assess the migration of several toxic metals from crayons, watercolor paints, and water-based paints. Migration of mercury from the art materials was determined by scraping flakes of the products into dichloromethane for 2 hours at 54°C. The degreased material was then placed in an aqueous HCl solution, shaken, and centrifuged. The supernatant was then filtered through a 0.45 µm

membrane filter and analyzed. The study authors reported that the migration of mercury from these art supplies was 0.24–5.98 mg/kg for red paint, 0.26–3.63 mg/kg for blue paint, 0.20–4.79 mg/kg for yellow paint, 0.22–5.68 mg/kg for green paint, and 0.17–3.63 mg/kg for white paint. Migration of mercury from the product occurred in 57% of the samples tested. The migration limit set by European Standard EN71-3 for mercury is 60 mg/kg. This value was not exceeded in any of the art supplies tested. The study authors, however, believe that children might be exposed not only to mercury, but to several other metals that also co-migrated from the paints. Mercury is not allowed in the manufacture of any paint products in the United States (DeVito and Brooks 2013).

Cigarettes. In a study conducted in West Germany, Pesch et al. (1992) analyzed mercury concentrations in 50 brands of cigarettes manufactured in two Western and six Eastern European countries. The study authors reported that in 1987, the average mercury concentration detected in cigarettes was 0.098 mg/kg (dry weight) (range 0.06–0.14 mg/kg dry weight). In 1991, the mean mercury concentrations for cigarettes were 0.034 mg/kg dry weight (range 0.007–0.092 mg/kg dry weight) for Eastern Europe and 0.015 mg/kg dry weight (range 0.006–0.037 mg/kg dry weight) for Western European countries. The study authors attributed the decline in mercury content of cigarettes to environmental protection measures instituted in the intervening years (Pesch et al. 1992).

Religious and Cultural Rituals, Ceremonies, and Practices. Most medicinal and pharmaceutical uses of mercury compounds have been discontinued. However, individuals in some cultural or religious groups may still use mercury in various rituals, practices, and ceremonies, resulting in exposure to elevated mercury concentrations. Media reports (Sawyer 2015; Vasquez 2012; Washam 2011), case reports, and scientific papers indicate that mercury is still being used in this way and can cause health effects (Pandalai and Morgan 2011; Rhee et al. 2020; Tarabar and Su 2003; Weinstein and Bernstein 2003).

Metallic mercury has been used in Latin American and Caribbean communities as part of certain religious practices (e.g., Voodoo, Santeria, and Espiritismo), predominantly in domestic settings (Riley et al. 2001; Wendroff 1990). Vietnamese and Indian people may also use mercury as alternative medicine. One case report details a Vietnamese person heating ‘pellets’ to vaporize the contents. After onset of malaise, dry skin, and poor appetite, the person saw a physician and blood tests indicated 409 μg mercury/L at 1 week postexposure. At 4 weeks postexposure, blood mercury was 61 μg/L, with 497 μg mercury/g creatinine in the urine (Pandalai and Morgan 2011). An unintentional poisoning occurred when 20-month-old Indian twins were given mercury ‘teething powder’ over the course of months. This resulted in the twins

becoming weak; exhibiting a rash; and swollen, red, painful hands and feet. Testing indicated diminished reflexes with blood mercury levels of 176 and 209 μmol/L (Weinstein and Bernstein 2003).

In the United States, people may obtain metallic mercury (sometimes under the name azogue) in shops called botanicas. These stores typically stock medicinal plants, traditional medicines, incense, candles, creams, and perfumes. Botanicas typically dispense mercury in gelatin capsules or sometimes in small glass vials. Some people carry a small amount of mercury in a vial, or mix mercury in bath water or perfumed soaps, devotional candles, ammonia, or camphor. Other people's religious practices involve sprinkling metallic mercury on the floor of a dwelling or car, mixing metallic mercury with soap and water to wash the floor, or placing it in an open container to rid the house of evil spirits. Any of these practices can liberate mercury vapor into the room air, exposing the occupants to elevated levels of mercury vapors (ATSDR 1997; Wendroff 1990, 1991). This use of mercury can contaminate a dwelling or automobile if the mercury is not completely removed from flooring, carpeting, and woodwork in an appropriate manner.

In addition to the individuals who intentionally use mercury in their dwellings, the opportunity exists for non-users to be inadvertently exposed when they visit the dwelling, or purchase or rent dwellings in which the former tenants used mercury for religious purposes (NDJEP 2007; Riley et al. 2006). The issuance of cautionary notices and information by health departments to members of these user populations is appropriate (Rogers et al. 2007).

5.6 GENERAL POPULATION EXPOSURE

Humans can be exposed to mercury in air, water, soil, and food. Diet is typically the major source of mercury absorption in the general population (non-occupational). However, mercury released from mercury amalgam dental restorations can also contribute to mercury absorption (Langworth et al. 1988; Mackert and Berglund 1997; Nylander et al. 1987). The dominant source of mercury intake and absorption from the diet derives from consumption of fish (Bloom 1992; Davis et al. 2014; De Winter-Sorkina et al. 2003; EFSA 2012; EPA 1999b; Kim et al. 2016b; Lescord et al. 2018; Mahaffey et al. 2004; Nielsen et al. 2015; Sirot et al. 2008; WHO 1990; You et al. 2014, 2018), in part because of the relative high concentrations of methylmercury in fish and shellfish (Bloom 1992; Lescord et al. 2018; Storelli et al. 2003; Wells et al. 2020) and near complete absorption of methylmercury in the human gastrointestinal tract (see Section 3.1 Toxicokinetics).

Consumption of rice can also make a substantial contribution to dietary mercury intake and, in some populations, rice has been shown to be the dominant sources of dietary intake (Rothenberg et al. 2016b; Wells et al. 2020; Zhang et al. 2010). Dietary mercury intake has been estimated from food surveys in various populations and, as can be expected, varies with diet and, in particular, the contribution of fish and shellfish and rice to the total diet (De Winter-Sorkina et al. 2003; EFSA 2012; Kim et al. 2016b; Vejrup et al. 2016; WHO 1990; You et al. 2014; Zhang et al. 2010). Total diet studies conducted in Asia, United States, and Europe suggest that intakes of total mercury ranging from 1 to 10 μg/day are typical (Carrington and Bolger 2002; EFSA 2014; EPA 1999b; Jenssen et al. 2012; Kim et al. 2016b; Sanga et al. 2001; WHO 1990). Intakes can be substantially higher in populations that consume higher amounts of fish (Dong et al. 2015; Juric et al. 2017; Marien and Patrick 2001; Passos et al. 2008).

The relative contribution of mercury released from dental amalgams has been estimated based on studies of release rates and assumptions regarding the fate and absorption of amalgam mercury. The contributions of mercury from dental amalgams were estimated based on results from measurements of releases of Hg^0 vapor and particulate Hg^0 from amalgams and models of intake and absorption of mercury released from amalgams (Mackert and Berglund 1997). Total mercury absorption in a person having 13 mercury amalgam dental restorations was estimated to be approximately 3 μg/day (range 0.6–9.3 μg/day), of which approximately one-third was absorbed from the gastrointestinal tract. Following removal of all dental amalgams, mean blood total mercury decreased 1.13 μg/L (SD 0.6) from a baseline of 2.18 μg/L (SD 0.90) over an 18-week period, a 49% decrease, in subjects who had an average of seven occlusal surfaces with amalgam restorations (Snapp et al. 1989). This would be consistent with amalgams contributing to approximately half of total mercury absorption. Removal of mercury amalgams can release Hg^0 to air and saliva (Halbach et al. 2000; Warwick et al. 2019).

The general population may also be exposed to mercury vapor released from liquid elemental mercury from breakage or spills of older mercury-containing items at home or at school, such as medical/scientific equipment, batteries, fluorescent lamps, electrical switches, and paints made prior to 1992 (CDC 2015). Disposal of older items and proper clean-up of spills reduces the change of exposure (CDC 2013, 2015).

Various consumer (e.g., skin lightening creams and soaps, herbal remedies, laxatives, tattooing dyes, fingerpaints, artists paints, and make-up paints) and medicinal products (e.g., thimerosal, an ethylmercury-containing compound that was used as a preservative in vaccines) that contain mercury or mercury compounds can also contribute to exposure to consumers (DeVito and Brooks 2013; McKelvey et al. 2011; Rastogi 1992; Wendroff 1990). Any mercury released into air, water, or soil via consumer

use or disposal of mercury-containing products would contribute to exposures detected in environmental media.

Mercury levels in blood and urine are measured as part of the NHANES (CDC 2019) (Tables 5-23–5-32). Based on survey data for the period 2015–2016 (the most recent data available in CDC 2019), the geometric mean total blood mercury level in the adult U.S. population was estimated to be 0.810 µg/L (95% CI 0.740, 0.886). The geometric mean methylmercury blood level was 0.518 µg/L (95% CI 0.456, 0.588). Total and methylmercury blood levels in young children were lower than in adults. The 50th percentiles for total blood mercury levels in children 1–5 years of age were less than the detection limit (0.28 µg/L) in 2015–2016. For the 2011–2012 period, the detection limits for total mercury were lower, reporting a geometric mean total blood mercury level of 0.262 µg/L (95% CI 0.237, 0.291) in children 1–5 years of age. The 50th percentiles for methylmercury blood levels in children 1–5 years of age were less than the detection limit (0.12 µg/L) during both time periods. For the 2015–2016 period, the 50th percentiles of total urinary mercury were 0.140 µg/L (95% CI 0.130, 0.150) in adults and below the detection limit (0.13 µg/L) in children 3–5 years of age.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to workers exposed to mercury (primarily mercury vapor) in the workplace, other population groups are at risk for potential exposure to high levels of mercury. These include: (1) people who live in proximity to former mercury mining or production sites, secondary production (recycling) facilities, municipal or medical incinerators, or coal-fired power plants; (2) people who consume large amounts of fish or marine mammals (Grandjean et al. 1992); (3) people who have mercury amalgam dental restorations (Mackert and Berglund 1997; Snapp et al. 1989); (4) people who use consumer products containing mercury such as traditional or herbal remedies, or cosmetics, including skin lightening creams (McKelvey et al. 2011); and (5) people use mercury as part of spiritual practices (Riley et al. 2001).

Table 5-23. Geometric Mean and Selected Percentiles of Total Mercury Blood Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2010

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a] 50th	75th	90th	95th	Sample size
Total	2003–2004	0.797 (0.703–0.903)	0.800 (0.700–0.900)	1.70 (1.50–1.90)	3.30 (2.90–3.90)	4.90 (4.30–5.50)	8,373
	2005–2006	0.863 (0.787–0.946)	0.830 (0.760–0.920)	1.66 (1.48–1.93)	3.20 (2.87–3.54)	4.64 (4.17–5.25)	8,407
	2007–2008	0.769 (0.689–0.859)	0.740 (0.660–0.830)	1.48 (1.29–1.69)	2.95 (2.46–3.59)	4.64 (3.74–5.79)	8,266
	2009–2010	0.863 (0.792–0.941)	0.790 (0.730–0.880)	1.68 (1.49–1.91)	3.43 (3.07–3.84)	5.13 (4.57–5.67)	8,793
Age group							
1–5 years	2003–2004	0.326 (0.285–0.372)	0.300 (0.300–0.300)	0.500 (0.500–0.700)	1.00 (0.800–1.60)	1.80 (1.30–2.50)	911
	2005–2006	NC	<LOD	0.500 (0.470–0.550)	.940 (0.820–1.24)	1.43 (1.25–1.59)	968
	2007–2008	NC	<LOD	0.440 (0.380–0.540)	.830 (0.620–1.12)	1.32 (0.960–2.40)	817
	2009–2010	NC	<LOD	0.490 (0.430–0.590)	.890 (0.740–1.08)	1.30 (1.08–1.52)	836
6–11 years	2003–2004	0.419 (0.363–0.484)	0.400 (0.400–0.500)	0.700 (0.700–0.900)	1.30 (1.00–1.60)	1.90 (1.40–3.50)	856
	2005–2006	NC	0.410 (0.330–0.460)	0.740 (0.630–1.00)	1.43 (1.21–1.87)	2.34 (1.53–3.42)	934
	2007–2008	NC	0.380 (0.340–0.440)	0.700 (0.600–0.790)	1.21 (0.970–1.36)	1.56 (1.34–1.80)	1,011
	2009–2010	NC	0.360 (<LOD–0.400)	0.670 (0.590–0.770)	1.22 (1.05–1.45)	1.88 (1.43–2.61)	1,009
12–19 years	2003–2004	0.490 (0.418–0.574)	0.500 (0.400–0.600)	1.00 (0.800–1.20)	1.80 (1.40–2.30)	2.60 (2.10–3.30)	2,081
	2005–2006	0.513 (0.461–0.570)	0.460 (0.390–0.530)	0.850 (0.740–1.04)	1.66 (1.31–1.98)	2.41 (2.12–2.90)	1,996
	2007–2008	0.469 (0.426–0.516)	0.440 (0.390–0.490)	0.800 (0.670–0.970)	1.55 (1.30–1.72)	2.05 (1.77–2.34)	1,074
	2009–2010	0.534 (0.473–0.602)	0.450 (0.370–0.540)	0.910 (0.770–1.11)	2.04 (1.53–2.55)	3.01 (2.53–3.63)	1,183
≥20 years	2003–2004	0.979 (0.860–1.12)	1.00 (0.800–1.10)	2.00 (1.70–2.30)	3.80 (3.20–4.40)	5.40 (4.60–6.70)	4,525
	2005–2006	1.06 (0.967–1.15)	1.03 (0.930–1.15)	1.98 (1.73–2.22)	3.64 (3.33–4.01)	5.31 (4.82–5.67)	4,509
	2007–2008	0.944 (0.833–1.07)	0.890 (0.780–1.03)	1.73 (1.47–2.09)	3.41 (2.82–4.17)	5.32 (4.32–6.72)	5,364
	2009–2010	1.04 (0.956–1.14)	0.970 (0.870–1.08)	2.00 (1.80–2.20)	3.96 (3.55–4.27)	5.75 (5.14–6.50)	5,765
Gender							
Males	2003–2004	0.814 (0.714–0.927)	0.800 (0.700–0.900)	1.80 (1.50–2.00)	3.70 (3.20–4.30)	5.40 (4.60–6.50)	4,132
	2005–2006	0.864 (0.783–0.954)	0.810 (0.720–0.940)	1.69 (1.48–2.01)	3.30 (2.86–3.73)	4.83 (4.08–5.45)	4,092
	2007–2008	0.809 (0.709–0.923)	0.760 (0.670–0.850)	1.56 (1.31–1.81)	3.21 (2.72–4.06)	5.16 (4.12–6.97)	4,147
	2009–2010	0.883 (0.810–0.962)	0.790 (0.730–0.870)	1.75 (1.54–2.02)	3.84 (3.35–4.26)	5.65 (5.13–6.34)	4,366
Females	2003–2004	0.781 (0.689–0.886)	0.800 (0.700–0.900)	1.60 (1.40–1.80)	3.00 (2.50–3.50)	4.40 (3.60–5.30)	4,241
	2005–2006	0.864 (0.791–0.943)	0.850 (0.770–0.920)	1.63 (1.44–1.89)	3.09 (2.75–3.46)	4.51 (4.01–5.28)	4,315
	2007–2008	0.748 (0.677–0.827)	0.720 (0.660–0.810)	1.42 (1.24–1.60)	2.70 (2.27–3.27)	3.93 (3.17–5.16)	4,119
	2009–2010	0.845 (0.772–0.924)	0.800 (0.720–0.880)	1.61 (1.43–1.81)	3.13 (2.76–3.48)	4.43 (4.04–5.11)	4,427

Table 5-23. Geometric Mean and Selected Percentiles of Total Mercury Blood Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2010

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a] 50th	75th	90th	95th	Sample size
Race/ethnicity							
Mexican Americans	2003–2004	0.563 (0.472–0.672)	0.600 (0.500–0.700)	1.00 (0.800–1.30)	1.90 (1.60–2.40)	3.00 (2.20–3.80)	2,085
	2005–2006	0.597 (0.524–0.679)	0.580 (0.490–0.670)	1.04 (0.870–1.24)	1.70 (1.40–2.12)	2.58 (1.96–3.31)	2,236
	2007–2008	0.594 (0.536–0.658)	0.580 (0.520–0.670)	1.03 (0.900–1.17)	1.73 (1.49–2.04)	2.48 (2.10–2.91)	1,712
	2009–2010	0.613 (0.571–0.659)	0.580 (0.540–0.630)	1.01 (0.890–1.15)	1.63 (1.47–1.90)	2.45 (2.03–2.93)	1,966
Non-Hispanic blacks	2003–2004	0.877 (0.753–1.02)	0.900 (0.800–1.00)	1.60 (1.40–1.80)	3.00 (2.30–4.00)	4.40 (3.30–6.00)	2,293
	2005–2006	0.823 (0.697–0.972)	0.800 (0.670–0.940)	1.50 (1.21–1.92)	2.72 (2.14–3.59)	4.09 (3.22–5.16)	2,193
	2007–2008	0.766 (0.711–0.825)	0.780 (0.710–0.830)	1.32 (1.23–1.42)	2.25 (1.99–2.58)	3.42 (2.74–3.90)	1,746
	2009–2010	0.928 (0.805–1.07)	0.900 (0.800–1.02)	1.67 (1.38–1.96)	2.93 (2.20–4.21)	4.56 (3.34–6.69)	1,593
Non-Hispanic whites	2003–2004	0.776 (0.655–0.919)	0.800 (0.700–0.900)	1.70 (1.40–2.00)	3.20 (2.60–3.90)	4.70 (4.00–5.60)	3,478
	2005–2006	0.891 (0.801–0.992)	0.870 (0.770–1.00)	1.74 (1.50–2.10)	3.37 (2.88–3.76)	4.76 (4.18–5.37)	3,310
	2007–2008	0.743 (0.651–0.847)	0.720 (0.620–0.820)	1.43 (1.18–1.70)	2.79 (2.33–3.41)	4.18 (3.57–4.83)	3,461
	2009–2010	0.856 (0.766–0.957)	0.790 (0.690–0.920)	1.70 (1.46–1.98)	3.43 (2.94–3.94)	4.92 (4.30–5.65)	3,760

[a]The limit of detection for survey years 2003–2004, 2005–2006, 2007–2008, and 2009–2010 were 0.2, 0.33, 0.33, and 0.33 µg/L, respectively.

CI = confidence interval; LOD = limit of detection; NC = not calculated (proportion of results below limit of detection was too high to provide a valid result)

Source: CDC 2019

Table 5-24. Geometric Mean and Selected Percentiles of Total Mercury Blood Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2011–2016

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a] 50th	75th	90th	95th	Sample size
Total	2011–2012	0.703 (0.0617–0.801)	0.640 (0.0580–0.730)	1.38 (1.14–1.72)	2.87 (2.39–3.62)	4.40 (3.50–5.71)	7,920
	2013–2014	0.683 (0.0621–0.751)	0.620 (0.0540–0.690)	1.29 (1.14–1.46)	2.65 (2.32–3.08)	4.36 (3.65–4.97)	5,215
	2015–2016	0.678 (0.0619–0.743)	0.600 (0.0540–0.690)	1.26 (1.07–1.47)	2.55 (2.17–3.10)	4.25 (3.44–4.94)	4,988
Age group							
1–5 years	2011–2012	0.262 (0.0237–0.291)	0.250 (0.0220–0.270)	0.390 (0.0340–0.450)	0.680 (0.0540–0.880)	0.99 (0.0790–1.21)	713
	2013–2014	NC	<LOD	0.410 (0.0370–0.450)	0.810 (0.0710–0.990)	1.21 (1.05–1.48)	818
	2015–2016	NC	<LOD	0.380 (0.0340–0.430)	0.690 (0.0540–0.830)	1.06 (0.0840–1.36)	790
6–11 years	2011–2012	0.330 (0.0287–0.379)	0.320 (0.0280–0.360)	0.530 (0.0480–0.600)	0.930 (0.0780–1.20)	1.40 (1.02–2.17)	1,048
	2013–2014	NC	0.300 (<LOD–0.360)	0.570 (0.0470–0.680)	1.12 (0.0980–1.36)	1.62 (1.38–2.19)	1,075
	2015–2016	NC	0.310 (0.0290–0.340)	0.480 (0.0430–0.570)	0.920 (0.0750–1.13)	1.33 (1.01–2.28)	1,023
12–19 years	2011–2012	0.411 (0.0355–0.476)	0.370 (0.0320–0.450)	0.680 (0.0590–0.800)	1.32 (1.08–1.75)	2.25 (1.46–2.87)	1,129
	2013–2014	0.412 (0.0367–0.463)	0.350 (0.0310–0.420)	0.630 (0.0530–0.750)	1.20 (0.0900–1.67)	1.87 (1.30–2.38)	627
	2015–2016	0.395 (0.0356–0.439)	0.340 (0.0300–0.370)	0.590 (0.0470–0.750)	1.00 (0.0850–1.35)	1.89 (1.02–3.34)	565
≥20 years	2011–2012	0.863 (0.0753–0.990)	0.790 (0.0690–0.940)	1.68 (1.36–2.12)	3.35 (2.71–4.31)	5.02 (3.94–6.96)	5,030
	2013–2014	0.814 (0.0736–0.900)	0.740 (0.0650–0.850)	1.54 (1.36–1.71)	3.08 (2.73–3.56)	4.88 (4.36–5.21)	2,695
	2015–2016	0.810 (0.0740–0.886)	0.740 (0.0660–0.830)	1.47 (1.28–1.75)	2.86 (2.50–3.44)	4.66 (3.91–5.96)	2,610
Gender							
Males	2011–2012	0.712 (0.0623–0.815)	0.650 (0.0570–0.730)	1.40 (1.17–1.72)	3.00 (2.44–3.91)	4.94 (3.50–6.79)	3,968
	2013–2014	0.688 (0.0617–0.767)	0.620 (0.0530–0.720)	1.30 (1.12–1.54)	2.76 (2.36–3.34)	4.52 (3.65–5.23)	2,587
	2015–2016	0.679 (0.0621–0.743)	0.610 (0.0530–0.700)	1.29 (1.06–1.60)	2.45 (2.06–3.31)	4.67 (3.77–5.39)	2,488
Females	2011–2012	0.694 (0.0609–0.791)	0.640 (0.0580–0.740)	1.36 (1.09–1.75)	2.81 (2.28–3.50)	4.03 (3.29–5.08)	3,952
	2013–2014	0.678 (0.0617–0.745)	0.610 (0.0530–0.700)	1.27 (1.14–1.42)	2.56 (2.17–3.08)	4.15 (3.37–4.93)	2,628
	2015–2016	0.677 (0.0608–0.754)	0.600 (0.0530–0.700)	1.23 (1.02–1.42)	2.57 (2.20–3.10)	3.95 (3.10–4.55)	2,500
Race/ethnicity							
Mexican Americans	2011–2012	0.483 (0.0424–0.550)	0.480 (0.0400–0.560)	0.810 (0.0720–0.900)	1.44 (1.16–1.63)	1.90 (1.57–2.19)	1,077
	2013–2014	0.487 (0.0433–0.547)	0.430 (0.0390–0.510)	0.760 (0.0690–0.870)	1.41 (1.14–1.69)	1.98 (1.70–2.38)	969
	2015–2016	0.540 (0.0522–0.559)	0.530 (0.0470–0.570)	0.840 (0.0790–0.920)	1.41 (1.19–1.60)	1.81 (1.54–2.33)	994
Non-Hispanic blacks	2011–2012	0.679 (0.0542–0.852)	0.630 (0.0500–0.790)	1.24 (0.0880–1.72)	2.45 (1.84–3.14)	3.80 (2.70–5.37)	2,195
	2013–2014	0.699 (0.0614–0.796)	0.650 (0.0570–0.750)	1.20 (1.08–1.40)	2.30 (1.65–2.96)	3.34 (2.35–5.93)	1,119
	2015–2016	0.698 (0.0587–0.829)	0.630 (0.0510–0.760)	1.21 (1.04–1.47)	2.49 (2.01–3.51)	4.51 (2.74–5.87)	1,070

Table 5-24. Geometric Mean and Selected Percentiles of Total Mercury Blood Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2011–2016

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a] 50th	75th	90th	95th	Sample size
Non-Hispanic whites	2011–2012	0.688 (0.0582–0.813)	0.630 (0.0550–0.750)	1.38 (1.09–1.82)	2.83 (2.18–3.82)	4.25 (3.02–6.24)	2,493
	2013–2014	0.672 (0.0598–0.755)	0.620 (0.0520–0.720)	1.30 (1.12–1.51)	2.61 (2.18–3.08)	4.15 (3.35–4.98)	1,848
	2015–2016	0.638 (0.0563–0.723)	0.570 (0.0500–0.670)	1.22 (0.0940–1.47)	2.29 (1.82–2.72)	3.95 (2.56–4.55)	1,511
All Hispanics	2011–2012	0.612 (0.0527–0.710)	0.590 (0.0490–0.700)	1.08 (0.0890–1.33)	1.96 (1.60–2.68)	3.03 (2.37–3.86)	1,931
	2013–2014	0.551 (0.0486–0.624)	0.490 (0.0420–0.580)	0.910 (0.0820–1.10)	1.76 (1.44–2.12)	2.59 (2.06–3.14)	1,481
	2015–2016	0.607 (0.0546–0.675)	0.570 (0.0520–0.640)	1.00 (0.0870–1.17)	1.75 (1.38–2.33)	2.60 (1.85–3.25)	1,664
Asians	2011–2012	1.86 (1.58–2.19)	2.30 (1.84–2.64)	4.32 (3.71–5.21)	7.71 (6.38–8.79)	10.3 (8.85–12.0)	1,005
	2013–2014	1.72 (1.46–2.03)	1.77 (1.42–2.26)	3.92 (3.35–4.55)	7.78 (6.39–9.16)	9.99 (9.16–13.7)	510
	2015–2016	1.73 (1.41–2.12)	2.03 (1.40–2.70)	4.21 (3.31–5.50)	7.66 (6.17–9.91)	11.3 (9.12–13.8)	479

[a]The limit of detection for survey years 2011–2012, 2013–2014, and 2015–2016 were 0.16, 0.28, and 0.28 µg/L, respectively.

CI = confidence interval; LOD = limit of detection; NC = not calculated (proportion of results below limit of detection was too high to provide a valid result)

Source: CDC 2019

Table 5-25. Geometric Mean and Selected Percentiles of Inorganic Mercury Blood Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2010

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a] 50th	75th	90th	95th	Sample size
Total	2003–2004	NC	<LOD	<LOD	0.600 (0.500–0.600)	0.700 (0.700–0.700)	8,147
	2005–2006	NC	<LOD	<LOD	0.540 (0.500–0.580)	0.660 (0.620–0.710)	8,371
	2007–2008	NC	<LOD	0.350 (<LOD–0.370)	0.520 (0.500–0.540)	0.650 (0.620–0.690)	8,162
	2009–2010	NC	<LOD	<LOD	0.390 (0.360–0.430)	0.510 (0.480–0.570)	8,733
Age group							
1–5 years	2003–2004	NC	<LOD	<LOD	<LOD	0.500 (<LOD–0.600)	792
	2005–2006	NC	<LOD	<LOD	0.430 (<LOD–0.470)	0.510 (0.430–0.670)	948
	2007–2008	NC	<LOD	<LOD	0.350 (<LOD–0.450)	0.500 (0.410–0.550)	726
	2009–2010	NC	<LOD	<LOD	<LOD	0.360 (<LOD–0.460)	789
6–11 years	2003–2004	NC	<LOD	<LOD	<LOD	0.600 (0.500–0.600)	842
	2005–2006	NC	<LOD	<LOD	0.450 (<LOD–0.520)	0.560 (0.470–0.640)	932
	2007–2008	NC	<LOD	<LOD	0.380 (0.350–0.410)	0.470 (0.420–0.520)	1,010
	2009–2010	NC	<LOD	<LOD	<LOD	0.380 (0.350–0.440)	1,006
12–19 years	2003–2004	NC	<LOD	<LOD	0.500 (<LOD–0.500)	0.600 (0.500–0.600)	2,060
	2005–2006	NC	<LOD	<LOD	0.430 (0.410–0.460)	0.540 (0.480–0.590)	1,984
	2007–2008	NC	<LOD	<LOD	0.370 (<LOD–0.400)	0.480 (0.410–0.530)	1,069
	2009–2010	NC	<LOD	<LOD	<LOD	0.420 (0.350–0.500)	1,184
≥20 years	2003–2004	NC	<LOD	<LOD	0.600 (0.500–0.600)	0.700 (0.700–0.800)	4,453
	2005–2006	NC	<LOD	<LOD	0.570 (0.530–0.610)	0.690 (0.650–0.750)	4,507
	2007–2008	NC	<LOD	0.380 (0.360–0.390)	0.550 (0.530–0.570)	0.700 (0.660–0.730)	5,357
	2009–2010	NC	<LOD	<LOD	0.420 (0.390–0.450)	0.540 (0.490–0.600)	5,754
Gender							
Males	2003–2004	NC	<LOD	<LOD	0.500 (0.500–0.600)	0.600 (0.600–0.700)	4,015
	2005–2006	NC	<LOD	<LOD	0.480 (0.450–0.520)	0.600 (0.550–0.640)	4,076
	2007–2008	NC	<LOD	<LOD	0.500 (0.470–0.520)	0.600 (0.570–0.650)	4,093
	2009–2010	NC	<LOD	<LOD	0.370 (<LOD–0.420)	0.500 (0.440–0.560)	4,336
Females	2003–2004	NC	<LOD	<LOD	0.600 (0.500–0.600)	0.700 (0.700–0.800)	4,132
	2005–2006	NC	<LOD	<LOD	0.580 (0.550–0.640)	0.700 (0.670–0.780)	4,295
	2007–2008	NC	<LOD	0.380 (0.360–0.390)	0.550 (0.520–0.570)	0.700 (0.670–0.740)	4,069
	2009–2010	NC	<LOD	<LOD	0.410 (0.380–0.440)	0.530 (0.490–0.600)	4,397

Table 5-25. Geometric Mean and Selected Percentiles of Inorganic Mercury Blood Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2010

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a] 50th	75th	90th	95th	Sample size
Race/ethnicity							
Mexican Americans	2003–2004	NC	<LOD	<LOD	0.500 (0.500–0.600)	0.700 (0.600–0.800)	2,007
	2005–2006	NC	<LOD	<LOD	0.530 (0.470–0.580)	0.670 (0.560–0.830)	2,224
	2007–2008	NC	<LOD	<LOD	0.430 (0.400–0.480)	0.560 (0.520–0.610)	1,685
	2009–2010	NC	<LOD	<LOD	<LOD	0.470 (0.390–0.530)	1,947
Non-Hispanic blacks	2003–2004	NC	<LOD	<LOD	0.600 (0.500–0.600)	0.700 (0.600–0.800)	2,240
	2005–2006	NC	<LOD	<LOD	0.530 (0.470–0.600)	0.670 (0.600–0.760)	2,183
	2007–2008	NC	<LOD	<LOD	0.490 (0.450–0.530)	0.610 (0.560–0.650)	1,729
	2009–2010	NC	<LOD	<LOD	0.370 (0.350–0.390)	0.480 (0.410–0.530)	1,580
Non-Hispanic whites	2003–2004	NC	<LOD	<LOD	0.600 (0.500–0.600)	0.700 (0.600–0.700)	3,406
	2005–2006	NC	<LOD	<LOD	0.540 (0.500–0.580)	0.650 (0.610–0.710)	3,298
	2007–2008	NC	<LOD	0.360 (<LOD–0.390)	0.530 (0.500–0.550)	0.660 (0.620–0.700)	3,421
	2009–2010	NC	<LOD	<LOD	0.410 (0.370–0.450)	0.520 (0.480–0.590)	3,739

[a]The limit of detection for survey years 2003–2004, 2005–2006, 2007–2008, and 2009–2010 were 0.42, 0.4, 0.35, and 0.35 µg/L, respectively.

CI = confidence interval; LOD = limit of detection; NC = not calculated (proportion of results below limit of detection was too high to provide a valid result)

Source: CDC 2019

Table 5-26. Geometric Mean and Selected Percentiles of Inorganic Mercury Blood Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2011–2016

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a]				Sample size
			50th	75th	90th	95th	
Total	2011–2012	NC	<LOD	<LOD	0.440 (0.390–0.480)	0.600 (0.520–0.680)	7,841
	2013–2014	NC	<LOD	<LOD	0.410 (0.380–0.440)	0.530 (0.490–0.570)	5,175
	2015–2016	NC	<LOD	<LOD	0.350 (0.300–0.400)	0.480 (0.430–0.530)	4,938
Age group							
1–5 years	2011–2012	NC	<LOD	<LOD	<LOD	0.280 (<LOD–0.360)	657
	2013–2014	NC	<LOD	<LOD	<LOD	<LOD	779
	2015–2016	NC	<LOD	<LOD	<LOD	0.270 (<LOD–0.340)	749
6–11 years	2011–2012	NC	<LOD	<LOD	0.280 (<LOD–0.320)	0.360 (0.290–0.450)	1,044
	2013–2014	NC	<LOD	<LOD	<LOD	0.340 (<LOD–0.420)	1,074
	2015–2016	NC	<LOD	<LOD	<LOD	0.330 (<LOD–0.450)	1,022
12–19 years	2011–2012	NC	<LOD	<LOD	0.280 (<LOD–0.350)	0.400 (0.300–0.540)	1,121
	2013–2014	NC	<LOD	<LOD	<LOD	0.360 (0.290–0.420)	627
	2015–2016	NC	<LOD	<LOD	<LOD	0.400 (<LOD–0.510)	565
≥20 years	2011–2012	NC	<LOD	0.290 (0.270–0.310)	0.470 (0.420–0.530)	0.630 (0.550–0.760)	5,019
	2013–2014	NC	<LOD	0.270 (<LOD–0.300)	0.440 (0.410–0.470)	0.560 (0.510–0.660)	2,695
	2015–2016	NC	<LOD	<LOD	0.380 (0.330–0.430)	0.500 (0.450–0.560)	2,602
Gender							
Males	2011–2012	NC	<LOD	<LOD	0.420 (0.370–0.480)	0.600 (0.490–0.680)	3,925
	2013–2014	NC	<LOD	<LOD	0.400 (0.340–0.430)	0.510 (0.450–0.560)	2,570
	2015–2016	NC	<LOD	<LOD	0.330 (0.280–0.400)	0.430 (0.400–0.490)	2,460
Females	2011–2012	NC	<LOD	0.280 (<LOD–0.300)	0.450 (0.390–0.490)	0.610 (0.520–0.700)	3,916
	2013–2014	NC	<LOD	<LOD	0.420 (0.390–0.450)	0.550 (0.510–0.590)	2,605
	2015–2016	NC	<LOD	<LOD	0.370 (0.320–0.450)	0.530 (0.450–0.620)	2,478
Race/ethnicity							
Mexican Americans	2011–2012	NC	<LOD	<LOD	0.390 (0.330–0.460)	0.580 (0.460–0.710)	1,058
	2013–2014	NC	<LOD	<LOD	0.380 (0.330–0.410)	0.540 (0.420–0.640)	958
	2015–2016	NC	<LOD	<LOD	0.420 (0.290–0.600)	0.560 (0.430–0.820)	988
Non-Hispanic blacks	2011–2012	NC	<LOD	<LOD	0.410 (0.370–0.470)	0.570 (0.480–0.670)	2,170
	2013–2014	NC	<LOD	<LOD	0.380 (0.330–0.430)	0.530 (0.440–0.630)	1,110
	2015–2016	NC	<LOD	<LOD	0.330 (0.270–0.380)	0.430 (0.370–0.490)	1,058

Table 5-26. Geometric Mean and Selected Percentiles of Inorganic Mercury Blood Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2011–2016

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a]				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2011–2012	NC	<LOD	0.270 (<LOD–0.300)	0.430 (0.370–0.490)	0.590 (0.480–0.690)	2,477
	2013–2014	NC	<LOD	<LOD	0.420 (0.360–0.450)	0.510 (0.460–0.570)	1,835
	2015–2016	NC	<LOD	<LOD	0.320 (0.280–0.400)	0.460 (0.400–0.540)	1,500
All Hispanics	2011–2012	NC	<LOD	<LOD	0.430 (0.370–0.490)	0.630 (0.540–0.760)	1,902
	2013–2014	NC	<LOD	<LOD	0.380 (0.330–0.410)	0.540 (0.440–0.650)	1,467
	2015–2016	NC	<LOD	<LOD	0.380 (0.300–0.490)	0.510 (0.430–0.650)	1,648
Asians	2011–2012	NC	<LOD	0.350 (0.310–0.390)	0.550 (0.500–0.590)	0.700 (0.630–0.760)	997
	2013–2014	NC	<LOD	0.330 (0.270–0.390)	0.570 (0.420–0.680)	0.750 (0.580–1.10)	508
	2015–2016	NC	<LOD	<LOD	0.430 (0.360–0.540)	0.600 (0.470–0.730)	473

[a]The limit of detection for survey years 2011–2012, 2013–2014, and 2015–2016 were 0.27, 0.27, and 0.27 µg/L, respectively.

CI = confidence interval; LOD = limit of detection; NC = not calculated (proportion of results below limit of detection was too high to provide a valid result)

Source: CDC 2019

Table 5-27. Geometric Mean and Selected Percentiles of Ethyl Mercury Blood Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2011–2016

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a]				Sample size
			50th	75th	90th	95th	
Total	2011–2012	NC	<LOD	<LOD	<LOD	<LOD	7,841
	2013–2014	NC	<LOD	<LOD	<LOD	<LOD	5,175
	2015–2016	NC	<LOD	<LOD	<LOD	<LOD	4,936
Age group							
1–5 years	2011–2012	NC	<LOD	<LOD	<LOD	<LOD	657
	2013–2014	NC	<LOD	<LOD	<LOD	<LOD	779
	2015–2016	NC	<LOD	<LOD	<LOD	<LOD	749
6–11 years	2011–2012	NC	<LOD	<LOD	<LOD	<LOD	1,044
	2013–2014	NC	<LOD	<LOD	<LOD	<LOD	1,074
	2015–2016	NC	<LOD	<LOD	<LOD	<LOD	1,022
12–19 years	2011–2012	NC	<LOD	<LOD	<LOD	<LOD	1,121
	2013–2014	NC	<LOD	<LOD	<LOD	<LOD	627
	2015–2016	NC	<LOD	<LOD	<LOD	<LOD	565
≥20 years	2011–2012	NC	<LOD	<LOD	<LOD	<LOD	5,019
	2013–2014	NC	<LOD	<LOD	<LOD	<LOD	2,695
	2015–2016	NC	<LOD	<LOD	<LOD	<LOD	2,600
Gender							
Males	2011–2012	NC	<LOD	<LOD	<LOD	<LOD	3,925
	2013–2014	NC	<LOD	<LOD	<LOD	<LOD	2,570
	2015–2016	NC	<LOD	<LOD	<LOD	<LOD	2,458
Females	2011–2012	NC	<LOD	<LOD	<LOD	<LOD	3,916
	2013–2014	NC	<LOD	<LOD	<LOD	<LOD	2,605
	2015–2016	NC	<LOD	<LOD	<LOD	<LOD	2,478
Race/ethnicity							
Mexican Americans	2011–2012	NC	<LOD	<LOD	<LOD	<LOD	1,058
	2013–2014	NC	<LOD	<LOD	<LOD	<LOD	958
	2015–2016	NC	<LOD	<LOD	<LOD	<LOD	988
Non-Hispanic blacks	2011–2012	NC	<LOD	<LOD	<LOD	<LOD	2,170
	2013–2014	NC	<LOD	<LOD	<LOD	<LOD	1,110
	2015–2016	NC	<LOD	<LOD	<LOD	<LOD	1,057

Table 5-27. Geometric Mean and Selected Percentiles of Ethyl Mercury Blood Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2011–2016

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a]				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2011–2012	NC	<LOD	<LOD	<LOD	<LOD	2,477
	2013–2014	NC	<LOD	<LOD	<LOD	<LOD	1,835
	2015–2016	NC	<LOD	<LOD	<LOD	<LOD	1,500
All Hispanics	2011–2012	NC	<LOD	<LOD	<LOD	<LOD	1,902
	2013–2014	NC	<LOD	<LOD	<LOD	<LOD	1,467
	2015–2016	NC	<LOD	<LOD	<LOD	<LOD	1,647
Asians	2011–2012	NC	<LOD	<LOD	<LOD	0.160 (<LOD–0.280)	997
	2013–2014	NC	<LOD	<LOD	<LOD	<LOD	508
	2015–2016	NC	<LOD	<LOD	<LOD	<LOD	473

[a]The limit of detection for survey years 2011–2012, 2013–2014, and 2015–2016 were 0.16, 0.16, and 0.16 µg/L, respectively.
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CI = confidence interval; LOD = limit of detection; NC = not calculated (proportion of results below limit of detection was too high to provide a valid result)

Source: CDC 2019

Table 5-28. Geometric Mean and Selected Percentiles of Methylmercury Blood Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2011–2016

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a] 50th	75th	90th	95th	Sample size
Total	2011–2012	0.498 (0.423–0.587)	0.480 (0.400–0.570)	1.25 (0.950–1.61)	2.81 (2.29–3.55)	4.43 (3.46–5.49)	7,841
	2013–2014	0.434 (0.381–0.495)	0.420 (0.340–0.510)	1.09 (0.940–1.27)	2.62 (2.18–3.04)	4.28 (3.74–4.93)	5,175
	2015–2016	0.413 (0.361–0.472)	0.380 (0.320–0.490)	1.02 (0.860–1.22)	2.30 (1.92–2.78)	3.92 (3.35–4.81)	4,938
Age group							
1–5 years	2011–2012	NC	0.140 (0.120–0.170)	0.270 (0.220–0.350)	0.540 (0.420–0.780)	0.970 (0.590–1.14)	657
	2013–2014	NC	<LOD	0.260 (0.230–0.310)	0.660 (0.550–0.810)	1.11 (0.960–1.48)	779
	2015–2016	NC	<LOD	0.200 (0.170–0.240)	0.470 (0.350–0.630)	0.830 (0.590–1.21)	749
6–11 years	2011–2012	0.209 (0.182–0.241)	0.180 (0.150–0.220)	0.400 (0.330–0.490)	0.820 (0.630–1.06)	1.34 (0.940–1.84)	1,044
	2013–2014	NC	0.150 (<LOD–0.200)	0.380 (0.280–0.530)	0.960 (0.700–1.26)	1.58 (1.26–2.11)	1,074
	2015–2016	NC	0.140 (<LOD–0.180)	0.290 (0.260–0.340)	0.730 (0.530–0.950)	1.11 (0.870–1.91)	1,022
12–19 years	2011–2012	0.276 (0.237–0.322)	0.270 (0.210–0.310)	0.570 (0.460–0.670)	1.27 (0.870–1.67)	2.15 (1.40–2.81)	1121
	2013–2014	0.233 (0.202–0.269)	0.190 (0.140–0.260)	0.480 (0.380–0.560)	1.02 (0.730–1.60)	1.84 (1.20–2.57)	627
	2015–2016	0.212 (0.180–0.249)	0.160 (0.120–0.220)	0.420 (0.310–0.620)	0.800 (0.690–1.23)	1.81 (0.800–3.14)	565
≥20 years	2011–2012	0.624 (0.523–0.746)	0.610 (0.500–0.760)	1.53 (1.18–2.00)	3.28 (2.56–4.31)	4.97 (3.91–6.89)	5,019
	2013–2014	0.541 (0.473–0.618)	0.540 (0.450–0.630)	1.32 (1.17–1.54)	3.05 (2.64–3.60)	4.92 (4.34–5.41)	2,695
	2015–2016	0.518 (0.456–0.588)	0.530 (0.420–0.630)	1.23 (1.05–1.46)	2.59 (2.25–3.36)	4.42 (3.66–5.58)	2,602
Gender							
Males	2011–2012	0.509 (0.433–0.598)	0.490 (0.400–0.590)	1.30 (0.990–1.62)	2.84 (2.29–3.68)	4.77 (3.44–6.74)	3,925
	2013–2014	0.448 (0.390–0.515)	0.430 (0.350–0.530)	1.10 (0.940–1.37)	2.67 (2.22–3.33)	4.44 (3.88–5.40)	2,570
	2015–2016	0.429 (0.379–0.486)	0.400 (0.330–0.520)	1.11 (0.900–1.33)	2.24 (1.85–2.86)	4.42 (3.60–5.05)	2,460
Females	2011–2012	0.489 (0.413–0.580)	0.470 (0.380–0.560)	1.19 (0.900–1.61)	2.72 (2.18–3.46)	3.99 (3.28–4.99)	3,916
	2013–2014	0.422 (0.367–0.485)	0.400 (0.330–0.490)	1.08 (0.900–1.22)	2.46 (2.03–2.92)	3.91 (3.32–4.93)	2,605
	2015–2016	0.399 (0.338–0.470)	0.370 (0.300–0.470)	0.950 (0.760–1.18)	2.36 (1.91–2.81)	3.58 (2.92–4.24)	2,478
Race/ethnicity							
Mexican Americans	2011–2012	0.320 (0.264–0.387)	0.330 (0.260–0.410)	0.610 (0.500–0.770)	1.23 (0.920–1.40)	1.66 (1.33–2.06)	1,058
	2013–2014	0.276 (0.239–0.318)	0.260 (0.210–0.310)	0.540 (0.440–0.650)	1.06 (0.770–1.43)	1.72 (1.27–2.34)	958
	2015–2016	0.292 (0.276–0.309)	0.290 (0.260–0.330)	0.610 (0.550–0.690)	1.13 (0.870–1.47)	1.54 (1.34–2.02)	988
Non-Hispanic blacks	2011–2012	0.517 (0.392–0.681)	0.510 (0.380–0.660)	1.13 (0.750–1.61)	2.37 (1.66–3.08)	3.63 (2.57–5.16)	2,170
	2013–2014	0.481 (0.407–0.569)	0.460 (0.370–0.580)	1.03 (0.900–1.22)	2.08 (1.55–2.72)	3.33 (2.15–5.12)	1,110
	2015–2016	0.461 (0.376–0.565)	0.430 (0.330–0.580)	1.05 (0.830–1.25)	2.34 (1.71–3.31)	4.08 (2.80–5.58)	1,058

Table 5-28. Geometric Mean and Selected Percentiles of Methylmercury Blood Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2011–2016

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a]				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2011–2012	0.478 (0.392–0.583)	0.470 (0.360–0.580)	1.25 (0.870–1.69)	2.76 (2.06–3.69)	4.24 (2.92–6.38)	2,477
	2013–2014	0.420 (0.357–0.495)	0.420 (0.310–0.530)	1.10 (0.910–1.32)	2.62 (2.07–3.12)	4.01 (3.46–5.00)	1,835
	2015–2016	0.380 (0.319–0.451)	0.350 (0.270–0.490)	0.960 (0.750–1.22)	2.04 (1.55–2.51)	3.50 (2.32–4.49)	1,500
All Hispanics	2011–2012	0.429 (0.350–0.525)	0.420 (0.340–0.520)	0.890 (0.700–1.17)	1.81 (1.39–2.46)	2.94 (2.19–3.71)	1,902
	2013–2014	0.326 (0.278–0.382)	0.310 (0.250–0.350)	0.680 (0.580–0.790)	1.50 (1.15–1.89)	2.34 (1.79–3.00)	1,467
	2015–2016	0.353 (0.305–0.409)	0.350 (0.300–0.390)	0.760 (0.630–0.930)	1.53 (1.14–1.98)	2.26 (1.60–3.03)	1,648
Asians	2011–2012	1.58 (1.29–1.94)	2.16 (1.68–2.55)	4.35 (3.64–5.13)	7.57 (6.21–8.61)	10.5 (8.48–12.5)	997
	2013–2014	1.42 (1.16–1.74)	1.71 (1.17–2.07)	3.90 (3.31–4.54)	7.93 (6.42–9.21)	10.8 (9.57–13.6)	508
	2015–2016	1.37 (1.08–1.73)	1.85 (1.18–2.51)	3.80 (3.11–4.83)	7.52 (5.60–9.63)	11.0 (8.65–12.4)	473

[a]The limit of detection for survey years 2011–2012, 2013–2014, and 2015–2016 were 0.12, 0.12, and 0.12 µg/L, respectively.

CI = confidence interval; LOD = limit of detection; NC = not calculated (proportion of results below limit of detection was too high to provide a valid result)

Source: CDC 2019

Table 5-29. Geometric Mean and Selected Percentiles of Total Mercury Urinary Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2010

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a]				Sample size
			50th	75th	90th	95th	
Total	2003–2004	0.447 (0.406–0.492)	0.420 (0.360–0.480)	1.00 (0.870–1.14)	2.08 (1.78–2.42)	3.19 (2.76–3.55)	2,538
	2005–2006	0.468 (0.426–0.514)	0.460 (0.410–0.510)	1.03 (0.900–1.12)	2.11 (1.88–2.36)	2.94 (2.58–3.26)	2,578
	2007–2008	0.443 (0.408–0.482)	0.440 (0.400–0.470)	0.880 (0.760–1.00)	1.74 (1.62–1.96)	2.66 (2.29–3.08)	2,634
	2009–2010	NC	0.400 (0.360–0.450)	0.850 (0.770–0.910)	1.53 (1.30–1.81)	2.42 (2.07–2.72)	2,865
Age group							
6–11 years	2003–2004	0.254 (0.213–0.304)	0.200 (0.160–0.250)	0.440 (0.330–0.580)	1.16 (0.610–1.61)	1.96 (1.13–2.97)	287
	2005–2006	0.333 (0.267–0.416)	0.320 (0.250–0.390)	0.650 (0.470–0.840)	1.32 (0.930–1.88)	2.18 (1.28–3.40)	355
	2007–2008	0.301 (0.260–0.347)	0.290 (0.230–0.340)	0.520 (0.430–0.620)	1.03 (0.770–1.23)	1.87 (1.03–3.48)	398
	2009–2010	NC	0.260 (0.220–0.320)	0.510 (0.430–0.620)	1.03 (0.730–1.31)	1.58 (1.18–1.88)	379
12–19 years	2003–2004	0.358 (0.313–0.408)	0.330 (0.290–0.370)	0.700 (0.530–0.840)	1.60 (1.14–2.52)	2.93 (1.88–3.66)	722
	2005–2006	0.372 (0.286–0.486)	0.350 (0.270–0.470)	0.740 (0.580–0.920)	1.61 (0.970–2.81)	2.59 (1.40–4.45)	703
	2007–2008	0.364 (0.326–0.406)	0.380 (0.320–0.450)	0.590 (0.550–0.650)	1.24 (0.830–1.71)	1.82 (1.41–2.29)	375
	2009–2010	NC	0.290 (0.230–0.360)	0.530 (0.470–0.630)	1.09 (0.890–1.31)	1.73 (1.28–2.31)	455
≥20 years	2003–2004	0.495 (0.442–0.555)	0.480 (0.410–0.570)	1.12 (0.930–1.29)	2.20 (1.85–2.65)	3.33 (2.76–3.88)	1,529
	2005–2006	0.505 (0.468–0.545)	0.510 (0.460–0.560)	1.11 (1.04–1.16)	2.23 (1.97–2.50)	3.11 (2.64–3.37)	1,520
	2007–2008	0.477 (0.435–0.523)	0.470 (0.430–0.520)	0.970 (0.850–1.10)	1.89 (1.69–2.20)	2.82 (2.33–3.56)	1,861
	2009–2010	NC	0.450 (0.390–0.510)	0.890 (0.810–1.00)	1.66 (1.40–2.01)	2.53 (2.21–2.84)	2,031
Gender							
Males	2003–2004	0.433 (0.405–0.463)	0.400 (0.350–0.460)	0.940 (0.840–1.05)	1.88 (1.63–2.18)	2.68 (2.34–3.05)	1,266
	2005–2006	0.464 (0.411–0.523)	0.450 (0.400–0.520)	0.980 (0.860–1.11)	2.03 (1.57–2.48)	3.00 (2.48–3.37)	1,270
	2007–2008	0.457 (0.417–0.501)	0.460 (0.400–0.520)	0.880 (0.780–1.01)	1.68 (1.53–1.77)	2.40 (2.11–2.76)	1,326
	2009–2010	NC	0.410 (0.340–0.480)	0.860 (0.750–0.950)	1.46 (1.29–1.66)	2.21 (1.93–2.53)	1,404
Females	2003–2004	0.460 (0.396–0.534)	0.430 (0.330–0.530)	1.07 (0.870–1.28)	2.26 (1.77–2.90)	3.54 (2.76–4.31)	1,272
	2005–2006	0.472 (0.424–0.525)	0.470 (0.390–0.550)	1.07 (0.900–1.19)	2.14 (1.84–2.50)	2.89 (2.60–3.38)	1,308
	2007–2008	0.431 (0.388–0.478)	0.430 (0.380–0.460)	0.870 (0.710–1.05)	1.88 (1.55–2.38)	2.92 (2.27–4.17)	1,308
	2009–2010	NC	0.390 (0.360–0.450)	0.840 (0.730–0.940)	1.61 (1.29–2.03)	2.61 (2.16–3.12)	1,461
Race/ethnicity							
Mexican Americans	2003–2004	0.416 (0.340–0.509)	0.360 (0.280–0.430)	0.960 (0.700–1.23)	2.19 (1.39–3.24)	3.16 (1.99–6.30)	619
	2005–2006	0.451 (0.369–0.551)	0.420 (0.310–0.560)	1.01 (0.780–1.25)	2.22 (1.48–2.64)	3.00 (2.27–4.01)	651
	2007–2008	0.409 (0.349–0.480)	0.370 (0.330–0.450)	0.780 (0.700–0.950)	1.82 (1.26–1.97)	2.55 (1.87–3.08)	514
	2009–2010	NC	0.350 (0.280–0.430)	0.670 (0.520–0.890)	1.53 (1.06–1.84)	2.29 (1.81–2.76)	615

Table 5-29. Geometric Mean and Selected Percentiles of Total Mercury Urinary Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2010

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a]				Sample size
			50th	75th	90th	95th	
Non-Hispanic blacks	2003–2004	0.476 (0.413–0.549)	0.430 (0.360–0.530)	0.890 (0.770–1.00)	1.96 (1.60–2.31)	3.09 (2.03–4.89)	713
	2005–2006	0.453 (0.384–0.533)	0.450 (0.380–0.550)	0.890 (0.710–1.13)	1.78 (1.34–2.29)	2.57 (2.21–3.15)	691
	2007–2008	0.478 (0.411–0.556)	0.460 (0.380–0.540)	0.910 (0.770–1.06)	1.85 (1.42–2.41)	2.76 (1.97–4.19)	589
	2009–2010	NC	0.410 (0.340–0.490)	0.840 (0.650–1.08)	1.66 (1.34–1.95)	2.64 (1.88–3.30)	546
Non-Hispanic whites	2003–2004	0.441 (0.382–0.509)	0.420 (0.330–0.520)	1.01 (0.840–1.23)	2.08 (1.67–2.46)	3.24 (2.67–3.60)	1,066
	2005–2006	0.459 (0.409–0.513)	0.440 (0.400–0.510)	1.00 (0.860–1.12)	2.07 (1.77–2.40)	2.81 (2.47–3.37)	1,044
	2007–2008	0.431 (0.378–0.493)	0.430 (0.380–0.480)	0.880 (0.700–1.07)	1.71 (1.50–2.18)	2.70 (2.18–3.59)	1,100
	2009–2010	NC	0.390 (0.330–0.470)	0.850 (0.750–0.950)	1.52 (1.26–2.01)	2.42 (1.93–2.85)	1,225

[a]The limit of detection for survey years 2003–2004, 2005–2006, 2007–2008, and 2009–2010 were 0.14, 0.11, 0.08, and 0.08 µg/L, respectively.

CI = confidence interval; LOD = limit of detection; NC = not calculated (proportion of results below limit of detection was too high to provide a valid result)

Source: CDC 2019

Table 5-30. Geometric Mean and Selected Percentiles of Total Mercury Urinary Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2011–2016

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a]				Sample size
			50th	75th	90th	95th	
Total	2011–2012	0.324 (0.285–0.368)	0.320 (0.280–0.370)	0.660 (0.580–0.770)	1.37 (1.15–1.59)	1.83 (1.62–2.14)	2,507
	2013–2014	0.246 (0.221–0.273)	0.200 (0.170–0.240)	0.470 (0.400–0.570)	1.07 (0.900–1.22)	1.64 (1.35–1.96)	2,666
	2015–2016	NC	<LOD	0.280 (0.250–0.320)	0.680 (0.570–0.780)	1.18 (0.920–1.29)	3,080
Age group							
3–5 years	2015–2016	NC	<LOD	<LOD	0.160 (<LOD–0.240)	0.280 (0.190–0.510)	496
6–11 years	2011–2012	0.241 (0.206–0.283)	0.220 (0.190–0.270)	0.450 (0.390–0.530)	0.930 (0.680–1.36)	1.37 (0.990–2.03)	401
	2013–2014	NC	<LOD	0.220 (0.150–0.310)	0.560 (0.340–0.840)	0.890 (0.640–1.10)	401
	2015–2016	NC	<LOD	<LOD	0.300 (0.200–0.380)	0.520 (0.360–0.700)	380
12–19 years	2011–2012	0.257 (0.212–0.312)	0.270 (0.220–0.340)	0.490 (0.390–0.600)	0.840 (0.650–1.24)	1.31 (0.920–1.75)	390
	2013–2014	NC	<LOD	0.240 (0.200–0.310)	0.560 (0.400–0.860)	1.02 (0.610–1.81)	452
	2015–2016	NC	<LOD	0.130 (<LOD–0.160)	0.350 (0.200–0.470)	0.610 (0.380–1.14)	402
≥20 years	2011–2012	0.346 (0.303–0.396)	0.340 (0.290–0.400)	0.720 (0.620–0.850)	1.49 (1.20–1.67)	1.93 (1.67–2.29)	1,716
	2013–2014	0.274 (0.246–0.305)	0.240 (0.200–0.280)	0.540 (0.450–0.630)	1.16 (1.00–1.33)	1.76 (1.44–2.04)	1,813
	2015–2016	NC	0.140 (0.130–0.150)	0.340 (0.310–0.380)	0.740 (0.650–0.890)	1.22 (0.970–1.43)	1,802
Gender							
Males	2011–2012	0.342 (0.293–0.399)	0.330 (0.290–0.380)	0.670 (0.580–0.810)	1.34 (1.03–1.67)	1.91 (1.54–2.51)	1,260
	2013–2014	0.243 (0.219–0.268)	0.200 (0.170–0.220)	0.480 (0.390–0.600)	1.07 (0.840–1.33)	1.55 (1.28–1.96)	1,319
	2015–2016	NC	<LOD	0.280 (0.230–0.330)	0.620 (0.540–0.710)	0.900 (0.760–1.18)	1,533
Females	2011–2012	0.307 (0.262–0.360)	0.300 (0.250–0.360)	0.660 (0.540–0.770)	1.37 (1.17–1.54)	1.82 (1.54–2.14)	1,247
	2013–2014	0.249 (0.218–0.284)	0.210 (0.170–0.260)	0.470 (0.390–0.570)	1.07 (0.820–1.27)	1.75 (1.25–2.26)	1,347
	2015–2016	NC	<LOD	0.290 (0.250–0.350)	0.730 (0.570–0.980)	1.27 (0.940–1.88)	1,547
Race/ethnicity							
Mexican Americans	2011–2012	0.301 (0.261–0.348)	0.300 (0.200–0.400)	0.620 (0.510–0.680)	1.25 (0.910–1.53)	1.75 (1.32–2.25)	317
	2013–2014	0.229 (0.198–0.265)	0.160 (0.150–0.210)	0.450 (0.300–0.620)	1.12 (0.780–1.35)	1.47 (0.970–2.38)	454
	2015–2016	NC	<LOD	0.230 (0.170–0.280)	0.530 (0.440–0.640)	0.900 (0.650–1.22)	586
Non-Hispanic blacks	2011–2012	0.360 (0.316–0.410)	0.360 (0.320–0.400)	0.670 (0.570–0.800)	1.33 (1.06–1.60)	1.99 (1.48–3.06)	671
	2013–2014	0.279 (0.228–0.340)	0.250 (0.190–0.320)	0.530 (0.400–0.690)	1.10 (0.900–1.49)	1.82 (1.11–2.48)	580
	2015–2016	NC	0.140 (<LOD–0.180)	0.370 (0.270–0.510)	0.800 (0.620–1.19)	1.38 (0.870–1.72)	676

Table 5-30. Geometric Mean and Selected Percentiles of Total Mercury Urinary Concentrations (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2011–2016

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a]				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2011–2012	0.308 (0.260–0.365)	0.290 (0.260–0.360)	0.630 (0.510–0.810)	1.37 (1.09–1.64)	1.77 (1.49–2.14)	819
	2013–2014	0.240 (0.211–0.271)	0.200 (0.160–0.230)	0.460 (0.370–0.580)	1.06 (0.840–1.24)	1.64 (1.24–2.04)	988
	2015–2016	NC	<LOD	0.260 (0.210–0.330)	0.700 (0.480–0.870)	1.18 (0.860–1.40)	932
All Hispanics	2011–2012	0.330 (0.299–0.364)	0.330 (0.270–0.390)	0.680 (0.610–0.760)	1.30 (1.15–1.53)	1.98 (1.61–2.42)	574
	2013–2014	0.239 (0.207–0.276)	0.180 (0.150–0.240)	0.460 (0.360–0.620)	1.14 (0.800–1.35)	1.57 (1.24–2.15)	702
	2015–2016	NC	<LOD	0.260 (0.210–0.330)	0.600 (0.470–0.740)	1.03 (0.730–1.37)	986
Asians	2011–2012	0.430 (0.351–0.527)	0.450 (0.330–0.580)	0.910 (0.750–1.12)	1.69 (1.31–2.06)	2.41 (1.77–3.53)	355
	2013–2014	0.313 (0.269–0.363)	0.270 (0.220–0.340)	0.620 (0.520–0.710)	1.18 (0.890–1.66)	1.78 (1.20–3.10)	291
	2015–2016	NC	0.180 (<LOD–0.250)	0.390 (0.330–0.510)	0.720 (0.610–0.820)	0.960 (0.790–1.49)	333

[a]The limit of detection for survey years 2011–2012, 2013–2014, and 2015–2016 were 0.05, 0.13, and 0.13 µg/L, respectively.

CI = confidence interval; LOD = limit of detection; NC = not calculated (proportion of results below limit of detection was too high to provide a valid result)

Source: CDC 2019

Table 5-31. Geometric Mean and Selected Percentiles of Total Mercury Creatinine Corrected Urinary Concentrations (µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2010

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a] 50th	75th	90th	95th	Sample size
Total	2003–2004	0.443 (0.404–0.486)	0.447 (0.392–0.498)	0.909 (0.785–1.00)	1.65 (1.40–1.86)	2.35 (1.88–2.85)	2,537
	2005–2006	0.460 (0.414–0.511)	0.450 (0.410–0.510)	0.870 (0.790–1.00)	1.63 (1.44–1.75)	2.26 (2.12–2.50)	2,578
	2007–2008	0.462 (0.425–0.502)	0.450 (0.400–0.490)	0.820 (0.750–0.960)	1.57 (1.38–1.73)	2.32 (2.00–2.89)	2,634
	2009–2010	NC	0.409 (0.367–0.459)	0.793 (0.691–0.893)	1.43 (1.24–1.67)	2.09 (1.79–2.39)	2,865
Age group							
6–11 years	2003–2004	0.297 (0.246–0.358)	0.276 (0.208–0.347)	0.485 (0.391–0.630)	1.25 (0.667–1.79)	1.79 (1.11–2.61)	286
	2005–2006	0.411 (0.323–0.524)	0.390 (0.290–0.500)	0.710 (0.510–0.960)	1.30 (0.990–2.12)	2.55 (1.38–3.50)	355
	2007–2008	0.393 (0.351–0.440)	0.350 (0.300–0.440)	0.630 (0.540–0.770)	1.15 (0.860–1.50)	1.68 (1.18–2.99)	398
	2009–2010	NC	0.357 (0.306–0.406)	0.632 (0.500–0.750)	1.04 (0.863–1.26)	1.62 (1.19–1.98)	379
12–19 years	2003–2004	0.255 (0.225–0.289)	0.217 (0.196–0.275)	0.464 (0.376–0.535)	1.06 (0.714–1.39)	1.67 (1.13–2.03)	722
	2005–2006	.286 (0.230–0.356)	0.260 (0.200–0.320)	0.500 (0.380–0.660)	1.09 (0.660–1.70)	1.76 (1.11–2.67)	703
	2007–2008	0.284 (0.251–0.320)	0.280 (0.230–0.300)	0.500 (0.400–0.550)	.890 (0.620–1.08)	1.18 (0.980–1.36)	375
	2009–2010	NC	0.226 (0.202–0.287)	0.481 (0.429–0.553)	.917 (0.736–1.18)	1.41 (1.12–1.62)	455
≥20 years	2003–2004	0.508 (0.455–0.566)	0.525 (0.447–0.616)	1.00 (0.875–1.09)	1.76 (1.46–2.11)	2.54 (2.04–3.00)	1,529
	2005–2006	0.503 (0.461–0.549)	0.510 (0.470–0.550)	0.940 (0.850–1.07)	1.69 (1.50–1.86)	2.31 (2.12–2.54)	1,520
	2007–2008	0.507 (0.463–0.555)	0.500 (0.450–0.550)	0.940 (0.810–1.02)	1.69 (1.51–2.01)	2.56 (2.09–3.17)	1,861
	2009–2010	NC	0.454 (0.395–0.517)	0.861 (0.731–0.988)	1.51 (1.29–1.85)	2.15 (1.88–2.57)	2,031
Gender							
Males	2003–2004	0.365 (0.333–0.400)	0.362 (0.309–0.417)	0.696 (0.620–0.784)	1.31 (1.18–1.44)	1.87 (1.51–2.30)	1,266
	2005–2006	0.380 (0.336–0.431)	0.390 (0.330–0.440)	0.740 (0.600–0.890)	1.27 (1.09–1.47)	1.73 (1.62–1.85)	1,270
	2007–2008	0.408 (0.374–0.445)	0.390 (0.350–0.450)	0.730 (0.650–0.810)	1.22 (1.11–1.36)	1.69 (1.54–2.11)	1,326
	2009–2010	NC	0.337 (0.298–0.391)	0.675 (0.585–0.802)	1.19 (1.06–1.29)	1.50 (1.33–1.78)	1,404
Females	2003–2004	0.532 (0.472–0.599)	0.545 (0.455–0.652)	1.06 (0.969–1.21)	1.88 (1.64–2.30)	2.77 (2.12–3.56)	1,271
	2005–2006	0.552 (0.494–0.617)	0.540 (0.490–0.620)	1.09 (0.850–1.27)	1.96 (1.72–2.14)	2.78 (2.35–3.17)	1,308
	2007–2008	0.520 (0.469–0.576)	0.490 (0.460–0.540)	0.960 (0.820–1.11)	1.92 (1.58–2.24)	2.83 (2.24–3.50)	1,308
	2009–2010	NC	0.475 (0.423–0.552)	0.890 (0.771–1.07)	1.81 (1.43–2.09)	2.57 (2.09–2.94)	1,461
Race/ethnicity							
Mexican Americans	2003–2004	0.384 (0.307–0.480)	0.365 (0.280–0.455)	0.768 (0.619–0.990)	1.62 (1.23–2.16)	2.32 (1.78–4.01)	618
	2005–2006	0.425 (0.337–0.536)	0.400 (0.310–0.490)	0.840 (0.560–1.29)	1.82 (1.30–2.47)	2.63 (2.22–3.20)	651
	2007–2008	0.409 (0.350–0.479)	0.380 (0.310–0.480)	0.790 (0.690–0.850)	1.55 (1.08–1.98)	2.03 (1.55–2.70)	514
	2009–2010	NC	0.333 (0.272–0.400)	0.660 (0.494–0.861)	1.29 (1.02–1.54)	1.95 (1.52–2.89)	615

Table 5-31. Geometric Mean and Selected Percentiles of Total Mercury Creatinine Corrected Urinary Concentrations (µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2003–2010

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a]				Sample size
			50th	75th	90th	95th	
Non-Hispanic blacks	2003–2004	0.343 (0.301–0.391)	0.306 (0.265–0.368)	0.587 (0.522–0.687)	1.28 (0.964–1.63)	2.13 (1.41–2.87)	713
	2005–2006	0.328 (0.285–0.378)	0.320 (0.270–0.370)	0.610 (0.470–0.780)	1.15 (0.930–1.40)	1.64 (1.29–1.96)	691
	2007–2008	0.350 (0.303–0.404)	0.330 (0.280–0.380)	0.590 (0.490–0.690)	1.10 (0.840–1.46)	1.85 (1.13–2.77)	589
	2009–2010	NC	0.317 (0.259–0.393)	0.582 (0.500–0.659)	1.05 (0.900–1.30)	1.55 (1.18–1.96)	546
Non-Hispanic whites	2003–2004	0.463 (0.400–0.537)	0.476 (0.385–0.588)	0.970 (0.800–1.07)	1.67 (1.32–2.11)	2.40 (1.88–2.90)	1,066
	2005–2006	0.475 (0.426–0.531)	0.490 (0.440–0.540)	0.890 (0.820–1.02)	1.61 (1.42–1.75)	2.23 (1.98–2.50)	1,044
	2007–2008	0.481 (0.423–0.546)	0.480 (0.390–0.540)	0.890 (0.750–1.03)	1.58 (1.34–2.02)	2.49 (1.89–3.18)	1,100
	2009–2010	NC	0.434 (0.370–0.500)	0.833 (0.689–1.04)	1.50 (1.26–1.87)	2.12 (1.80–2.64)	1,225

[a]The limit of detection was based on non-creatinine corrected urinary concentrations, which were 0.14, 0.11, 0.08, and 0.08 µg/L for survey years 2003–2004, 2005–2006, 2007-2008, and 2009–2010, respectively.

CI = confidence interval; NC = not calculated (proportion of results below limit of detection was too high to provide a valid result)

Source: CDC 2019

Table 5-32. Geometric Mean and Selected Percentiles of Total Mercury Creatinine Corrected Urinary Concentrations (µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2011–2016

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a]				Sample size
			50th	75th	90th	95th	
Total	2011–2012	0.367 (0.333–0.405)	0.353 (0.306–0.394)	0.676 (0.623–0.754)	1.33 (1.13–1.50)	1.75 (1.49–2.32)	2,505
	2013–2014	0.283 (0.260–0.309)	0.270 (0.250–0.290)	0.571 (0.511–0.644)	1.20 (1.05–1.36)	1.61 (1.47–1.81)	2,665
	2015–2016	NC	<LOD	0.356 (0.318–0.391)	0.708 (0.628–0.817)	1.10 (0.912–1.25)	3,077
Age group							
3–5 years	2015–2016	NC	<LOD	<LOD	0.667 (<LOD–0.818)	0.994 (0.818–1.13)	495
6–11 years	2011–2012	0.345 (0.298–0.398)	0.306 (0.276–0.344)	0.537 (0.441–0.613)	1.08 (0.884–1.43)	1.62 (1.07–2.34)	400
	2013–2014	NC	<LOD	0.429 (0.310–0.529)	0.750 (0.563–0.897)	1.11 (0.713–1.72)	401
	2015–2016	NC	<LOD	<LOD	0.474 (0.409–0.529)	0.643 (0.500–1.00)	380
12–19 years	2011–2012	0.246 (0.219–0.277)	0.221 (0.190–0.269)	0.405 (0.368–0.453)	0.735 (0.571–1.11)	1.21 (0.742–1.49)	390
	2013–2014	NC	<LOD	0.257 (0.200–0.281)	0.580 (0.391–0.735)	0.846 (0.580–1.07)	452
	2015–2016	NC	<LOD	0.194 (<LOD–0.220)	0.320 (0.246–0.568)	0.650 (0.385–0.967)	402
≥20 years	2011–2012	0.393 (0.351–0.439)	0.383 (0.330–0.437)	0.750 (0.673–0.805)	1.38 (1.17–1.63)	1.95 (1.50–2.48)	1,715
	2013–2014	0.318 (0.291–0.349)	0.304 (0.281–0.333)	0.644 (0.561–0.741)	1.32 (1.13–1.47)	1.76 (1.50–1.88)	1,812
	2015–2016	NC	0.198 (0.184–0.210)	0.391 (0.349–0.449)	0.776 (0.692–0.886)	1.15 (1.00–1.32)	1,800
Gender							
Males	2011–2012	0.320 (0.278–0.368)	0.294 (0.267–0.358)	0.558 (0.478–0.667)	1.11 (0.791–1.44)	1.57 (1.21–2.00)	1,259
	2013–2014	0.242 (0.223–0.263)	0.231 (0.206–0.259)	0.476 (0.429–0.542)	0.902 (0.779–1.11)	1.31 (1.13–1.49)	1,318
	2015–2016	NC	<LOD	0.274 (0.246–0.300)	0.563 (0.490–0.628)	0.818 (0.705–0.994)	1,533
Females	2011–2012	0.418 (0.374–0.466)	0.409 (0.355–0.453)	0.800 (0.706–0.900)	1.46 (1.29–1.65)	2.00 (1.63–2.60)	1,246
	2013–2014	0.330 (0.297–0.367)	0.315 (0.273–0.356)	0.692 (0.600–0.822)	1.44 (1.18–1.68)	1.83 (1.60–2.12)	1,347
	2015–2016	NC	<LOD	0.415 (0.375–0.473)	0.875 (0.750–1.00)	1.30 (1.06–1.86)	1,544
Race/ethnicity							
Mexican Americans	2011–2012	0.339 (0.288–0.399)	0.286 (0.225–0.393)	0.641 (0.433–0.789)	1.17 (1.00–1.42)	1.70 (1.31–2.24)	317
	2013–2014	0.261 (0.231–0.295)	0.237 (0.209–0.273)	0.516 (0.409–0.709)	1.04 (0.810–1.48)	1.62 (1.11–2.55)	454
	2015–2016	NC	<LOD	0.283 (0.236–0.360)	.692 (0.530–0.810)	1.04 (0.791–1.30)	585
Non-Hispanic blacks	2011–2012	0.280 (0.245–0.320)	0.261 (0.224–0.294)	0.467 (0.411–0.529)	.896 (0.638–1.14)	1.43 (1.10–1.57)	671
	2013–2014	0.211 (0.169–0.264)	0.202 (0.152–0.269)	0.409 (0.333–0.516)	.794 (0.643–1.10)	1.34 (0.880–1.52)	580
	2015–2016	NC	0.136 (<LOD–0.163)	0.303 (0.237–0.367)	.642 (0.450–0.848)	0.901 (0.695–1.18)	674

Table 5-32. Geometric Mean and Selected Percentiles of Total Mercury Creatinine Corrected Urinary Concentrations (µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2011–2016

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)[a]				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2011–2012	0.372 (0.323–0.428)	0.364 (0.294–0.433)	0.700 (0.619–0.805)	1.35 (1.05–1.63)	1.75 (1.41–2.48)	817
	2013–2014	0.295 (0.269–0.323)	0.278 (0.257–0.310)	0.602 (0.516–0.689)	1.27 (1.08–1.45)	1.64 (1.46–1.82)	987
	2015–2016	NC	<LOD	0.349 (0.300–0.400)	0.708 (0.563–0.886)	1.10 (0.827–1.32)	932
All Hispanics	2011–2012	0.369 (0.342–0.399)	0.331 (0.283–0.384)	0.674 (0.612–0.772)	1.24 (1.13–1.44)	1.86 (1.47–2.92)	574
	2013–2014	0.267 (0.237–0.300)	0.237 (0.214–0.273)	0.541 (0.448–0.634)	1.07 (0.837–1.36)	1.61 (1.24–1.86)	702
	2015–2016	NC	<LOD	0.348 (0.284–0.408)	0.717 (0.574–0.917)	1.15 (0.948–1.36)	985
Asians	2011–2012	0.577 (0.473–0.705)	0.562 (0.467–0.700)	1.16 (0.872–1.44)	1.82 (1.54–2.00)	2.29 (1.90–3.12)	355
	2013–2014	0.488 (0.422–0.565)	0.475 (0.373–0.600)	0.917 (0.779–1.06)	1.88 (1.35–2.19)	2.57 (1.88–4.24)	291
	2015–2016	NC	0.290 (<LOD–0.375)	0.594 (0.457–0.706)	1.02 (0.808–1.22)	1.38 (1.11–1.80)	333

[a]The limit of detection was based on non-creatinine corrected urinary concentrations, which were 0.05, 0.13, and 0.13 µg/L for survey years 2011–2012, 2013–2014, and 2015–2016, respectively.

CI = confidence interval; LOD = limit of detection; NC = not calculated (proportion of results below limit of detection was too high to provide a valid result)

Source: CDC 2019

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of mercury is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to ensure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) from exposure to mercury.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to mercury that are discussed in Chapter 2 are summarized in Figure 6-1 for elemental mercury, Figure 6-2 for inorganic mercury, Figure 6-3 for organic mercury, and Figure 6-4 for predominant form of mercury exposure unknown in general populations. The purpose of these figures is to illustrate the information concerning the health effects of mercury compounds. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

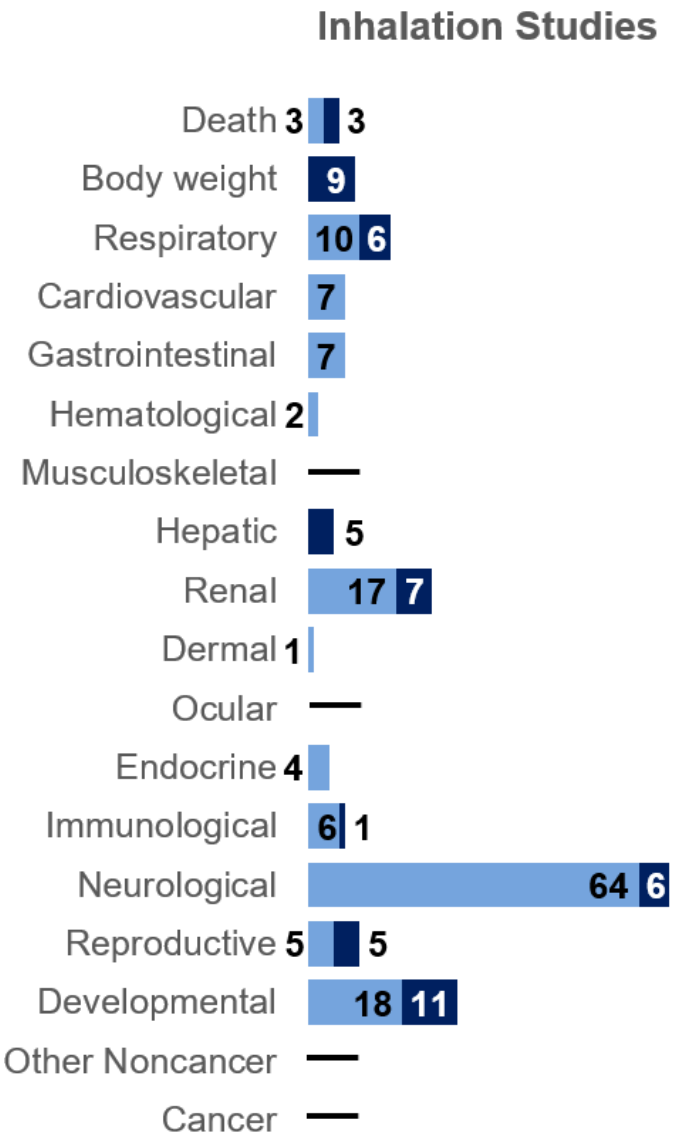
6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figures 6-1, 6-2, 6-3, and 6-4 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 6-1. Summary of Existing Health Effects Studies on Elemental Mercury by Route and Endpoint*

The most studied endpoints (in humans & animals) were potential neurological, developmental, and renal effects resulting from inhalation exposure

Inhalation exposure studies in humans comprised the majority of elemental mercury health effects research

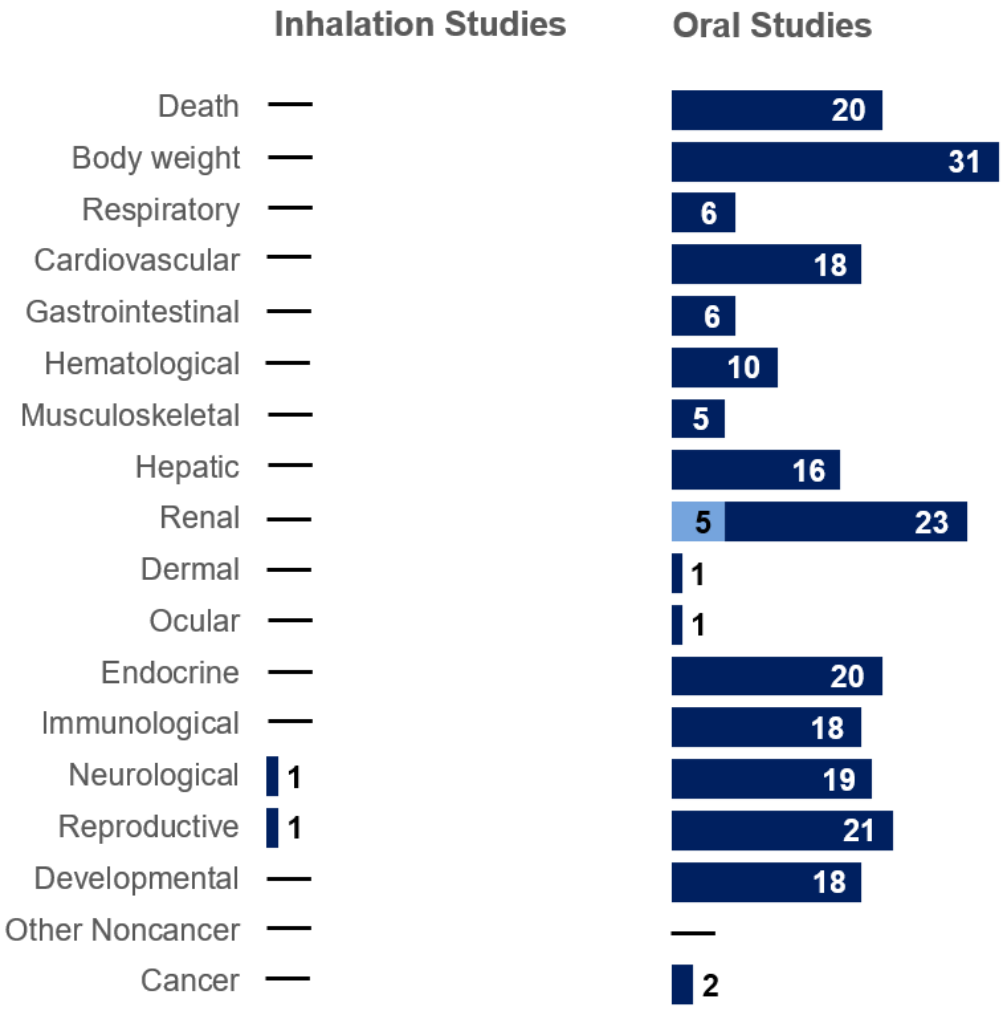


*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Most studies examined multiple endpoints. No oral or dermal studies in humans or animals were located.

Figure 6-2. Summary of Existing Health Effects Studies on Inorganic Mercuric Salts by Route and Endpoint*

The most studied endpoints (in humans & animals) were potential hematological, immune, neurological, renal, and cardiac system effects resulting from oral exposure in animals

Oral exposure studies in animals comprised the majority of inorganic mercury health effects research

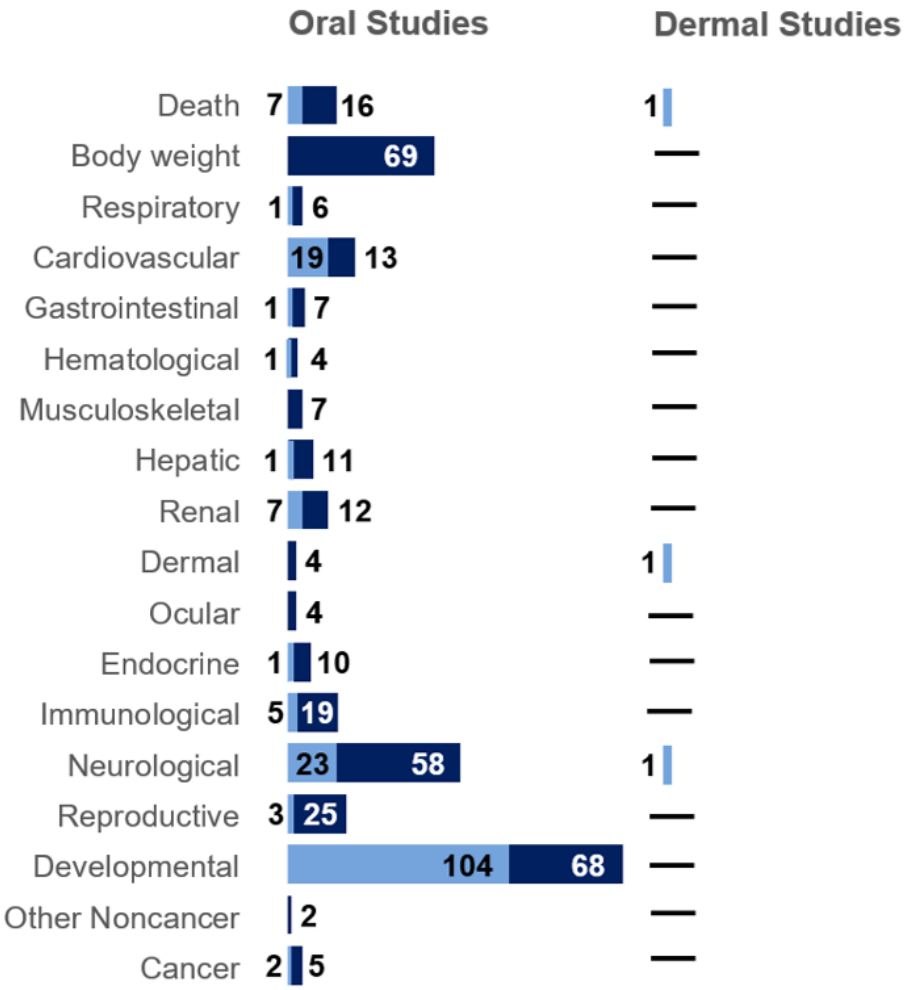


*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Most studies examined multiple endpoints. No dermal studies in humans or animals were located.

Figure 6-3. Summary of Existing Health Effects Studies on Organic Mercury by Route and Endpoint*

The most studied endpoints (in humans & animals) were potential developmental, neurological, and body weight effects resulting from oral exposure

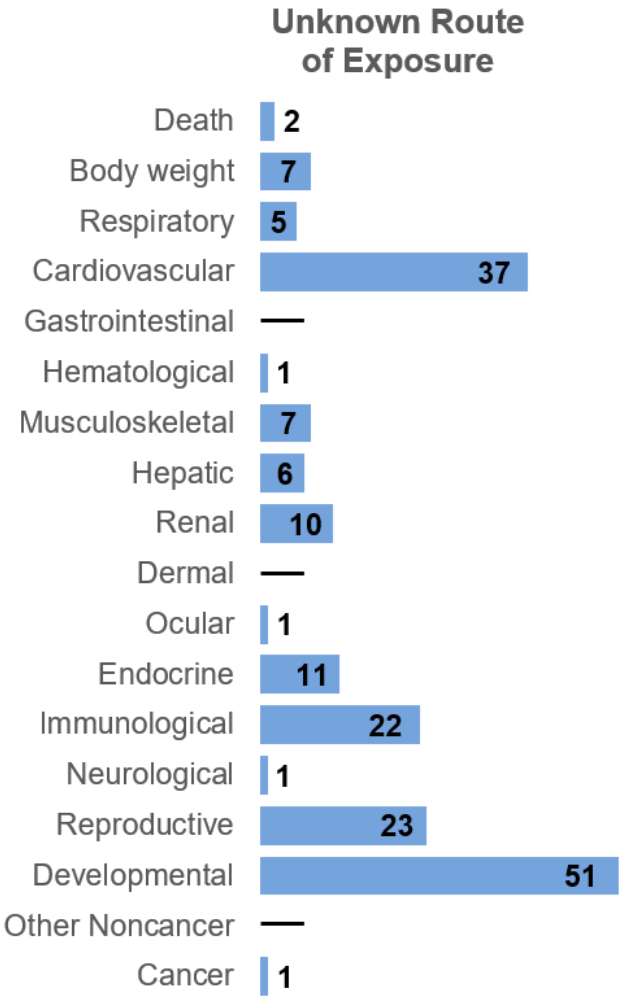
Oral exposure studies in humans and animals comprised the majority of inorganic mercury health effects research



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Most studies examined multiple endpoints. No inhalation studies in humans or animals were located.

Figure 6-4. Summary of Existing Health Effects Studies on General Population Exposure to Mercury (Unspecified Route and Form)*

The most studied endpoints (in humans) were potential developmental, cardiovascular, and reproductive effects resulting from unknown exposure sources



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Most studies examined multiple endpoints.

Elemental Mercury Inhalation MRLs. A chronic-duration inhalation MRL was developed for elemental mercury based on neurological effects (tremor) in mercury workers. Additional data may provide further definition of the NOAEL-LOAEL boundary.

The acute-duration animal inhalation database identified neurodevelopmental effects as the critical effect in animals. However, the database was not considered adequate for identification of a point of departure. The studies that identified the lowest LOAEL values involved whole-body exposure for relative short daily durations (1 or 4 hours/day) and did not control for potential oral exposure from preening or volatilization of mercury deposited on the skin/fur. Studies limiting the inhalation exposure to nose-only that examine neurodevelopmental endpoints, test multiple concentrations, and are for longer daily durations would be useful for establishing an acute-duration inhalation MRL for elemental mercury.

The available data from animal intermediate-duration inhalation studies suggest that neurodevelopmental toxicity is the most sensitive target of toxicity. However, most of the studies in the database only tested one concentration and were not considered adequate for establishing concentration-response relationships. Additional studies evaluating neurodevelopmental endpoints and testing several concentrations would be useful for developing an intermediate-duration MRL for elemental mercury.

Elemental Mercury Oral MRLs. No oral MRLs for elemental mercury have been derived for any exposure duration due to lack of data. The primary route of exposure to elemental mercury is inhalation. Oral exposure to elemental mercury is not considered an important route of environmental exposure. Therefore, there is not a data need for elemental mercury and oral exposure.

Inorganic Mercury Salts Inhalation MRLs. No inhalation MRLs for inorganic mercury salts have been derived for any exposure duration due to lack of data. The primary route of exposure to inorganic mercury salts is oral. While inorganic salts can release mercury vapor into the air, inhalation exposure to inorganic mercury compounds is not currently considered an important route of environmental exposure. Therefore, there is not a data need for inorganic mercury compounds and inhalation exposure

Inorganic Mercury Salts Oral MRLs. Acute- and immediate-duration oral MRLs were derived for inorganic mercury salts based on renal effects in rats (Apaydin et al. 2016; Dieter et al. 1992; NTP 1993). However, data for chronic-duration exposure are insufficient to derive an MRL. For chronic-duration exposure, the lowest LOAEL identified is 0.66 mg Hg/kg/day for increased systolic blood pressure in rats exposed to mercuric chloride in drinking water for 1 year, with a NOAEL of 0.33 mg Hg/kg/day (Perry

and Erlanger 1974). Thus, the lowest chronic-duration LOAEL is 44-fold higher than the lowest intermediate-duration LOAEL of 0.015 mg Hg/kg/day, which was identified in the study used in development of the intermediate-duration oral MRL. Studies examining effects of chronic-duration oral exposure at lower levels, particularly ones evaluating sensitive systems identified in Section 1.2 (neurological and neurodevelopmental, renal, cardiovascular, hematological, immunological, and male reproductive), may provide sufficient data to derive a chronic-duration oral MRL.

Organic Mercury Inhalation MRLs. No inhalation MRLs for organic mercury have been derived for any exposure duration due to lack of data. The primary route of exposure to organic mercury compounds is oral. Inhalation exposure to organic mercury is not considered an important route of environmental exposure. Therefore, there is not a data need for organic mercury compounds and inhalation exposure.

Organic Mercury Oral MRLs. A chronic-duration oral MRL for methylmercury was derived based on a meta-analysis of three epidemiological studies for neurodevelopmental effects. Additional data may lead to more accurate definition of the NOAEL-LOAEL boundary.

No acute- or intermediate-duration oral MRLs were derived for organic mercury compounds. The human database is limited to dietary exposure for chronic-durations. The animal database provides data for acute- and intermediate-duration oral exposure. However, if MRLs were based on available animal data, the acute- and intermediate-duration oral MRLs would be lower than the chronic-duration oral MRLs based on data in humans. Additional studies in animals would provide important information regarding effects of organic mercury at low levels of exposure, but additional animal data would not be useful to derive acute- and intermediate-duration oral MRLS for organic mercury.

Health Effects.

Neurological and Neurodevelopmental. The nervous system, including the developing nervous system, is well-established as a sensitive target for all forms of mercury. Epidemiological studies have identified associations between exposure to elemental mercury and neurological effects and between methylmercury exposure and neurodevelopmental effects. Additional studies evaluating neurological and neurodevelopmental effects at low exposures would provide additional data to better define population NOAELs.

The oral database evaluating neurological effects in animals following exposure to inorganic or organic mercury compounds clearly identifies the developing and the adult nervous system as a

sensitive target of mercury toxicity. Additional studies conducted at low doses for inorganic mercury compounds would provide additional information to define NOAELs and LOAELs at the low end of the dose-response curve. Evidence for neurological effects in animals following inhalation exposure to elemental mercury is less robust, particularly regarding neuro-developmental effects. Additional inhalation studies in adult and developing animals may better inform dose-response relationships following exposure to mercury vapor.

Renal. The kidney is a well-established target of mercury in humans and animals. Additional epidemiological studies for elemental mercury and organic mercury would provide additional data to define the low end of the dose-response curve for these mercury classes. The renal toxicity of inorganic mercury salts has been well-characterized in animal studies. Additional low-dose, oral studies on inorganic mercury salts in animals would provide important information to define NOAEL and LOAEL values for renal effects.

Cardiovascular. Results of epidemiological studies on populations exposed to elemental mercury and methylmercury do not provide conclusive evidence that the cardiovascular system is a sensitive target in humans exposed to mercury.

Epidemiological studies are inconsistent, with some studies showing an association between biomarkers and cardiovascular effects and other studies showing no associations. Additional study populations exposed to elemental mercury and methylmercury would provide important information to determine if the cardiovascular system is a target of mercury at occupational (elemental mercury) and environmental (general populations and populations with high fish diets) exposure levels.

The majority of animal studies show that oral exposure to mercuric chloride or methylmercury is associated with altered cardiovascular function (increased blood pressure, positive cardiac inotropism, decreased baroreflex sensitivity). Mechanistic studies would help to determine mechanisms of action and human relevance of cardiovascular findings in animals.

Hematological. Few epidemiological studies have evaluated hematological effects of mercury compounds. Although there are plausible mechanisms for mercury to adversely affect erythrocytes, data from epidemiological studies are insufficient to determine if exposure to mercury produces adverse hematological effects in humans. Additional epidemiological studies

on elemental and methylmercury would provide important information to determine if the hematological system is a target of occupational or environmental exposure to mercury.

There is limited evidence of impaired clotting, decreases in RBC parameters, and increases in WBC counts in animals following oral exposure to inorganic mercury salts. However, biological relevance of available findings is unclear due to limited data, small magnitude of effect, and/or inconsistent findings. Additional multi-dose studies of various durations in multiple species are needed to better define potential hematological effects and inform dose-response relationships for inorganic mercury salts. Additional animal studies on hematological effects of elemental and organic mercury compounds could provide information on the potential for hematological effects.

Immunological. Immunological effects of mercury compound have not been well-investigated in epidemiological studies, and there is currently no clear evidence that elemental or methylmercury is associated with altered immune function. Epidemiological studies of populations exposed to elemental and organic mercury could provide information on potential associations between exposure and immune system function.

Mercury-induced autoimmunity has been reported in autoimmune-susceptible mice following oral exposure to mercuric chloride or methylmercury, including autoimmune-susceptible mice exposed during development. Data in non-susceptible animal strains exposed to methylmercury generally report immune suppression following oral exposure; however, there are limited data suggesting that very low exposure levels may stimulate the immune system. Additional low-dose studies of mercuric chloride or methylmercury in non-susceptible strains may help elucidate potential non-monotonic immune responses associated with mercury exposure. Mechanistic studies would help determine mechanisms of action and human relevance of findings in autoimmune susceptible mice.

Reproductive. Epidemiological studies are available for workers exposed to elemental mercury, populations with high fish diets, and general populations. Few studies have examined the same reproductive endpoints, and those that did often report conflicting results. The available epidemiological studies do not provide convincing evidence that the reproductive system is a sensitive target of mercury exposure in males or females. Additional epidemiological studies could provide evidence to determine if reproductive effects are associated with environmental exposures in humans.

Laboratory animal studies evaluating reproductive endpoints following oral exposure to mercuric chloride or methylmercury consistently reported dose-related impairments in fertility. A few inorganic mercuric chloride studies suggest that the male reproductive system may be a sensitive target of toxicity at very low oral doses; however, findings from these studies need to be confirmed with additional low-exposure, multi-dose oral studies reporting quantitative endpoints to better define potential male reproductive effects and inform dose-response relationships.

Developmental. Epidemiological studies have assessed effects in workers exposed to elemental mercury, populations with high fish diets, and general populations. These studies examined mercury exposure and anthropometric measures in newborns (e.g., birth weight and size) and postnatal growth in children. Results are conflicting, with no strong evidence of associations between mercury exposure and *in utero* or postnatal growth. Additional epidemiological studies would provide important information to determine if gestational exposure to elemental or organic mercury alters the developing fetus.

Laboratory animal studies evaluating developmental endpoints following oral exposure to methylmercury reported adverse effects (decreased offspring weight and survival, increased fetal malformations and variations) at concentrations 3–4-fold higher than the lowest LOAELs associated with neurodevelopmental or immunodevelopmental effects. Since the nervous and immune systems appear to be the most sensitive targets during development, additional studies evaluating standard developmental effects are not a high priority.

Epidemiology and Human Dosimetry Studies. Most epidemiology studies of associations between exposure to mercury and health outcomes have relied on biomarkers (blood, hair, urine) as exposure metrics. Use of these studies for estimating risks from exposures to mercury require applications of dosimetry models for converting biomarkers into equivalent exposures. Steady-state mass balance models have been used to convert blood or hair mercury levels into equivalent daily average intakes of methylmercury (ATSDR 1997; IRIS 2001). Additional studies would be helpful for addressing uncertainties in key parameter in these models. These include central estimates of population variability for the following parameters, including during pregnancy: (1) fraction of ingested methylmercury absorbed; (2) fraction of mercury body burden in blood; (3) terminal elimination half-time of mercury from blood; and (4) hair-blood mercury ratio. Steady-state mass-balance models can also be used to convert urinary mercury levels to equivalent exposure concentrations of elemental mercury vapor in air.

Additional studies would be helpful for addressing uncertainties in key parameters of these models. These include central estimates and population variability for the following parameters: (1) fraction of inhaled mercury absorbed; (2) fraction of absorbed dose excreted in urine; and (3) relationship between steady-state urinary mercury (μg/g creatinine or μg/L) and urinary excretion rate (μg/day).

Steady-state models can be used for dosimetry extrapolations of exposures that are constant for a period of approximately 1 year, the exposure duration needed to achieve >95% of steady state (see Section 3.1). Dosimetry extrapolations for exposures of shorter duration (e.g., acute-duration MRLs) require PBPK models that can reliably predict the kinetics of change in blood mercury levels prior to achieving steady state. Several pharmacokinetics models of inorganic mercury (mercury vapor, mercuric) in humans have been published (Abass et al. 2018; Farris et al. 2008; Jonsson et al. 1999; Leggett et al. 2001 (see Section 3.1.5). Pharmacokinetics models of methylmercury have been developed for humans (Byczkowski and Lipscomb 2001; Carrier et al. 2001a; Gearhart et al. 1995; Young et al. 2001) and a variety of other animal species (Carrier et al. 2001b; Farris et al. 1993; Young et al. 2001). The developing fetus and neonate are highly sensitive to exposures to methylmercury; therefore, predictions of exposures during fetal and postnatal development are potentially valuable for improving dosimetry extrapolations (Byczkowski and Lipscomb 2001; Gearhart et al. 1995). Additional studies that evaluate performance of these models for predicting maternal blood and hair mercury levels during pregnancy and fetal (cord) blood levels would be helpful for assessing uncertainty in application of these models to human dosimetry extrapolation.

PBPK models for inorganic mercuric mercury in humans have been developed (Abass et al. 2018; Farris et al. 2008); however, no models are available for use in interspecies dosimetry extrapolation. PBPK models of inorganic mercuric mercury in monkeys, mice, and rats would be helpful for extrapolating external dose-response relationships (e.g., NOAELs, LOAELs) observed in these species to equivalent external doses in humans.

Biomarkers of Exposure and Effect. Epidemiology studies of health effects of mercury have relied on mercury levels in blood and hair as biomarkers of exposure to methylmercury and mercury in urine as a biomarker of exposure to inorganic (elemental or mercuric) mercury (see Section 3.3.1, Biomarkers of Exposure). These biomarkers are most useful in studies of populations in which the dominant exposures are to methylmercury (e.g., high fish consumers) or inorganic mercury (e.g., workers exposed to relatively high levels of mercury vapor). In high fish consumers, most of the mercury in hair and blood will derive from methylmercury, whereas in workers exposed to high levels of mercury vapor, most of the mercury in

urine will derive from exposure to mercury vapor. Interpretation of biomarkers measured in general populations that experience relatively low exposures to all forms of mercury is more uncertain because exposure to any form of mercury will contribute mercury to blood, hair, and urine. Additional studies would be helpful for identifying biomarkers of exposure to methylmercury and inorganic mercury (elemental and mercuric) in general populations, to facilitate studies of dose-response relationships at the lower exposure levels expected in these populations.

No biomarkers specific for the health effects of mercury are available. Exposure biomarkers that reflect mercury body burden (mercury levels in blood, hair, urine) are used to attribute signs and symptoms to mercury exposure.

Absorption, Distribution, Metabolism, and Excretion. Mercury toxicokinetics have been extensively studied in humans and animals (see Section 3.1, Toxicokinetics). However, additional studies would be helpful for increasing confidence in estimates of certain toxicokinetics parameters that are important in dosimetry models, in particular, conversion of biomarker measurements, such as mercury in blood, hair, or urine, to equivalent exposures (see Epidemiology and Human Dosimetry Studies section above). These include, for all forms of mercury, the absorption fractions for oral and inhalation exposure, fractions of absorbed mercury distributed to blood, and half-time for elimination of mercury from blood.

Comparative Toxicokinetics. Mercury toxicokinetics have been studied in the animal models used to estimate dose-response relationships for methylmercury, elemental mercury vapor, and inorganic mercury compounds (humans, monkeys, mice, rats). Toxicokinetics models of methylmercury for a variety of animal species have been developed (see Section 3.1.5). Models of mercury vapor and inorganic mercuric mercury in monkeys, mice, and rats would be helpful for extrapolating external dose-response relationships (e.g., NOAELs, LOAELs) observed in these species to equivalent external doses in humans.

Children's Susceptibility. All forms of mercury are toxic to the developing nervous system and studies conducted in humans and animals suggest that the developing nervous system is more vulnerable than the fully-developed nervous system. Additional epidemiological studies of neurodevelopmental outcomes in populations exposed to low levels of methylmercury (levels experienced in general populations) would be helpful for establishing toxicity thresholds, if they exist. Outcomes of particular interest are attainment of language proficiency, which was found to be inversely associated with mercury intake from dietary fish in a large general population prospective study (Vejrup et al. 2016, 2018), but

was not studied in two other important prospective studies of high fish consumers who experienced higher exposures to methylmercury (Faroe Islands, Seychelle Islands).

Physical and Chemical Properties. The physical and chemical properties of metallic mercury and its inorganic and organic compounds have been well characterized to permit estimation of their environmental fate (Budavari 1989; Lewis 1993; Osol 1980; Spencer and Voigt 1968; Verschueren 1983; Weast 1988; Weiss 1986). Most values are available for the log K_{ow}, log K_{oc}, Henry's law constant, vapor pressure, and solubility in water. Experimental data exist that allow characterization of the environmental fate of metallic mercury and inorganic and organic mercury compounds in a variety of environmental media. No data needs are identified.

Production, Import/Export, Use, Release, and Disposal. Information on mercury production, import/export, and use are well documented (EPA 2020b; USGS 2020).

Information on disposal methods and recycling of mercury and mercury containing wastes are available (DOI 1985, 1989, 1993).

One area that requires additional study is the use of elemental mercury by members of specific religious or cultural groups in their ceremonies, rituals, and practices so an assessment of the magnitude of these activities can be made. In addition, information on how mercury is used in these ceremonies and rituals, as well as the methods of mercury disposal used, would be helpful in assessing the potential pathways for human exposure and environmental releases.

Environmental Fate. Mercury released to the atmosphere may be transported long distances before being removed by wet or dry deposition. Residence time in the atmosphere has been estimated to range from 60–90 days to 0.3–2 years (EPA 1984; Glass et al. 1991). Volatile forms of mercury released in water or soil can enter the atmosphere, but most mercury is adsorbed to soil and sediment (EPA 1984; Meili et al. 1991). Sorbed mercury may be reduced to elemental mercury or bioconverted to volatile organic forms (EPA 1984). The major transport and transformation processes involved in the environmental fate of mercury have been fairly well defined; the most important fate process for human exposure, bioaccumulation of methylmercury in aquatic food chains is also well defined (EPA 1979, 1984; Stein et al. 1996; UNEP 2018). Additional information on mercury transport and flux in waterbodies and in tropical environments, in general, would be helpful.

Bioavailability from Environmental Media. Metallic mercury vapors in the air are readily absorbed through the lungs following inhalation exposure, while inorganic and organic mercury compounds are poorly absorbed via this route (Berlin et al. 1969a). Gastrointestinal absorption of methylmercury is nearly 100%, while gastrointestinal absorption of inorganic mercury is low (typically <10%) (Clarkson 1989; Friberg and Nordberg 1973). Metallic mercury vapor can be absorbed following dermal exposure; however, dermal absorption of the vapor accounts for a much smaller percentage (2.6% of the total absorbed through the lungs) than absorption through the inhalation route (Hursh et al. 1989). Toxicokinetic data indicate that inorganic mercury salts and organomercury compounds are dermally absorbed to some extent (Friberg et al. 1961; Moody et al. 2009; Sartorelli et al. 2003; Skowronski et al. 2000); however, certain organomercury compounds (dimethylmercury, phenylmercury) are readily absorbed through the skin (Blayney et al. 1997; Gotelli et al. 1985; Nierenberg et al. 1998; Siegler et al. 1999; Toribara et al. 1997). Data are needed regarding the bioavailability of elemental, inorganic, and organic mercury forms from contaminated surface water, groundwater, soil, or plant material. Data are also needed regarding the bioavailability of mercuric chloride in air because of the possibility of inhalation of volatilized mercuric chloride near emission sources. Additional data on the bioavailability of elemental mercury, inorganic mercury compounds, and organic mercury compounds (specifically, methylmercury) in soil would also be useful in assessing the risks from dermal and oral exposures at mining, industrial, or hazardous waste sites.

Food Chain Bioaccumulation. Mercury is known to bioconcentrate in aquatic organisms and biomagnify in aquatic food chains (ASTER 1997; EPA 1984; Kohler et al. 1990; Watras and Bloom 1992; UNEP 2018). While bioconcentration in the aquatic food chain is well studied, little is known about the bioaccumulation potential for terrestrial food chains, although it appears to be smaller than in aquatic systems (Lindqvist et al. 1991). Additional information on the potential for terrestrial food chain biomagnification would be useful since mercury binds to organic matter in soils and sediment. Information on foliar uptake of mercury and of plant/mercury chemistry is needed to determine whether plants convert elemental or divalent mercury into other forms of mercury that are more readily bioaccumulated and whether plants are able to emit these different forms to the air. Additional information is also needed to improve biotransfer factors for mercury from soil to plants to animals.

Exposure Levels in Environmental Media. Environmental monitoring data are available for mercury in ambient air, surface water, groundwater, drinking water, soils, sediments, and foodstuffs (see Section 3.3.1 for citations); however, additional monitoring data on mercury levels in all environmental media, particularly drinking water, would be helpful in determining current exposure levels.

Estimates of human intake from inhalation of ambient air and ingestion of contaminated foods and drinking water are available (Burger et al. 1992), although the estimates may be based on specific intake scenarios (e.g., information is most extensive for fish and other seafood products). Better estimates of fish consumption rates for high-volume consumers (subsistence fishers) and recreational fishers are needed, as is information on fish-specific consumption rates by these populations.

Additional information on the levels of mercury in foods other than fish and seafood would be very useful in determining total dietary intakes. Additional research is needed to characterize mercury exposures via consumption of marine mammal species. Available data indicate that the ratio of methylmercury to total mercury varies within tissues, and that only a small portion of mercury is methylated in the marine mammal liver. Also, other trace metal constituents of marine mammal tissues such as selenium, cadmium, and other metals may interact with and influence the bioavailability of mercury. Additional studies are needed to understand why the relatively high concentrations of mercury measured in marine mammal tissues do not appear to result in elevation of hair mercury levels among Alaskan natives that consume marine mammal tissues.

Reliable monitoring data for the levels of mercury in contaminated media at hazardous waste sites are needed so that the information obtained on levels of mercury in the environment can be used in combination with the known body burden of mercury to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Mercury has been measured in human blood, hair, breast milk, urine, feces, and saliva (see Section 3.3.1). Continued biomonitoring data are needed to determine the temporal trends of mercury exposure to the U.S. population and for integrating these data into existing health information systems.

Exposures of Children. Children are exposed to mercury by a variety of exposure pathways depending on their age. The most important pathways appear to be ingestion of methylmercury in foods, primarily fish and shellfish (FDA 2017a), intake of inorganic mercury associated with dental amalgams in children up to 18 years old, and inhalation of metallic mercury vapors. These are the same important pathways of exposure for adults as well. Nursing infants can also be exposed to mercury in breastmilk. More data are needed on the levels of mercury exposure in nursing women from inhalation of metallic mercury in occupational or domestic situations, including religious and ethnic uses (ATSDR 1997; Riley

et al. 2006; Wendroff 1990, 1991; Zayas and Ozuah 1996); from use of commercial or hobby arts and crafts (Grabo 1997; Rastogi and Pritzl 1996); from mercury-containing herbal remedies, cosmetics, and prescription drugs (Al-Saleh and Al-Doush 1997; Espinoza et al. 1996; Lauwerys et al. 1987; Perharic et al. 1994; Washam 2011); and from consumption of mercury-contaminated fish and wildlife, including marine mammals (ADPH 1998; CRITFC 1994; Oskarsson et al. 1996).

There are numerous ongoing studies supported by the National Institutes of Health (NIH) evaluating the potential adverse effects of mercury exposure in humans and laboratory animals, as well as underlying mechanisms of toxicity (Table 6-1). Most ongoing human studies are focused on neurodevelopmental endpoints, while most ongoing animal studies are focused on autoimmune effects.

Table 6-1. Ongoing Studies on Mercury Sponsored by the National Institutes of Health (NIH)

Investigator	Affiliation	Research description	Sponsor
Human studies			
Andres Cardenas	University of California Berkeley	Prenatal and postnatal exposure to environmental mixtures: neurodevelopment and DNA methylation biomarkers	NIEHS
Celia Chen	Dartmouth College	Sources and protracted effects of early life exposure to arsenic and mercury	NIEHS
Danielle Fallin	Johns Hopkins University	Prenatal exposure to metals and risk for autism spectrum disorder in MARBLES and EARLI	NIEHS
Ka He	Columbia University Health Sciences	Trace mineral levels, metabolomics, and diabetes risk	NIDDK
Irva Hertz-Picciotto	University of California at Davis	The CHARGE Study: Childhood Autism Risks from Genetics and the Environment	NIEHS
Sek Won Kong	Boston Children's Hospital	An environment-wide association study in autism spectrum disorders using novel bioinformatics methods and metabolomics via mass spectrometry	NIMH
Jonathan Levy	Boston University Medical Campus	Assessing the relation of chemical and non-chemical stressors with risk-taking behavior and related outcomes among adolescents living near the New Bedford Harbor Superfund Site	NIEHS
Simin Liu	Brown University	Environmental heavy metals and risk of ischemic heart disease and stroke in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)	NIEHS
Mohammad Rahbar	University of Texas Health Science Center Houston	Epidemiological research on autism in Jamaica, Phase II	NIEHS
Sarah Rothenberg	Oregon State University	Exploratory use of stable mercury isotopes to distinguish dietary sources of methylmercury and their relation to neurodevelopment	NIEHS

Table 6-1. Ongoing Studies on Mercury Sponsored by the National Institutes of Health (NIH)

Investigator	Affiliation	Research description	Sponsor
Alison Sanders	Icahn School of Medicine at Mount Sinai	Children's exposure to metals, microRNAs and biomarkers of renal health	NIEHS
Dale Sandler	NIEHS	Environmental and genetic risk factors for breast cancer: the sister study	NIEHS
James Saunders	Dartmouth-Hitchcock Clinic	Central auditory processing abnormalities as an indicator of pediatric heavy metal neurotoxicity	NIDCD
Mary Ellen Turyk	University of Illinois at Chicago	Endocrine disruption by perfluoroalkyl substances and mercury	NIEHS
Edwin van Wijngaarden	University of Rochester	Factors modifying the toxicity of methylmercury in a fish-eating population	NIEHS
Edwin van Wijngaarden	University of Rochester	Leveraging investments in the Seychelles Child Development Study to enable novel investigations of long-term methylmercury exposure, toxicity mechanisms, and health across the life course	NIEHS
Guoying Wang	Johns Hopkins University	*In utero* exposure to metals and vitamin b on placenta and child cardiometabolic outcomes	NIEHS
Xiaobin Wang	Johns Hopkins University	Maternal exposure to low level mercury, metabolome, and child cardiometabolic risk in multi-ethnic prospective birth cohorts	NIEHS
Ganesa Rebecca Wegienka	Henry Ford Health System	Environmental risk factors for uterine fibroids: a prospective ultrasound study	NIEHS
Clarice Weinberg	NIEHS	The Two Sister Study (breast cancer)	NIEHS
Alexandra White	NIEHS	Environment and cancer epidemiology	NIEHS
Tongzhang Zheng	Brown University	A nested case-control study of exposure to toxic metals, essential metals and their interaction on the risk of Type 2 diabetes	NIEHS
Wilco Zijlmans	Academisch Ziekenhuis Paramaribo	Neurotoxicant exposures: impact on maternal and child health in Suriname	FIC
Animal toxicity studies (some with associated mechanistic studies)			
William Atchison	Michigan State University	Environmental metals, excitotoxicity, and ALS (methylmercury)	NIEHS
David Lawrence	Wadsworth Center	Prenatal environmental toxicants induce neuroinflammation causing autistic behaviors (mercuric chloride)	NIEHS
Kenneth Michael Pollard	Scripts Research Institute	The effect of age on xenobiotic-induced autoimmunity (mercuric chloride)	NIEHS
Kenneth Michael Pollard	Scripts Research Institute	Do xenobiotics exacerbate idiopathic autoimmunity	NIEHS
Kenneth Michael Pollard	Scripts Research Institute	Modeling xenobiotic-induced autoimmunity using collaborative cross strains (mercuric chloride)	NIEHS

Table 6-1. Ongoing Studies on Mercury Sponsored by the National Institutes of Health (NIH)

Investigator	Affiliation	Research description	Sponsor
Allen Rosenspire	Wayne State University	Understanding the connection between exposure to mercury, autoimmunity, and tolerance in B cells	NIEHS
Mechanistic studies			
Michael Aschner	Albert Einstein College of Medicine	Mechanisms of methylmercury induced neuronal toxicity	NIEHS
Christy Bridges	Mercer University Macon	Uptake of mercury at the basolateral membrane of isolated proximal tubules	NIEHS
Stuart Macdonald	University of Kansas Lawrence	Toxicogenomics of metal response in genetically-variable *Drosophila* populations	NIEHS
Joel Newman Meyer	Duke University	Exposure to mitochondrial toxicants during germ cell development result in lifeline alterations in mitochondrial function mediated by epigenetic changes (methylmercury)	NIEHS
Matthew Rand	University of Rochester	Mechanisms of methylmercury toxicity in neuromuscular development	NIEHS
Caren Weinhouse	Oregon Health & Science University	Understanding the causes of DNA methylation response to methylmercury: a novel approach to quantify genetic, environmental, and stochastic factors	NIEHS
Toxicokinetics			
Matthew Rand	University of Rochester	Microbial mechanisms of methylmercury metabolism in humans	NIEHS
Biomarkers			
Joe Schwartz	Harvard School of Public Health	Air particulate, metals, and cognitive performance in aging cohort-roles of circulating extracellular vesicles and non-coding RNAs	NIEHS

ALS = Amyotrophic lateral sclerosis; DNA = deoxyribonucleic acid; EARLI = Early Autism Risk Longitudinal Investigation; FIC = Fogarty International Center; MARBLES = Markers of Autism Risk in Babies-Learning Early Signs; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; NIDCD = National Institute on Deafness and Other Communication Disorders; NIEHS = National Institute of Environmental Health Sciences; NIMH = National Institute of Mental Health; RNA = ribonucleic acid

Source: RePORTER 2020

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding mercury in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for mercury.

Table 7-1. Regulations and Guidelines Applicable to Mercury (Hg)

Agency	Description	Information	Reference
	Air		
EPA	RfC		IRIS 1995a
	Mercury, elemental	$3x10^{-4}$ mg/m^3 (0.00004 ppm)	
WHO	Air quality guidelines		WHO 2000
	Mercury vapor	1 µg/m^3 annual average (0.0001 ppm)	
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	Mercury, inorganic		
	1-Day health advisory (10-kg child)	0.002 mg/L	
	10-Day health advisory (10-kg child)	0.002 mg/L	
	DWEL	0.01 mg/L	
	Lifetime health advisory	0.002 mg/L	
	National primary drinking water regulations	No data	EPA 2009
	Mercury, inorganic		
	MCL	0.002 mg/L	
	RfD		
	Mercuric chloride	$3x10^{-4}$ mg/kg/day	IRIS 1995b
	Methylmercury	$1x10^{-4}$ mg/kg/day	IRIS 2001
	Phenylmercuric acetate	$8x10^{-5}$ mg/kg/day	IRIS 1987
WHO	Drinking water quality guidelines		WHO 2017
	Mercury, inorganic		
	Guideline value	0.006 mg/L	
	TDI	2 µg/kg body weight	

Table 7-1. Regulations and Guidelines Applicable to Mercury (Hg)

Agency	Description	Information	Reference
	Provisional tolerable weekly intake		
	Mercury, inorganic	4 µg/kg body weight	WHO 2011
	Methylmercury	1.6 µg/kg body weight	WHO 2007
FDA	Substances added to food[a]	No data	FDA 2020
	Action level in human food and animal feed		
	Mercury		FDA 2018a
	Wheat (pink kernels only)	1 ppm on pink kernels and an average of 10 or more pink kernels/500 g	
	Methylmercury (as Hg)		FDA 2018b
	Fish, shellfish, crustaceans, other aquatic animals (fresh, frozen, or processed)	1 ppm in edible portion	
	Allowable level in bottled water		
	Mercury	0.002 mg/L	FDA 2017b
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification		
	Mercury, elemental	D[b]	IRIS 1995a
	Mercuric chloride	C[c]	IRIS 1995b
	Methylmercury	C[c]	IRIS 2001
IARC	Carcinogenicity classification		IARC 1993
	Mercury and inorganic mercury compounds	Group 3[d]	
	Methylmercury compounds	Group 2B[e]	
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction		OSHA 2005, 2020a, 2020b, 2020c
	Mercury, except (organo) alkyl compounds (as Hg)	1 mg/10 m³ (0.1 mg/m³)[f]	
	Mercury (organo) alkyl compounds	0.01 mg/m³ [f]	
	PEL (ceiling) for general industry		
	Mercury (organo) alkyl compounds	0.04 mg/m³ [f]	
NIOSH	REL (up to 10-hour TWA)		
	Mercury vapor	0.05 mg/m³ [f]	NIOSH 2019a
	Mercury (organo) alkyl compounds (as Hg)	0.01 mg/m³ [f]	NIOSH 2019b
	REL (ceiling)		
	Mercury compounds except (organo) alkyls (as Hg)	0.1 mg/m³ [f]	NIOSH 2019a
	STEL[g]		
	Mercury (organo) alkyl compounds (as Hg)	0.03 mg/m³ [f]	NIOSH 2019b

Table 7-1. Regulations and Guidelines Applicable to Mercury (Hg)

Agency	Description	Information	Reference
	IDLH		
	Mercury compounds except (organo) alkyls (as Hg)	10 mg/m^3	NIOSH 1994a
	Mercury (organo) alkyl compounds (as Hg)	2 mg/m^3	NIOSH 1994b
	Emergency Criteria		
EPA	AEGLs-air		EPA 2018b
	Mercury vapor		
	AEGL 1[h]	Not recommended	
	AEGL 2[h]		
	10-minute	3.1 mg/m^3	
	30-minute	2.1 mg/m^3	
	60-minute	1.7 mg/m^3	
	4-hour	0.67 mg/m^3	
	8-hour	0.33 mg/m^3	
	AEGL 3[h]		
	10-minute	16 mg/m^3	
	30-minute	11 mg/m^3	
	60-minute	8.9 mg/m^3	
	4-hour	2.2 mg/m^3	
	8-hour	2.2 mg/m^3	
DOE	PACs-air		DOE 2018a
	Mercury vapor		
	PAC-1[i]	0.15 mg/m^3	
	PAC-2[i]	1.7 mg/m^3	
	PAC-3[i]	8.9 mg/m^3	
	Mercury(II) chloride		
	PAC-1[i]	0.1 mg/m^3	
	PAC-2[i]	0.14 mg/m^3	
	PAC-3[i]	38 mg/m^3	
	Mercury(I) chloride		
	PAC-1[i]	0.088 mg/m^3	
	PAC-2[i]	0.12 mg/m^3	
	PAC-3[i]	33 mg/m^3	
	Mercuric acetate		
	PAC-1[i]	0.048 mg/m^3	
	PAC-2[i]	0.64 mg/m^3	
	PAC-3[i]	3.2 mg/m^3	
	Dimethylmercury		
	PAC-1[i]	0.034 mg/m^3	
	PAC-2[i]	0.046 mg/m^3	
	PAC-3[i]	2.3 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Mercury (Hg)

Agency	Description	Information	Reference
	Phenylmercury acetate		
	PAC-1[i]	2 mg/m^3	
	PAC-2[i]	22 mg/m^3	
	PAC-3[i]	47 mg/m^3	
	Methylmercury		
	PAC-1[i]	0.032 mg/m^3	
	PAC-2[i]	0.043 mg/m^3	
	PAC-3[i]	2.1 mg/m^3	

[a]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited from use in food, delisted color additives, and some substances "no longer FEMA GRAS".
[b]D: not classifiable as to human carcinogenicity.
[c]C: possible human carcinogen.
[d]Group 3: not classifiable as to its carcinogenicity to humans.
[e]Group 2B: possibly carcinogenic to humans.
[f]Skin notation.
[g]Short-term exposure limit, a 15-minute TWA exposure that should not be exceeded at any time during a workday.
[h]Definitions of AEGL terminology are available from U.S. Environmental Protection Agency (EPA 2018c).
[i]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; MCL = maximum contaminant level; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TDI = tolerable daily intake; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Elemental mercury
CAS Number: 7439-97-6
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for elemental mercury.

Rationale for Not Deriving an MRL: No epidemiological studies investigating effects of acute exposure to inhaled elemental mercury were identified. Acute-duration inhalation studies in humans are limited to accidental or intentional exposure to fatal or near-fatal levels of elemental mercury vapor.

Studies in rats and mice have identified several targets of toxicity including neurological alterations, neurodevelopmental effects, and renal effects. Acute duration studies have also reported developmental outcome effects and reproductive effects in rats; however, given the limited number of studies reporting these effects, the data are insufficient to draw conclusions as to whether reproductive and developmental outcome effects are sensitive targets for elemental mercury. It is noted that the reported developmental and reproductive effects occur at higher elemental mercury concentrations than the neurological effects. Summaries of the lowest LOAELs for neurological, neurodevelopmental, renal, developmental, and reproductive endpoints are presented in Table A-1.

Table A-1. Selected NOAEL and LOAEL Values in Animals Acutely Exposed to Inhaled Elemental Mercury

		NOAEL/LOAEL (mg Hg/m^3)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Neurodevelopmental					
Rat	7 days PNDs 11–17 1 hour/day (WB)	ND	0.05	Increased spontaneous locomotion and total activity and decreased rearing counts at 4 months of age; impaired spatial learning at 6 months of age	Fredriksson et al. 1992
Rat	7 days PNDs 11–17 4 hours/day (WB)	ND	0.05	Increased spontaneous locomotion and total activity and decreased rearing counts at 2 months of age; decreased spontaneous locomotion, total activity, and rearing counts at 4 months of age; and impaired spatial learning at 6 months of age	Fredriksson et al. 1992
Rat	6 days GDs 14–19 1.5 hours/day (WB)	ND	1.8	Increased spontaneous locomotion, rearing, and total activity at 4 months of age; impaired spatial learning	Fredriksson et al. 1996

Table A-1. Selected NOAEL and LOAEL Values in Animals Acutely Exposed to Inhaled Elemental Mercury

		NOAEL/LOAEL (mg Hg/m^3)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Rat	8 days GDs 11–14 + GDs 17–20 1 or 3 hours/day (WB)	ND	1.8	Decreased spontaneous locomotion, rearing, and total activity at 3 months; reduced novel environment habituation at 7 months	Danielsson et al. 1993
Neurological					
Mouse	4 hours (WB)	ND	0.5	Reduced grip strength 4–7 months post-exposure, decreased motor axon diameter 7 months post-exposure	Stankovic 2006
Rat	GDs 6–15 2 hours/day (N)	4	8	Mild tremor, lethargy, unsteady gait	Morgan et al. 2002
Reproductive					
Rat	11 days 2 hours/day (N)	1	2	Prolonged estrous cycle	Davis et al. 2001
Rat	1–8 days 2 hours/day (N)	ND	2	Prolonged estrous cycle after 6–8 days exposure; immature corpora lutea during estrus and metestrus phases	Davis et al. 2001
Renal					
Rat	GDs 6–15 2 hours/day (N)	2	4	Elevated maternal relative kidney weight (32% on GD 15); increased urinary protein (80%) and ALP (943%)	Morgan et al. 2002
Developmental					
Rat	GDs 6–15 2 hours/day (N)	4	8	Increased resorptions, decreased litter size, decreased pup weight	Morgan et al. 2002

ALP = alkaline phosphatase; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; (N) = nose-only exposure; ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day; (WB) = whole-body exposure

The lowest LOAEL is 0.05 mg Hg/m^3 for neurodevelopmental effects in rats exposed on PNDs 11–17 for 1 or 4 hours/day (Fredriksson et al. 1992). When the animals exposed for 4 hours/day were examined at 2 months of age, increased spontaneous locomotion and total activity and decreased rearing were observed. At 4 months of age, spontaneous locomotion and total activity were decreased in the group exposed for 4 hours/day and increased in the group exposed for 1 hour/day. At 6 months of age, impaired spatial learning was observed in the groups exposed for 1 and 4 hours/day. Similar effects were also observed in offspring of rats exposed to 1.8 mg Hg/m^3 for 1.5 hours/day on GDs 14–19 and tested at 4 months of age (Fredriksson et al. 1996). Neurological effects consisting of reduced grip strength and

decreased motor axon diameter were reported in adult mice 4–7 months after a single 4-hour exposure (Stankovic 2006). At higher concentrations, non-neurological effects such as prolonged estrus cycle (Davis et al. 2001), increased resorptions and decreased pup weight (Morgan et al. 2002), and evidence of renal damage (Morgan et al. 2002) were observed.

Although there is strong evidence from epidemiological studies involving chronic exposure and acute- and intermediate-duration animal studies supporting the identification of neurotoxicity/ neuro-developmental toxicity as the critical effect, the acute-duration inhalation database was not considered adequate for derivation of an MRL. The Fredriksson et al. (1992) study, which identified the lowest LOAEL was not considered a suitable principal study for several reasons: (1) the daily exposure was short (1 or 4 hours/day) and there is uncertainty that the observed effects may not be predictive of continuous exposure; (2) the control group treatment was not identical to the exposed groups (i.e., the controls were placed in exposure chamber for 2 hours/day compared to 1 or 4 hours/day for the exposed groups); and (3) animals received whole-body exposure and no measures were taken to prevent mercury ingestion during preening or inhalation exposure from volatilization of mercury deposited on fur/skin.

Agency Contacts (Chemical Manager): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Elemental mercury
CAS Number: 7439-97-6
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for elemental mercury.

Rationale for Not Deriving an MRL: No intermediate-duration epidemiological studies were identified for elemental mercury. A number of animal studies have evaluated the toxicity of elemental mercury following intermediate-duration inhalation exposure. The results of these studies suggest that neurological and/or neurodevelopmental effects are the most sensitive outcomes. At higher concentrations, renal and male reproductive effects have also been reported. Neurological and/or neurodevelopmental effects observed in monkeys, rats, mice, and rabbits include decreased motor activity, impairments in learning and memory, and tremors (Fukuda 1971; Kishi et al. 1978; Newland et al. 1996; Yoshida et al. 2018). Renal effects include slight degenerative changes in the renal tubular epithelium (Kishi et al. 1978). The male reproductive effects included seminiferous tubule atrophy, and decreased spermatocyte and spermatids (Altunkaynak et al. 2015); it is noted that this is the only reproductive toxicity study on elemental mercury that examined male reproductive effects and the database is considered insufficient to draw conclusions.

Selected NOAEL and LOAEL values are presented in Table A-2. The lowest LOAEL is 0.188 mg Hg/m^3 for decreased motor activity on PND 77 in the offspring of mice continuously exposed to elemental mercury on PNDs 2–28 (Yoshida et al. 2018); the study only tested one concentration (in addition to a control group). The study did not find alterations in passive avoidance tests or working memory tests. Earlier studies by this group found no alterations in motor activity, learning, or memory in the offspring of mice exposed to 0.03 mg Hg/m^3 during GDs 0–18 (Yoshida et al. 2011) or in mice exposed to 0.057 mg Hg/m^3 on PNDs 1–20 (Yoshida et al. 2013).

Table A-2. Selected NOAEL and LOAEL Values in Animals Exposed to Inhaled Elemental Mercury for Intermediate Durations

		NOAEL/LOAEL (mg Hg/m^3)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Neurodevelopmental					
Mouse	PNDs 2–28 24 hours/day (WB)	ND	0.188	Decreased motor activity at PND 77	Yoshida et al. 2018
Monkey	15–17 weeks gestational exposure 5 days/week 4 or 7 hours/day (WB)	ND	0.5	Impaired operant training in offspring tested at 0.8–4 years of age	Newland et al. 1996

Table A-2. Selected NOAEL and LOAEL Values in Animals Exposed to Inhaled Elemental Mercury for Intermediate Durations

Species	Duration	NOAEL/LOAEL (mg Hg/m^3) NOAEL	LOAEL	Effect	Reference
Mouse	GDs 0–18 6 hours/day (WB)	0.03	ND	No effect on motor activity, learning, or memory assessed on PND56	Yoshida et al. 2011
Mouse	PNDs 1–20 24 hours/day (WB)	0.057	ND	No effect on motor activity, learning, or memory assessed at 3 or 15 months of age	Yoshida et al. 2013
Neurological					
Rat	8 weeks 4–5 days/week 5 hours/day (WB)	ND	0.5	Irritability, aggressiveness; loss of Purkinje and granular cells in cerebellum	Sørensen et al. 2000
Reproductive					
Rat	6 weeks 7 days/week 9 hours/day (WB)	ND	1	Seminiferous tubule atrophy; damage to spermatogenic cells; decreased testicular and seminiferous tubule volume, decreased seminiferous tubule diameter; decreased Sertoli cells, spermatogonia, spermatocytes, and spermatids	Altunkaynak et al. 2015
Renal					
Rat	12–42 weeks 5 days/week 3 hour/day (WB)	ND	3	Slight degenerative changes (i.e., dense deposits in tubule cells and lysosomal inclusions) in the renal tubular epithelium	Kishi et al. 1978

GD = gestation day; LOAEL = lowest-observed-adverse-effect level ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day; (WB) = whole-body exposure

The intermediate-duration inhalation database for elemental mercury was not considered adequate for MRL derivation. Although several studies have identified NOAELs and LOAELs for neuro-developmental effects (the presumed critical effect), most of the studies only tested a single concentration and the database was considered insufficient for establishing concentration-response relationships. It should also be noted that the highest NOAEL (0.057 mg Hg/m^3) for the intermediate-duration database is similar to the lowest LOAEL (0.05 mg Hg/m^3) identified for neurodevelopmental effects in the acute-duration inhalation database; this may be due to, but not limited to, species differences (mice versus rats) and/or differences in the study design (e.g., age at dosing and assessment, exposure duration, total exposure concentration, etc.).

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Elemental mercury
CAS Number:	7439-97-6
Date:	April 2022
Profile Status:	Draft for Public Comment
Route:	Inhalation
Duration:	Chronic
MRL	0.3 μg Hg/m^3 ($3x10^{-4}$ mg Hg/m^3)
Critical Effect:	Tremors
Reference:	Bast-Pettersen et al. 2005; Boogaard et al. 1996; Chapman et al. 1990; Ellingsen et al. 2001; Fawer et al. 1983; Langworth et al. 1992a; Wastensson et al. 2006, 2008
Point of Departure:	2.84 μg Hg/m^3 (95% lower confidence limit of weighted median of seven principal studies)
Uncertainty Factor:	10
LSE Graph Key:	26
Species:	Human

MRL Summary: A chronic-duration inhalation MRL of 0.3 μg Hg/m^3 was derived for elemental mercury based on tremors reported in several occupational exposure studies. The MRL is based on 2.84 μg Hg/m^3, which is the 95% lower confidence limit of the weighted median of 4.92 μg Hg/m^3 calculated using estimated air concentrations from seven studies, reported in eight publications (Bast-Pettersen et al. 2005; Boogaard et al. 1996; Chapman et al. 1990; Ellingsen et al. 2001; Fawer et al. 1983; Langworth et al. 1992a; Wastensson et al. 2006, 2008) and a total uncertainty factor of 10 for human variability.

Selection of the Critical Effect: The available information on the toxicity of elemental mercury vapor comes from a large number of epidemiological studies of workers in the chloralkali, fluorescent lamp, lithium-6 purification, natural gas production, gold mining and processing, and thermometer industries and of dental workers. Most epidemiological studies used urinary mercury levels (expressed as μg Hg/L or μg Hg/g creatinine) as a biomarker of exposure, and some studies also provided work area or breathing zone mercury levels. Reported urine mercury levels were converted to equivalent exposure concentrations by applying a steady-state mass balance model (see the *Calculation of Estimated Air Concentration* section below for additional information). No reliable chronic-duration animal studies were identified.

The epidemiological studies provide consistent evidence of neurological effects, specifically alterations in color vision, tremor, nerve conduction velocity, and cognitive function. There is also suggestive evidence of renal effects, particularly glomerular function decrements and tubular injury from epidemiological studies. Neurotoxicity was selected as the critical effect based on the stronger weight of evidence supporting an association with elemental mercury exposure.

Over 35 epidemiological studies have evaluated neurological outcomes among workers exposed to mercury vapor; the most commonly assessed endpoints were decrements or loss in color vision, tremors, and alterations in motor speed and fine motor coordination, and cognitive function (memory, and integrative function), typically compared to a reference group. A list of the studies examining these neurological effects is presented in Table A-3. For each study, observed biomarkers of exposure (e.g., urine mercury) were converted to estimates of exposure air concentrations and categorized as either an adverse-effect level (AEL) if an adverse effect was observed or a no-adverse-effect level (NAEL) if no adverse effect was observed (see Appendix E for definition of AEL and NAEL). The aggregate median

AEL estimated air concentrations for the types of effects observed are similar, ranging from 8.8 to 13.9 μg Hg/m^3 (for more details on how air concentrations were estimated, see the *Calculation of Estimated Air Concentration* section below).

Table A-3. Summary of Adverse Effect Levels for Neurological Effects Reported in Epidemiological Studies of Elemental Mercury

	Median (range) estimated air concentrations (μg Hg/m^3)	Number of exposed workers examined in each study	References
Color vision			
NAEL	ND (2.58)	21	Cavalleri and Gobba 1998
AEL	8.76 (0.914–8.74)	15–40	Barboni et al. 2008, 2009; Canto-Pereira et al. 2005; Cavalleri and Gobba 1998; Urban et al. 2003; Ventura et al. 2005
Tremor			
NAEL	4.75 (0.914–8.74)	43–200	Bast-Pettersen et al. 2005; Boogaard et al. 1996; Ellingsen et al. 2001; Harari et al. 2012; Langworth et al. 1992a; Wastensson et al. 2006, 2008
AEL	11.72 (0.422–63.1)	15–13,905	Albers et al. 1988; Anglen et al. 2015; Bittner et al. 1998; Chapman et al. 1990; Echeverria et al. 2005; Fawer et al. 1983; Frumkin et al. 2001; Harari et al. 2012; Iwata et al. 2007; Langolf et al. 1978; Letz et al. 2000; Miller et al. 1975; Roels et al. 1982; Tang and Li 2006; Verberk et al. 1986
Cognitive function			
NAEL	1.44 (0.072–4.57)	49–550	Bast-Pettersen et al. 2005; Factor-Litvak et al. 2003; Ritchie et al. 2002; Sletvold et al. 2012
AEL	13.9 (0.405–30.5)	26–426	Bluhm et al. 1992; Echeverria et al. 1998, 2005; Mathiesen et al. 1999; Ngim et al. 1992; Piikivi and Hanninen 1989; Piikivi et al. 1984; Sletvold et al. 2012; Smith et al. 1983

AEL = adverse-effect level; NAEL = no-adverse-effect level

The tremor endpoint was selected as the critical effect because more studies (20 studies) with larger populations have evaluated tremor compared to color vision (5 studies). Alterations in cognitive function was not selected as the critical effect because the studies evaluated various domains of cognitive function and the number of studies evaluating similar domains is small, as compared to the number of studies evaluating tremors. The NAELs and AELs for the epidemiological studies evaluating tremors are presented in Table A-4.

Table A-4. NAEL and AEL Values for Epidemiological Studies Evaluating Tremor

Study	Population	Number of subjects	Estimated air concentration (μg Hg/m^3)	
			NAEL	AEL
Albers et al. 1988	Lithium 6 workers	247		42.6
Anglen et al. 2015	Dental workers	13,906		1.00
Bast-Pettersen et al. 2005	Chloralkali workers	49	4.57	
Bittner et al. 1998	Dental workers	230		11.7
Boogaard et al. 1996	Gas production	40	8.74	
Chapman et al. 1990	Chloralkali workers	18		4.92
Echeverria et al. 2005	Dental workers	427		0.422
Ellingsen et al. 2001	Chloralkali workers	47	4.43	
Fawer et al. 1983	Lamp and chloralkali workers	26		5.57
Frumkin et al. 2001	Chloralkali workers	139		18.7
Harari et al. 2012	Gold miners	200	0.914	
Harari et al. 2012	Gold merchants	37		10.2
Iwata et al. 2007	Cinnabar miners and smelters	27		63.1
Langolf et al. 1978	Chloralkali workers	79		51.1
Langworth et al. 1992a	Chloralkali workers	85	7.03	
Letz et al. 2000	Lithium 6 workers	104		38.4
Miller et al. 1975	Chloralkali workers	77		27.5
Roels et al. 1982	Chloralkali workers	43		13.8
Tang and Li 2006	Thermometer workers	143		10.7
Verberk et al. 1986	Lamp workers	20		9.88
Wastensson et al. 2006, 2008	Chloralkali workers	43	4.90	

AEL = adverse-effect level; NAEL = no-adverse-effect level

Selection of the Principal Study: Rather than selecting an individual study as the principal study, a group of seven studies, reported in eight publications, that provide information on the NAEL/AEL boundary were selected as the principal studies (see the *Selection of the Point of Departure* section for information on criteria for selecting these studies). Citations for the principal studies are listed below; summaries of these studies are included in Table A-5.

Bast-Pettersen R, Ellingsen DG, Efskind J, et al. 2005. A neurobehavioral study of chloralkali workers after the cessation of exposure to mercury vapor. Neurotoxicology 26(3):427-437.

Boogaard PJ, Houtsma A-T AJ, Journée HL, et al. 1996. Effects of exposure to elemental mercury on the nervous system and the kidneys of workers producing natural gas. Arch Environ Health 51(2):108-115.

Chapman LJ, Sauter SL, Henning RA, et al. 1990. Differences in frequency of finger tremor in otherwise asymptomatic mercury workers. Br J Ind Med 47(12):838-843.

Ellingsen DG, Bast-Pettersen R, Efskind J, et al. 2001. Neuropsychological effects of low mercury vapor exposure in chloralkali workers. Neurotoxicology 22(2):249-258.

Fawer RF, DeRibaupierre Y, Guillemin M, et al. 1983. Measurement of hand tremor induced by industrial exposure to metallic mercury. Br J Ind Med 40:204-208.

Langworth S, Almkvist O, Soderman E, et al. 1992a. Effects of occupational exposure to mercury vapour on the central nervous system. Br J Ind Med 49(8):545-555.

Wastensson G, Lamoureux D, Sällsten G, et al. 2006. Quantitative tremor assessment in workers with current low exposure to mercury vapor. Neurotoxicol Teratol 28(6):681-693.

Wastensson, G, Lamoureux, D, Sallsten G, et al. 2008. Quantitative assessment of neuromotor function in workers with current low exposure to mercury vapor. Neurotoxicol 29(4):596-604.

Table A-5. Summary of the Principal Studies Examining Tremor in Workers Exposed to Elemental Mercury

Reference: Bast-Pettersen et al. 2005

Study type and population: Retrospective cohort of 49 former chloralkali workers and 49 referents from Norway. Average duration of exposure of workers was 13.1 years. Average time elapsed since exposure ceased was 4.8 years.

Biomarkers:

UHg working (average µg Hg/g Cr/year, range)
Referent: NA
Exposed: 16.5 (7.1–45)

UHg at testing (mean µg Hg/g Cr, range)
Referent: 2.0 (0.6–5.7)
Exposed: 2.9 (0.4–9.2)

Estimated air concentration[a]: 4.57 µg Hg/m^3 (based on exposed working average)

Analysis: Subjects were excluded for history of alcohol abuse, major head injuries; or metabolic, major psychiatric or neurological disease that caused severe disability. Data were analyzed using ANOVA for comparison of means between exposure groups and referents.

Results:

Mean (range) of tremor intensity (m/s^2)
- Dominant hand, NS
  - Exposed: 0.12 (0.07–0.33)
  - Referent: 0.13 (0.07–0.40)
  - Mean ratio: 0.96 (95% CI 0.85, 1.10)
- Non-dominant hand, NS
  - Exposed: 0.12 (0.07–0.31)
  - Referent: 0.12 (0.06–0.51)
  - Mean ratio: 1.01 (95% CI 0.87, 1.17)

Mean (range) of frequency dispersion (Hz)
- Dominant hand, NS
  - Exposed: 2.9 (1.2–4.4)

Mean (range) of center frequency (Hz)
- Dominant hand, NS
  - Exposed: 7.4 (6.0–9.6)
  - Referent: 7.5 (5.8–10.6)
  - Mean difference: -0.1 (95% CI -0.5, 0.3)
- Non-dominant hand, NS
  - Exposed: 7.6 (5.9–10.8)
  - Referent: 7.4 (2.4–9.9)
  - Mean difference: 0.2 (95% CI -0.3, 0.6)

Mean (range) of harmonic index
- Dominant hand, NS
  - Exposed: 0.92 (0.80–0.97)
  - Referent: 0.91 (0.82–0.98)
  - Mean difference: 0.01 (95% CI -0.01, 0.02)

Table A-5. Summary of the Principal Studies Examining Tremor in Workers Exposed to Elemental Mercury

- Referent: 2.8 (0.9–4.3)
- Mean difference: 0.1 (95% CI -0.2, 0.4)

- Non-dominant hand, NS
  - Exposed: 3.3 (1.0–4.9)
  - Referent: 3.3 (1.1–6.4)
  - Mean difference: 0 (95% CI -0.3, 0.3)

- Non-dominant hand, NS
  - Exposed: 0.89 (0.82–0.98)
  - Referent: 0.89 (0.78–0.97)
  - Mean difference: 0 (95% CI -0.02, 0.02)

Interpretation: Tremor was not significantly different between exposed and referent groups; therefore, the working mean UHg in the exposed group (16.5 µg/g Cr) was considered to be a NAEL for tremor. The equivalent air Hg concentration (4.57 µg Hg/m^3) was weighted by the number of subjects in the exposed group (49).

Reference: Boogaard et al. 1996

Study type and population: Retrospective cohort of 40 natural gas workers (18 with "high" exposure; 22 with "low" exposure) and 19 referents from the Netherlands. Median (range) exposure time for high- and low-exposure workers was 9 years (1–15 years) and 10 years (3–20 years), respectively. Time elapsed since exposure ceased was not reported.

Biomarkers:

UHg working (median µg Hg/L, range)
Referent: 3 (1–8)
High exposure: 41 (7–72)
Low exposure: 12 (7–53)

UHg at testing (median µg Hg/L, range)
Referent: 2 (0.5–6.8)
High exposure: 17 (3.5–71.9)
Low exposure: 5 (0.6–8.8)

Estimated air concentration[a]: 8.74 µg Hg/m^3 (based on high working median)

Analysis: Subjects were excluded for history of nonoccupational neuropathies or disorders with potential renal sequelae. Data were analyzed using MANOVA for comparison of means between exposure groups and referents. Multivariate regression analysis was performed for the entire population (referents plus exposed).

Results:

Mean (median; range) of resting tremor

- Right hand, NS
  - High exposed: 6.49 (6.5; 1.4–10.3)
  - Low exposed: 6.45 (5.95; 2.3–10.2)
  - Referent: 6.34 (6.0; 3.9–9.2)
- Left hand, NS
  - High exposed: 5.94 (4.9; 2.9–10.4)
  - Low exposed: 6.60 (6.8; 2.9–10.5)
  - Referent: 6.64 (6.8; 3.6–10.1)

Mean (median; range) of intention tremor

- Right hand, NS
  - High exposed: 5.09 (4.85; 3.9–8.0)
  - Low exposed: 5.38 (5.2; 3.7–10.8)
  - Referent: 5.22 (5.2; 3.9–6.7)
- Left hand, NS
  - High exposed: 5.15 (4.9; 4.2–8.0)
  - Low exposed: 5.50 (5.3; 4.2–10.6)
  - Referent: 5.39 (5.6; 3.9–6.2)

No significant correlation between tremor measures and present or historical UHg levels (data not shown).

Table A-5. Summary of the Principal Studies Examining Tremor in Workers Exposed to Elemental Mercury

Mean (median; range) of action tremor

- Right hand, NS
  - High exposed: 6.61 (7.05; 2.2–10.3) (lower end of range reported as 97.05)
  - Low exposed: 7.39 (7.4; 2.0–12.3)
  - Referent: 6.67 (7.5; 2.4–9.0)
- Left hand, NS
  - High exposed: 6.76 (6.8; 2.3–12.0
  - Low exposed: 7.75 (7.55; 1.6–11.4)
  - Referent: 7.00 (7.7; 2.5–9.5)

Interpretation: No significant association between UHg and tremor; therefore, the working median UHg in the high exposure group (41 µg/L) is a NAEL for tremor. The equivalent air Hg concentration (8.74 µg Hg/m^3) was weighted by the number of subjects in the high exposure group (40).

Reference: Chapman et al. 1990

Study type and population: Cross-sectional cohort of 18 mercury battery workers and 18 referents from the United States. Average exposure time (range) for workers was 5.3 (0.3–32) years.

Biomarkers:
UHg at testing (mean µg Hg/L, SD)
Exposed: 23.1 (28.3)
Referent: Not measured

Estimated air concentration[a]: 4.92 µg Hg/m^3

Analysis: Subjects were excluded for previous or current injuries or illnesses with neuropathic potential and neurotoxic drug or chemical exposures. Data were analyzed using non-parametric Mann-Whitney test to compare means between exposed and referent subjects, adjusted for the four comparison metrics.

Results:
Mean (SD) of hand tremor amplitude, NS

- Exposed: 35.6 (2.5)
- Referent: 23.0 (6.5)

Mean (SD) of hand tremor power, p<0.01

- Exposed: 315.0 (37.0)
- Referent: 68.0 (5.0)

Mean (SD) of hand tremor half power frequency, NS

- Exposed: 7.8 (0.9) Hz
- Referent: 7.5 (0.6) Hz

Mean (SD) of tremor highest band power (5–15 Hz), p<0.001

- Exposed: 2.6 (2.3)
- Referent: 1.5 (0.6)

Interpretation: Tremor was significantly higher in the exposed group; therefore, the mean UHg in the exposed group (23.1 µg/L) is an AEL for tremor. The equivalent air Hg concentration (4.92 µg Hg/m^3) was weighted by the number of subjects in the exposed group (18).

Table A-5. Summary of the Principal Studies Examining Tremor in Workers Exposed to Elemental Mercury

Reference: Ellingsen et al. 2001

Study type and population: Retrospective cohort of 47 former chloralkali workers exposed for at least one year, and 47 referents; from Norway. Average exposure duration of 13.3 years.

Biomarkers:

UHg working (average µg Hg/g Cr/year, range)
Referent: NA
Exposed: 16.0 (7.1–35)

UHg at testing (mean µg Hg/g Cr, range)
Referent: 2.3 (0.4–8.9)
Exposed: 10.5 (2.0–30)

Estimated air concentration[a]: 4.43 µg Hg/m^3 (exposed)

Analysis: Subjects were excluded for alcohol abuse, major heads injuries; or metabolic, psychiatric, neurologic or other diseases causing severe disability. Data on intentional hand steadiness were analyzed by ANOVA of means between exposed and referents.

Results:

Mean (SD) of static steadiness (number of hits)

- Dominant hand, NS
  - Exposed: 126.5 (113.3)
  - Referent: 123.4 (117.0)
- Non-dominant hand, NS
  - Exposed: 112.5 (71.6)
  - Referent: 120.0 (90.7)

Mean (SD) of static steadiness (duration of hits, s)

- Dominant hand, NS
  - Exposed: 7.2 (5.5)
  - Referent: 6.8 (4.4)
- Non-dominant hand, NS
  - Exposed: 7.6 (5.0)
  - Referent: 7.9 (5.1)

Interpretation: Tremor was not significantly different between exposed and referent groups; therefore, the working mean UHg in the exposed group (16.0 µg/g Cr) is a NAEL for tremor. The equivalent air Hg concentration (4.43 µg Hg/m^3) was weighted by the number of subjects in the exposed group (47).

Reference: Fawer et al. 1983

Study type and population: Cross-sectional cohort of florescent lamp workers (n=7), chloralkali workers (n=12), acetaldehyde production workers (n=7), and 25 referents from Belgium. Average exposure time (±SE) for workers was 15.3±2.6 years

Biomarkers:

UHg at testing (mean µg Hg/g Cr, SE)[b]
Referent: 6.0 (1.2)
Exposed: 20.1 (2.1)

Estimated air concentration: 5.57 µg Hg/m^3

Analysis: Criteria for excluding participation in the study were not reported. Data were analyzed by t-test of means between exposed and referents or paired t-test for changes between rest and load.

Table A-5. Summary of the Principal Studies Examining Tremor in Workers Exposed to Elemental Mercury

Results:

Mean (SE) for highest peak frequency of hand tremor

- At rest, p<0.001
  - Referent: 6.40 (0.19) Hz
  - Exposed: 7.60 (0.22) Hz
- Changes between rest and load, p<0.001
  - Referent: 2.69 (0.19) Hz
  - Exposed: 3.62 (0.29) Hz

Mean (SE) for second moment

- At rest, p>0.002
  - Referent: 10.9 (1.1) Hz
  - Exposed: 13.3 (0.9) Hz
- Changes between rest and load, p<0.002
  - Referent: 0.9 (1.1) Hz
  - Exposed: 4.1 (1.2) Hz

Interpretation: Tremor was significantly higher in the exposed group; therefore, the mean UHg in the exposed group (20.1 μg/g Cr) is an AEL for tremor. The equivalent air Hg concentration (5.57 μg Hg/m^3) was weighted by the number of subjects in the exposed group (26).

Reference: Langworth et al. 1992a

Study type and population: Cross-sectional cohort of 89 chloralkali workers and 75 referents from Sweden. Average exposure time (±SD) for workers was 13.5±8.7 years.

Biomarkers:

UHg at testing and while working[b] (median μg Hg/g Cr, range)

Referent: 1.9 (0–7.6)

Exposed: 25.4 (0.5–83.3)

Estimated air concentration[a]: 7.03 μg Hg/m^3

Analysis: Subjects were excluded for alcohol abuse, exposure to other heavy metals or organic solvents; or chronic neurological or kidney disease. Data analyzed using the Student's t test.

Results:

Incidence of slight finger tremor, NS

- Referent: 13/75 (17%)
- Exposed: 17/89 (19%)

Forearm tremor (exposed vs referents), NS

- Tremor frequency spectrum
- Tremor acceleration amplitude

Interpretation: Tremor was not significantly different in the exposed and referent group; therefore, the median UHg in the exposed group (24.4 μg/g Cr) is a NAEL for tremor. The equivalent air concentration (7.03 μg Hg/m^3) was weighted by the number of subjects in the exposed group who were evaluated for tremor (85 of 89).

Table A-5. Summary of the Principal Studies Examining Tremor in Workers Exposed to Elemental Mercury

Reference: Wastensson et al. 2006, 2008

Study type and population: Retrospective cohort of 43 chloralkali workers and 22 referents from Sweden. The average exposure time for workers was 15 years.

Biomarkers:
UHg cumulative work index (mean µg year/g Cr, range)
266 (8–1,440)
UHg average (calculated as 266/15 mean years worked)
17.7 µg/g Cr
UHg at testing (median µg Hg/g Cr, range)
Exposed: 5.9 (1.3–25)
Referent: 0.7 (0.2–4.1)

Estimated air concentration: 4.90 µg Hg/m^3 (based on cumulative work mean/mean years worked)

Analysis: Subjects were excluded based on medications, diseases (e.g., diabetes), essential tremor, skull or whiplash injury, or other circumstances that could affect tremor or coordination (e.g., pain in upper limb, lack of sleep, nervousness, colds). Data were analyzed using Student's t-test (n >20), Wilcoxon's rank sum test, chi-squared test, or Fisher's exact test to compare means between exposed and referents. Associations between the tremor measures and UHg were evaluated using Spearman's correlation coefficients (exposed and referent subjects combined). Multivariate linear regression was conducted, adjusting for age, shift work, and smoking.

Results:
Incidence (%) of clinically diagnosed tremor, NS

- Any tremor
  - Referent: 3/22 (14)
  - Exposed: 7/43 (16)
- Rest tremor
  - Referent: 0/22 (0)
  - Exposed: 1/43 (2)
- Postural tremor
  - Referent: 3/22 (14)
  - Exposed: 5/43 (12)
- Intention tremor
  - Referent: 2/22 (9)
  - Exposed: 5/43 (12)

Spearman's correlation coefficients for:
Postural hand tremor in laser-based system

- Amplitude (RMS), NS
  - Dominant hand: -0.01
  - Non-dominant hand: -0.11
- Proportional power (4–6 Hz), p<0.05
  - Dominant hand: -0.07
  - Non-dominant hand: 0.26

Spearman's correlation coefficients for:
Postural hand tremor in CATSYS system

- Tremor intensity (RMS), NS
  - Dominant hand: 0.00
  - Non-dominant hand: 0.03
- Tremor index, NS
  - Dominant hand: -0.06
  - Non-dominant hand: 0.04

Static hand tremor in laser-based system (1st recording, 2nd recording)

- Amplitude (RMS), NS
  - Dominant hand: -0.05, -0.07
  - Non-dominant hand: -0.10, -0.17

Kinetic hand tremor in laser-based system

- Mean tracking error, NS
  - Dominant hand: 0.00
  - Non-dominant hand: 0.01

Hand tremor detected during rapid pointing movements

- Tremor, NS
  - Dominant hand: -0.03
  - Non-dominant hand: -0.09

Table A-5. Summary of the Principal Studies Examining Tremor in Workers Exposed to Elemental Mercury

						▪ Adjusted linear regression NS after exclusion of one outlier	

Interpretation: The outcome was designated as a NAEL because the weight of evidence did not support a significant difference in tremor between exposed and referents. Tremor based on all laser measurements was not significant. The only metric that was significant based on the CATSYS measurement was tremor index, which was different when means were assessed by the t-test, but was not significant when medians were assessed by the Wilcoxon rank sum test. Therefore, the UHg average in the workers (17.7 µg/g Cr) is a NAEL for tremor. The equivalent air concentration (4.90 µg Hg/m^3) was weighted by the number of subjects in the exposed group (43).

[a]See the *Calculation of Estimated Air Concentration* section below for how air concentrations were calculated.
[b]Reported as µmol Hg/mol creatinine and converted to µg Hg/g creatinine as follows: (µmol Hg/mol Cr x µg Hg/µmol Hg)/g Cr/mol Cr.

AEL = adverse-effect level; ANOVA = analysis of variance; CI = confidence interval; Cr = creatinine; MANOVA = multivariate analysis of variance; NAEL = no-adverse-effect level; NS = not significant; RMS = root mean square; SD = standard deviation; SE = standard error; UHg = urine mercury

Selection of the Point of Departure: The MRL was based on a 95% lower confidence limit of the weighted median estimated air concentration of 2.84 µg Hg/m^3, based on the seven principal studies.

Typically, the point of departure (POD) would be highest NAEL or lowest AEL. The problem with this approach being applied to the occupational worker tremor studies is that there is substantial overlap in reported NAELs and AELs. The overlap between the lower end of the AEL range and the NAEL range does not support selection of any single NAEL or AEL as a POD. As an alternative approach, the following was assumed:

1. A NAEL/AEL boundary exists and is located somewhere within the range of overlapping NAELs and AELs.
2. Each NAEL and AEL in this range represents an independent estimate of the NAEL/AEL boundary.
3. The best estimate of the NAEL/AEL boundary is the weighted median of the set of overlapping NAELs and AELs (weighted for study size which assumes greater confidence in estimates from larger studies).
4. The lower 95% confidence limit on the median was selected as the POD, to account for uncertainty in the estimated weighted median.

This approach avoids having to make a highly uncertain selection of a single study as the basis for the POD and, instead, utilizes information from multiple studies to identify an exposure that is most likely to be the NAEL/AEL boundary.

Overlapping NAELs and AELs include all AELs that are less than or equal to the highest NAEL for the outcome, plus all NAELs that are greater than or equal to the lowest AEL. For tremor, the highest NAEL is 8.74 µg Hg/m^3 (Boogaard et al. 1996) and the lowest reliable AEL is 4.90 µg Hg/m^3 (Wastensson et al. 2006, 2008). For selection of the studies to include in the estimate of the POD, all AELs that were <9 µg/m^3 and all NAELs that were >4 µg/m^3 were included in the calculation of the weighted mean. The NAELs and AELs for the principal studies that met the selection criteria are presented in Table A-6. Note

that the Anglen et al. (2015) study was omitted for the following reasons: (1) during the 32-year retrospective period, mean urine mercury levels declined from 20 to 2 µg Hg/L, making it difficult to assign a central estimate urine mercury level to the outcome; and (2) tremor outcome was self-reported. The Echeverria et al. (2005) study was omitted because of the extremely low AEL and low confidence in the reported mean urine mercury levels being representative of the steady state, given the expected highly intermittent exposures of dentists to mercury vapor.

Table A-6. NAEL and AEL Values for Studies Defining the NAEL/AEL Boundary for Tremor

Study	Population	Number of subjects	POD	Estimated air concentration (µg Hg/m^3)
Bast-Pettersen et al. 2005	Chloralkali workers	49	NAEL	4.57
Boogaard et al. 1996	Gas production	40	NAEL	8.74
Ellingsen et al. 2001	Chloralkali workers	47	NAEL	4.43
Langworth et al. 1992a	Chloralkali workers	85	NAEL	7.03
Wastensson et al. 2006, 2008	Chloralkali workers	43	NAEL	4.90
Chapman et al. 1990	Chloralkali workers	18	AEL	4.92
Fawer et al. 1983	Lamp and chloralkali workers	26	AEL	5.57
Median: 4.92 µg/m^3 (95% CI 3.02, 6.82)				
Weighted median: 4.92 µg/m^3 (95% CI 2.84, 7.00)				

AEL = adverse-effect level; CI = confidence interval; NAEL = no-adverse-effect level; POD = point of departure

For the principal studies, the unweighted median estimated air concentration is 4.92 µg Hg/m^3 (95% CI 3.02, 6.82) and the weighted median estimated air concentration is 4.92 µg Hg/m^3 (95% CI 2.84, 7.00). The 95% lower confidence limit of the weighted median is 2.84 µg Hg/m^3, which was selected as the POD for the MRL. Sensitivity of the POD to individual studies was tested by recomputing the POD after removing one of the studies. The POD was not highly influenced by removal of any single study. The mean of PODs calculated from censored data sets was 3.30 (range: 2.51–3.86).

Calculation of Estimated Air Concentration: Total mercury levels in urine (µg Hg/L or µg Hg/g creatinine) were used as the exposure metric for estimating human exposures (µg Hg/m^3) to mercury vapor. The urine biomarker is considered to be a more accurate reflection of mercury body burden than reported measurements of room air or breathing zone mercury concentrations, which were likely to be highly intermittent and variable. Non-occupational sources, including diet and mercury amalgam dental restorations, are likely to have contributed to the urinary mercury observed in the occupational studies that provide the basis for the chronic inhalation MRL. However, occupational exposures are likely to have been the dominant source of urinary mercury in the principal studies and support the use of urinary mercury for estimating air exposure concentrations. For example, it is unlikely that diet could account for the urinary mercury levels observed in the principal studies. Based on the urinary levels, the estimated inhaled mercury doses in the principal studies ranged from 1 to 2 µg/kg/day (approximately 70–140 µg/day for a 70-kg adult). By contrast, dietary mercury intakes have been estimated to range from 1 to 10 µg/day (see Section 5.6, General Population Exposure). Another possible contributor to urinary mercury in the occupational studies would have been mercury released from mercury amalgam restorations. However, total mercury absorption in a person having 13 restorations was estimated to be approximately 3 µg/day (range 0.6–9.3; see Section 5.6, General Population Exposure). Based on these estimates, it is likely that the dominant source of urinary mercury in the principal studies was

occupational exposure to mercury, predominantly inhalation of mercury vapor, given the working environments described in these studies.

Reported urine mercury levels (mean or median for the study population) were converted to equivalent exposure concentrations by applying a steady-state mass balance model which did the following: (1) converted the reported urine level (assumed to represent steady state) to an equivalent steady-state excretion rate (µg Hg/day/kg body weight), and (2) converted the steady-state excretion rate to an equivalent steady-state exposure (µg Hg/m^3). The assumption of steady state requires that the exposures were relatively constant for periods >272 days. This is the exposure duration that would achieve 95% of steady-state body burden, assuming a terminal elimination half-time of 62 days (Jonsson et al. 1999; Equation 1):

$$Time\ to\ steady\ state = \frac{\ln(1-0.95)}{k_e} \quad \text{Eq. (1)}$$

where 0.95 is the fraction of steady state and k_e is ln(2)/half-time.

An alternative to the steady-state mass balance model would be to implement the complete biokinetics model described by Jonsson et al. (1999). However, this is not needed for the epidemiology or clinical studies used in the derivation of the MRL because the steady-state assumption can be reasonably assured for the exposures in these study groups. However, it must be assumed that the mean or median urine levels in each study adequately represent the corresponding steady-state exposures. Although there is an unknown level of uncertainty in this assumption, the same assumption would also apply to the application of the complete biokinetic model.

The calculated exposure concentration represents the continuous exposure that would achieve a steady-state urine mercury level equal to the observed mean urinary mercury level. Calculated exposure concentrations based on urinary levels are likely to be less than measured air concentrations observed during the workday by at least a factor of 3, assuming an 8-hour workday, because continuous exposure is assumed to occur 7 days/week 24 hours/day.

Conversion of urine mercury levels to equivalent steady-state excretion rates. Urine mercury levels reported as µg Hg/g creatinine were converted to equivalent excretion rates (µg Hg/day) assuming a standard steady-state excretion rate of creatinine per kg of lean body mass. A more detailed example of this approach is given in ATSDR (2012) where it was used in the derivation of MRLs for cadmium. The rate of excretion of mercury (Hg_{ur}, µg Hg/day) was calculated as the product of the urinary level (µg Hg/g creatinine) and the urinary excretion rate of creatinine (g creatinine/day; Equation 2).

$$Hg_{ur} = Hg\ conc_{ur} \cdot Cr_{ur} \quad \text{Eq. (2)}$$

where Hg_{ur} is the rate of excretion of mercury (µg/day), $Hg\ conc_{ur}$ is the mercury concentration (µg/g creatinine) and Cr_{ur} is the rate of excretion of creatinine (g creatinine/day).

The rate of creatinine excretion (Cr_{ur}; g creatinine/day) was calculated from the relationship between lean body mass (LBM) and Cr_{ur} (Equation 3):

$$LBM = 27.2 \cdot Cr_{ur} + 8.58 \quad \text{Eq. (3)}$$

where the constants 27.2 and 8.58 are the sample size-weighted arithmetic mean of estimates of these variables from eight studies reported in Forbes and Bruining (1976). LBM was estimated as follows (ICRP 1981; Equation 4 and 5):

$$LBM\ of\ adult\ females = BW\ \cdot 0.85 \quad \text{Eq. (4)}$$

$$LBM\ of\ adult\ males = BW\ \cdot 0.88 \quad \text{Eq. (5)}$$

where the central tendency for adult body weight for males and females were assumed to be 70 and 58 kg for adult European/American males and females, respectively (ICRP 1981). Equation 5 predicts a lean body mass of 61.6 kg for a 70-kg male, which is similar to a mean lean body mass of 58.3 kg estimated for adults in the NHANES 1999–2006 (Lee et al. 2017c). These equations are applicable to higher average U.S. adult body weights (EPA 2011) because increases in average body weight in the United States derive primarily from increased body fat rather than increased average lean body mass (Hales et al. 2020). Urine mercury levels reported as µg Hg/L were converted to equivalent excretion rates (µg Hg/day) assuming a standard rate of urine output of 1.5 L/day (approximately 1 L/day/kg body weight; CDC 2002; Equation 6).

$$Hg_{ur} = Hg\ conc_{ur} \cdot V_{ur} \quad \text{Eq. (6)}$$

where $Hg\ conc_{ur}$ is the mercury concentration (µg/L) and V_{ur} is the urine output (L/day).

The validity of the above approach was evaluated based on data reported in Frumkin et al. (2001) that reported mean urine mercury levels in units of µg Hg/g creatinine and µg Hg/L for 147 exposed chloralkali workers and 132 referents. For workers, the mean urinary levels were 3.42 µg Hg/L and 2.76 µg Hg/creatinine. The model predicted 3.6 µg Hg/L for an assumed 2.76 µg Hg/g creatinine. For referents, the mean urinary levels were 3.12 µg Hg/L and 2.31 µg Hg/creatinine, and the model predicted 3.0 µg Hg/L for an assumed 2.31 µg Hg/g creatinine.

Conversion of mercury excretion rate (µg Hg/day/kg) to an equivalent steady-state exposure (µg Hg/m^3). Steady-state exposures corresponding to steady-state rates of urinary excretion of mercury were calculated based on a simplified steady-state mass balance implementation of the biokinetic models reported by Jonsson et al. (1999). The simplified model is given by Equation 7:

$$Hg_{air} = \frac{Hg_{ur}}{f_r \cdot f_u \cdot IR} \quad \text{Eq. (7)}$$

where Hg_{ur} is the mercury excretion rate (µg Hg/day) calculated from urine mercury levels reported as µg Hg/g creatinine or µg Hg/L as described above; f_r is the fraction of the inhaled dose initially retained in the body (0.80; Leggett et al. 2001); f_u is the fraction of the retained mercury excreted in urine (0.55; Jonsson et al. 1999); and IR is the inhalation rate (16 m^3/day; EPA 2011).

Results from the mass balance model were compared to the results obtained from the Jonsson et al. (1999) biokinetics model (implemented in MATLAB). Both models predicted 0.5 for the inhalation dose (µg Hg/day)/urine mercury excretion rate (µg Hg/day) ratio.

Predictions of dose conversion coefficients from the steady-state mass balance model. The model predicts the following steady-state relationships between exposure levels and urine mercury levels:

Steady-state air concentration (µg Hg/m^3) = steady-state urine mercury (µg Hg/g creatinine) × 0.258
Steady-state air concentration (µg Hg/m^3) = steady-state urine mercury (µg Hg/L) × 0.198

*Example of conversion of steady-state urine mercury levels (20.1 µg Hg/g creatinine; Fawer et al. 1983) to equivalent steady-state air mercury levels (5.57 µg Hg/m^3)***:**

Convert body weight (BW, kg) to lean body mass (LBM, kg; Equation 5):

$$LBM\ of\ adult\ males = BW\ \times 0.88$$

$$LBM = 70\ \times 0.88 = 61.6$$

where 0.88 is the proportionality coefficient for males at 70 kg body weight (ICRP 1981).

Convert lean body mass (LBM, kg) to rate of urinary excretion of creatinine (Cr_{ur}; g creatinine/day; Equation 3):

$$LBM = 27.2\ \times Cr_{ur} + 8.58$$

which rearranges to:

$$Cr_{ur} = \frac{LBM - 8.58}{27.2}$$

$$Cr_{ur} = \frac{61.6 - 8.58}{27.2} = 1.949$$

where the constants 27.2 and 8.58 are the sample size-weighted arithmetic mean of estimates of these variables from eight studies reported in (Forbes and Bruining 1976).

Convert urinary mercury (UHg_{cr}, 20.1 µg Hg/g creatinine, Fawer et al. 1983) to rate of urinary excretion of mercury (Hg_{ur}, µg/day; Equation 2):

$$Hg_{ur} = UHg_{cr} \times Cr_{ur}$$

$$Hg_{ur} = 20.1 \times 1.949 = 39.17$$

where f_r is the fraction of the inhaled dose initially retained in the body (0.80; Leggett et al. [2001]); f_u is the fraction of the retained mercury excreted in urine (0.55; Jonsson et al. 1999); and IR is the inhalation rate (16 m^3/day; EPA 2011).

Convert rate of urinary excretion of Hg (Hg_{ur}, µg Hg/day) to air concentration (Hg_{air}, µg Hg/m^3; Equation 7):

$$Hg_{air} = \frac{Hg_{ur}}{f_r\ \times\ f_u\ \times\ IR}$$

$$Hg_{air}\ = \frac{39.17}{0.80 \times 0.55 \times 16} = 5.57$$

Example of conversion of steady-state urine mercury levels (41.0 µg Hg/L; Boogaard et al. 1996) to equivalent steady-state air mercury levels (8.74 µg Hg/m^3):

Convert urinary mercury (UHg_L, 41.0 µg Hg/L, Boogaard et al. 1996) to rate of urinary excretion of mercury (Hg_{ur}, µg/day; Equation 6):

$$Hg_{ur} = UHg_L \times UFR$$

$$Hg_{ur} = 41.0 \times 1.5 = 61.50$$

where UFR is the urine flow rate (1.5 L/day; approximately 1 L/day/kg body weight; CDC 2002).

Convert rate of urinary excretion of Hg (Hg_{ur}, µg Hg/day) to air concentration (Hg_{air}, µg Hg/m^3; Equation 7):

$$Hg_{air} = \frac{Hg_{ur}}{f_r \times f_u \times IR}$$

$$Hg_{air} = \frac{61.50}{0.80 \times 0.55 \times 16} = 8.74$$

where f_r is the fraction of the inhaled dose initially retained in the body (0.80; Leggett et al. [2001]); f_u is the fraction of the retained mercury excreted in urine (0.55; Jonsson et al. 1999); and IR is the inhalation rate (16 m^3/day; EPA 2011).

Uncertainty Factor: The 95% lower confidence limit (LCL) of the weighted median of the seven principal studies (Table A-6) is divided by a total uncertainty factor (UF) of 10.

- 10 for human variability

Weighted Median$_{95\%LCL}$ ÷ UFs = MRL
2.84 µg Hg/m^3 ÷ 10 = 0.28 g Hg/m^3 ≈ 0.3 µg Hg/m^3

Other Additional Studies or Pertinent Information: A large number of studies in workers exposed to mercury vapor in various industries provide consistent evidence of the neurotoxicity of elemental mercury (see Section 2.16.2, Elemental Mercury—Epidemiological Studies, for citations). A few shorter-term studies in animals also demonstrate neurotoxicity in animals exposed as adults; observed effects include impaired motor function and damage to the central nervous system (Ashe et al. 1953; Fukuda 1971; Sørensen et al. 2000; Stankovic 2006). Additionally, several animal studies have reported neurodevelopmental effects including altered motor activity and altered learning (Danielsson et al. 1993; Fredriksson et al. 1992, 1996; Yoshida et al. 2018).

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Elemental mercury
CAS Number: 7439-97-6
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for elemental mercury.

Rationale for Not Deriving an MRL: No acute-duration oral studies in humans or animals were identified.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Elemental mercury
CAS Number: 7439-97-6
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for elemental mercury.

Rationale for Not Deriving an MRL: No intermediate-duration oral studies in humans or animals were identified.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Elemental mercury
CAS Number: 7439-97-6
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for elemental mercury.

Rationale for Not Deriving an MRL: No chronic-duration oral studies in humans or animals were identified.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mercury, inorganic salts (mercuric acetate, mercuric chloride, mercuric sulfide)
CAS Numbers: 1600-27-7, 7487-94-7, 1344-48-5
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for inorganic mercury salts.

Rationale for Not Deriving an MRL: No human or animal studies evaluating acute-duration inhalation exposure to inorganic mercury salts or other inorganic mercury compounds were identified. Therefore, an acute-duration inhalation MRL was not derived.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mercury, inorganic salts (mercuric acetate, mercuric chloride, mercuric sulfide)
CAS Numbers: 1600-27-7, 7487-94-7, 1344-48-5
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for inorganic mercury salts.

Rationale for Not Deriving an MRL: No human studies or animal studies evaluating intermediate-duration inhalation exposure to inorganic mercury salts were identified. Two studies in rats evaluated effects of inhalation exposure to mercuric oxide on neurological (Altunkaynak et al. 2019) and female reproductive systems (Altunkaynak et al. 2016). In rats exposed to 1 mg Hg/m^3 for 45 days (9 hours/day), cerebellar gliosis and perineuronal and perivascular vacuolization, reduced cerebellar volume, and decreased number and density of Purkinje cells were observed (Altunkaynak et al. 2019). Purkinje cells from treated animals showed irregular cellular boundaries, eosinophilic cytoplasm, and heterochromatic nuclei. In female rats exposed to 0.9 mg Hg/m^3 for 45 days (24 hours/day), significant ovarian damage was observed, including thickened tunica albuginea, increased fibrils within connective tissue, congested capillaries and blood vessels, thinned walls of large and dilated veins, fibrin deposits in veins, edema and maldeveloped follicles in the stroma, and irregular oocyte borders within follicles (Altunkaynak et al. 2016). Treated females also showed reduced ovary volume and decreased number of follicles. Both studies evaluated a single exposure level and other systems were not evaluated. Therefore, effects of inhalation exposure to inorganic mercury have not been sufficiently characterized to derive an intermediate-duration inhalation MRL for inorganic mercury salts or other inorganic compounds.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mercury, inorganic salts (mercuric acetate, mercuric chloride, mercuric sulfide)
CAS Numbers: 1600-27-7, 7487-94-7, 1344-48-5
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for inorganic mercury salts.

Rationale for Not Deriving an MRL: No human or animal studies evaluating chronic-duration inhalation exposure to inorganic mercury salts or other inorganic mercury compounds were identified. Therefore, a chronic-duration inhalation MRL was not derived.

Agency Contacts (Chemical Manager): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mercury, inorganic salts (mercuric acetate, mercuric chloride, mercuric sulfide)
CAS Numbers: 1600-27-7, 7487-94-7, 1344-48-5
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute
Provisional MRL: 0.002 mg Hg/kg/day ($2x10^{-3}$ mg Hg/kg/day; 2 µg Hg/kg/day)
Critical Effect: Renal effects
Reference: Dieter et al. 1992; NTP 1993
Point of Departure: $BMDL_{1SD}$ of 0.29 mg Hg/kg/day ($BMDL_{ADJ}$ of 0.21 mg Hg/kg/day)
Uncertainty Factor: 100
LSE Graph Key: 5
Species: Rat

MRL Summary: A provisional acute-duration oral MRL of 0.002 mg Hg/kg/day ($2x10^{-3}$ mg Hg/kg/day; 2 µg Hg/kg/day) was derived based on renal effects (increased relative kidney weight) in male rats exposed to mercuric chloride by gavage for 5 days/week for 16 days (Dieter et al. 1992; NTP 1993). The provisional MRL is based on a $BMDL_{1SD}$ of 0.29 mg Hg/kg/day adjusted to a $BMDL_{ADJ}$ of 0.21 mg Hg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from rats to humans, and 10 for human variability).

The acute-duration oral MRL based on mercuric chloride is expected to be protective for all inorganic mercury salts. Mercuric chloride is water soluble (see Section 3.1, Toxicokinetics) and the bioavailability of mercury salts is directly related to their solubility. Other mercuric salts are less soluble than mercury chloride and are expected to have lower oral bioavailability and, therefore, lower toxicity. For example, acute-duration oral LOAELs for mercuric sulfide and mercuric acetate range from 5 to 86 mg/kg/day (see Section 2.1, Table 2-3), compared to the LOAEL of 1.8 mg/kg/day observed in the critical study.

Selection of the Critical Effect: Effects associated with acute-duration exposure of humans to inorganic mercury is limited to accidental or intentional exposure to near-fatal or fatal doses. Therefore, human data are not suitable for derivation of an acute-duration oral MRL. Several acute-duration oral studies have been conducted in laboratory animals. To identify the critical effect, ATSDR focused on: (1) reported effects associated with clear biological significance, and (2) high-quality acute-duration studies including, at minimum, five animals. The most sensitive LOAELs meeting these criteria are summarized in Table A-7.

Table A-7. Select LOAELs for Acute-Duration Oral Exposure to Mercuric Chloride

		NOAEL/LOAEL (mg Hg/kg/day)			
Species (n)	Duration	NOAEL	LOAEL	System: Effect	Reference
Rat (n=5)	16 days (5 days/week)	0.923	1.8	***Renal:*** 17% increase in relative kidney weight	Dieter et al. 1992; NTP 1993[a]
Rat (n=6)	3 or 7 days	ND	3	***Reproductive:*** Decreased sperm number and motility; non-monotonic changes in serum testosterone	Boujbiha et al. 2009

Table A-7. Select LOAELs for Acute-Duration Oral Exposure to Mercuric Chloride

Species (n)	Duration	NOAEL/LOAEL (mg Hg/kg/day) NOAEL	LOAEL	System: Effect	Reference
Mouse (n=16)	2 weeks	ND	3.7	***Endocrine:*** ~17% increase in baseline plasma insulin and ~60% decrease in fasting plasma insulin; ~15% decrease in blood glucose and impaired glucose tolerance; apoptosis in pancreatic islet cells	Chen et al. 2012
Mouse (n=5)	16 days (5 days/week)	ND	4	***Renal:*** 19% increase in relative kidney weight	NTP 1993[a]
Hamster (n=3–10)	Once (GD 7)	2.5	5	***Developmental:*** Decreased crown-rump length	Gale 1974

[a]These 16-day studies were classified as acute-duration studies because exposure only occurred on 12 of 16 days.

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; n = number; ND = not determined; NOAEL = no-observed-adverse-effect level

Renal toxicity was selected as the critical effect following acute-duration oral exposure to inorganic mercury because it represents the lowest reliable LOAEL (Dieter et al. 1992; NTP 1993). There is a preponderance of evidence that the kidney is a sensitive target for inorganic mercury salts, with substantial mechanistic support. Observed effects in acute-duration studies include elevated kidney weight at doses >1 mg Hg/kg/day (Dieter et al. 1992; Kim et al. 2003; NTP 1993) that progressed to histopathological changes (protein casts, cellular casts, interstitial sclerosis, necrosis) at ≥7.4 mg Hg/kg/day (Dieter et al. 1992; Lecavalier et al. 1994; Nielsen et al. 1991; NTP 1993). Nephrotoxicity of inorganic mercury is characterized primarily by damage to the *pars recta* segment of the proximal tubule, with involvement of the proximal convoluted tubule and distal tubule in severe toxicity (Berlin et al. 2015; Zalups and Diamond 2005). Damage to the *pars recta* segment of the proximal tubule is consistent with localized uptake of mercury in the renal cortex and outer stripe of the outer medulla (Section 3.1.2). In the proximal tubule, early changes include loss of the brush border membrane, resulting in urinary excretion of brush border enzymes, such as ALP and GGT. As damage to the proximal tubule becomes more severe and progresses to necrosis, intracellular enzymes, such as AAP and NAG, are excreted in the urine, and renal function declines. Substantial evidence from animal studies shows dose- and duration-dependent related damage to the kidneys.

Selection of the Principal Study: The acute-duration oral study in male rats reported by Dieter et al. (1992) and NTP (1993) was selected as the principal study because it identified the lowest LOAEL for the critical effect (renal toxicity).

Summary of the Principal Study:

Dieter MP, Boorman GA, Jameson CW, et al. 1992. Development of renal toxicity in F344 rats gavaged with mercuric chloride for 2 weeks, or 2, 4, 6, 15, and 24 months. J Toxicol Environ Health 36(4):319-340. http://doi.org/10.1080/15287399209531642.

NTP. 1993. Toxicology and carcinogenesis studies of mercuric chloride (CAS no. 7487-94-7) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC: National Toxicology Program. NTP TR 408. NIH publication no. 91-3139.

Fischer 344 rats (5/sex/group) were administered mercuric chloride for 16 days (5 days/week) at doses of 0, 1.25, 2.5, 5, 10, or 20 mg $HgCl_2$/kg/day (equivalent to 0, 0.923, 1.8, 4, 7.4, or 15 mg Hg/kg/day) via gavage in deionized water. Body weights were measured and a complete necropsy was performed. Urinalysis was conducted in the control and 4 mg Hg/kg/day dose groups only. Organ weights were obtained for the brain, heart, kidney, liver, lung, and thymus. Histopathology was evaluated in all dose groups for kidney, stomach, preputial gland (males), and clitoral gland (females). Other organs were microscopically evaluated only in the high-dose group.

Two high-dose males died during the first week of exposure (exposure day 4 and 5). Body weight gains were significantly decreased by 17–18% at 7.4 mg Hg/kg/day and 30–41% at 15 mg Hg/kg/day. In females, final body weight was significantly decreased by 11% at 15 mg Hg/kg/day. Absolute and relative kidney weights were significantly increased by ≥17% in males at ≥1.8 mg Hg/kg/day and ≥28% in females at ≥4 mg Hg/kg/day. Decreases in other absolute organ weights in high-dose females is attributed to decreased body weight. Urinary ALP and AST were significantly elevated in males at 4 mg Hg/kg/day by approximately 80 and 83% (estimated from graphically presented data); these changes were not observed in females. No changes in urinary LDH or GGT were observed in males or females at 4 mg Hg/kg/day. Increased incidence and severity of acute renal necrosis was observed in males at ≥7.4 mg Hg/kg/day and in females at 15 mg Hg/kg/day. No histopathological findings in the stomach, preputial gland, or clitoral gland were reported.

Selection of the Point of Departure for the MRL: In order to identify the POD, BMD modeling was conducted for relative kidney weight data from the acute oral study in the rat (Dieter et al. 1992; NTP 1993). Male rat relative kidney weight data (Table A-8) were fit to all available continuous models in EPA's BMDS (version 3.2) using a BMR of 1 SD. Adequate model fit was judged by four criteria: goodness-of-fit statistics (chi-square p-value >0.1); visual inspection of the dose-response curve; BMDL that is not 10 times lower than the lowest non-zero dose; and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest BMDL values were selected as potential PODs when the difference between the BMDL estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) was chosen.

Table A-8. Relative Kidney Weights in Male Rats Exposed to Mercuric Chloride via Gavage 5 days/week for 16 Days

Dose level (mg Hg/kg/day)	Number of animals	Relative kidney weight (mg/g body weight)		
		Mean	Reported SE	Calculated SD
0	5	4.83	0.16	0.36
0.923	5	5.36	0.17	0.38
1.8	5	5.63[a]	0.10	0.22
4	5	5.74[a]	0.16	0.36
7.4	5	6.54[a]	0.46	1.03
15	5	6.89[a]	0.32	0.72

[a]Significantly different from control, p<0.05.

SD = standard deviation; SE = standard error

Source: Dieter et al. 1992; NTP 1993

For elevated relative kidney weight in male rats, the Exponential 4 and 5-degree and Hill models provided adequate fit to the data using non-constant variance. BMDLs were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Hill). The frequentist, restricted Hill model estimated a BMD_{1SD} and $BMDL_{1SD}$ of 0.64 and 0.29 mg Hg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-9 and the model fit for the selected model is shown in Figure A-1.

The $BMDL_{1SD}$ of 0.29 mg Hg/kg/day for increased relative kidney weight in male rats was selected as the POD for deriving a provisional MRL for acute-duration oral exposure to inorganic mercury salts.

Table A-9. Results from BMD Analysis (Nonconstant Variance) of Relative Kidney Weight in Male Rats Exposed to Mercuric Chloride via Gavage 5 Days/Week for 16 Days (Dieter et al. 1992; NTP 1993)

Model	BMD_{1SD} (mg Hg/kg/day)	$BMDL_{1SD}$ (mg Hg/kg/day)	Test 4 p-value[a]	AIC	Scaled residuals[b]	
					Dose below BMD	Dose above BMD
Exponential 2[c]			0.02	56.24	1.23	0.18
Exponential 3[c]			0.02	56.24	1.23	0.18
Exponential 4[c,]	0.75	0.37	0.27	50.10	-0.57	0.75
Exponential 5[c]	0.75	0.37	0.27	50.10	-0.57	0.76
Hill[c,d]	**0.64**	**0.29**	**0.29**	**49.98**	**-0.40**	**0.62**
Polynomial Degree 5[c]			0.04	54.41	1.28	-0.01
Polynomial Degree 4[c]			0.04	54.41	1.28	-0.01
Polynomial Degree 3[c]			0.04	54.41	1.28	-0.01
Polynomial Degree 2[c]			0.04	54.41	1.28	-0.01

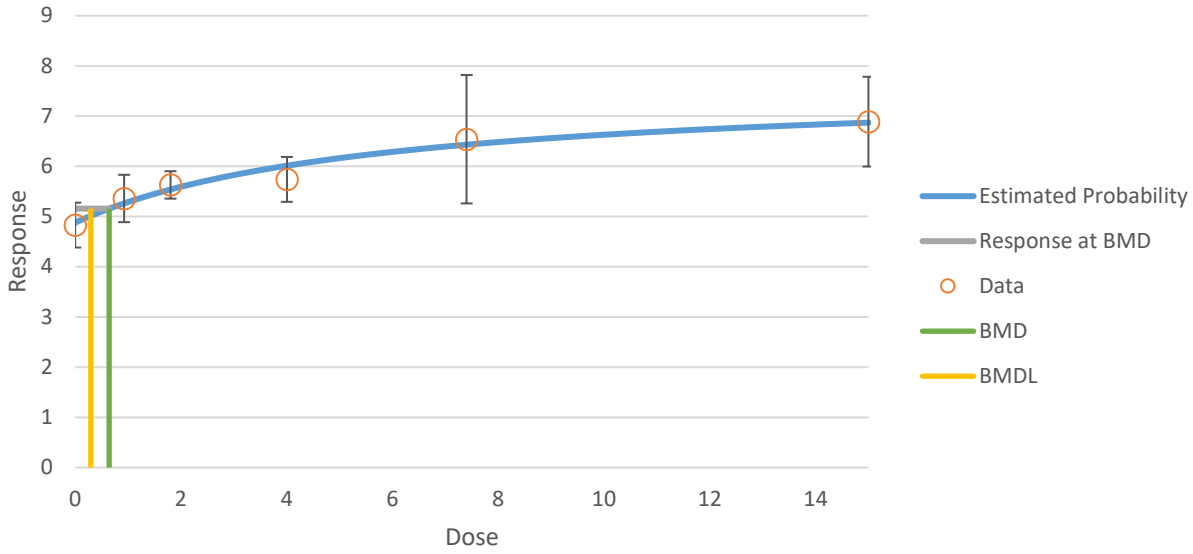
Table A-9. Results from BMD Analysis (Nonconstant Variance) of Relative Kidney Weight in Male Rats Exposed to Mercuric Chloride via Gavage 5 Days/Week for 16 Days (Dieter et al. 1992; NTP 1993)

Model	BMD_{1SD} (mg Hg/kg/day)	$BMDL_{1SD}$ (mg Hg/kg/day)	Test 4 p-value[a]	AIC	Scaled residuals[b]	
					Dose below BMD	Dose above BMD
Power[c]			0.04	54.41	1.28	-0.01
Linear			0.04	54.41	1.28	-0.01

[a]Values <0.1 fail to meet adequate fit.
[b]Scaled residuals at doses immediately below and above the BMD.
[c]Restricted model.
[d]Recommended model. There was an adequate fit to the variance when assuming nonconstant variance. The Exponential 4- and 5-degree and Hill models provided adequate fit to the data. BMDLs were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Hill).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control); NA = not applicable, goodness-of-fit test could not be performed

Figure A-1. Fit of Hill Model to Data for Relative Kidney Weight in Male Rats Exposed to Mercuric Chloride via Gavage 5 days/week for 16 Days (Dieter et al. 1992; NTP 1993)



Adjustment for Intermittent Exposure: The $BMDL_{1SD}$ was adjusted from intermittent exposure to account for a continuous exposure scenario:

$BMDL_{ADJ}$ = 0.29 mg Hg/kg/day ppm x (5 days/7 days) = 0.21 mg Hg/kg/day

Uncertainty Factor: The $BMDL_{ADJ}$ of 0.21 mg Hg/kg/day was divided by a total uncertainty factor of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

Provisional MRL = $BMDL_{ADJ}$ ÷ UFs
Provisional MRL = 0.21 mg Hg/kg/day ÷ (10x10)
Provisional MRL = 0.0021 mg Hg/kg/day ≈ 0.002 mg Hg/kg/day = 2 µg Hg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: There is strong evidence for adverse renal effects in laboratory animals following oral exposure to mercuric chloride. Findings in acute-duration studies in rats and mice exposed to mercuric chloride include increased relative kidney weight, proximal tubular damage, and acute renal necrosis (Dieter et al. 1992; Kim et al. 2003; Lecavalier et al. 1994; Nielsen et al. 1991; NTP 1993). Numerous intermediate-duration studies in mice and rats also report elevated kidney weight, markers of altered renal function or renal damage, histopathological changes, and nephropathy and/or nephrosis (see Table A-11, Renal Effects in Laboratory Animals Exposed to Oral Mercuric Chloride for Intermediate-Durations in the intermediate-duration inorganic mercury oral MRL worksheet for citations). Chronic-duration oral studies in rats and mice observed increased relative kidney weight and degeneration and atrophy of the proximal tubule, and increased incidence and/or severity of renal nephropathy (Dieter et al. 1992; NTP 1993). Kidney toxicity has been observed in human case studies of acute poisoning from ingestion of inorganic mercury compounds (Cappelletti et al. 2019).

Agency Contacts (Chemical Manager): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mercury, inorganic salts (mercuric acetate, mercuric chloride, mercuric sulfide)
CAS Numbers: 1600-27-7, 7487-94-7, 1344-48-5
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
Provisional MRL: 0.00001 mg Hg/kg/day ($1x10^{-5}$ mg Hg/kg/day; 0.01 µg Hg/kg/day)
Critical Effect: Renal effects
Reference: Apaydin et al. 2016
Point of Departure: LOAEL of 0.015 mg Hg/kg/day
Uncertainty Factor: 1,000
LSE Graph Key: 32
Species: Rat

MRL Summary: A provisional intermediate-duration oral MRL of 0.00001 mg Hg/kg/day ($1x10^{-5}$ mg Hg/kg/day; 0.01 µg Hg/kg/day) for inorganic mercury salts was derived based on renal effects (decreased renal function and histopathological changes) in rats exposed to mercuric chloride by gavage for 28 days (Apaydin et al. 2016). The provisional MRL is based on a LOAEL of 0.015 mg Hg/kg/day and a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from rats to humans, and 10 for human variability).

The intermediate-duration oral MRL based on mercuric chloride is expected to be protective for all inorganic mercury salts. Mercuric chloride is water soluble (see Section 3.1, Toxicokinetics) and the bioavailability of mercury salts is directly related to their solubility. Other mercuric salts are less soluble than mercury chloride and are expected to have lower oral bioavailability and, therefore, lower toxicity. For example, LOAELs for intermediate-duration oral exposure to mercuric sulfide, a poorly soluble salt, are approximately 3–380-fold greater than the corresponding LOAELs identified for mercuric chloride (Table A-10).

Selection of the Critical Effect: No epidemiological studies evaluating intermediate-duration oral exposure to mercuric salts were identified. Toxicity data for intermediate-duration oral exposure to mercuric chloride and mercuric sulfide are available from studies in animals; no intermediate-duration oral studies on other inorganic mercury salts were identified. The lowest NOAEL and LOAEL values reported for mercuric chloride and mercuric sulfide for each organ system are summarized in Table A-10.

Table A-10. Summary of Lowest LOAELs for Intermediate-Duration Oral Exposure to Mercuric Chloride and Mercuric Sulfide

		NOAEL/LOAEL (mg Hg/kg/day)			
Species	Duration	NOAEL	LOAEL	System: Effect	Reference
Mercuric chloride					
Rat	28 days	ND	0.015	***Renal:*** Decreased renal function and histopathological changes	Apaydin et al. 2016
Rat	21 days	ND	0.033	***Hematological:*** Decreased clotting time, 13% decrease in erythrocyte count, 5% decrease	Mahour and Saxena 2009

Table A-10. Summary of Lowest LOAELs for Intermediate-Duration Oral Exposure to Mercuric Chloride and Mercuric Sulfide

Species	Duration	NOAEL/LOAEL (mg Hg/kg/day) NOAEL	LOAEL	System: Effect	Reference
				in hemoglobin, and 17% increase in leukocyte count	
Rat	12 weeks	ND	0.07	***Cardiovascular:*** Transient increase in systolic blood pressure	Takahashi et al. 2000b
Rat	21 weeks	ND	0.07	***Hepatic:*** Decreased plasma HDL cholesterol and triglycerides	Takahashi et al. 2000b
Mouse	10 weeks	0.07	0.118	***Immunological:*** Polyclonal B-cell activation	Hultman and Nielsen 2001; Nielsen and Hultman 2002
Mouse	61–79 days	ND	0.18	***Reproductive:*** Decreased fertility index	Khan et al. 2004
Rat	45 days	ND	0.277	***Neurological:*** Impaired motor coordination and balance; apoptosis and loss of neurons and astrocytes in motor cortex; decreased motor activity; impaired learning and memory	Teixeira et al. 2014, 2018
Rat	7 weeks	ND	0.4	***Developmental (neurodevelopmental):*** Decreased peripheral sensory nerve conduction velocity	Huang et al. 2011
Rat	3 months	ND	2.2	***Endocrine:*** Impaired thyroid function	Goldman and Blackburn 1979
Mercuric sulfide					
Mouse	4 weeks	ND	6	***Endocrine:*** Decreased plasma T4 (28–41%)	Sin and Teh 1992
Mouse	4 weeks	ND	17	***Immunological:*** Altered T-cell populations in spleen	Son et al. 2010
Guinea pig	21 days	ND	86	***Neurological:*** Abnormal vestibular ocular reflex	Chuu et al. 2001b

HDL = high-density lipoprotein; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; T4 = thyroxine

For mercuric chloride, the most sensitive effect for intermediate-duration oral exposure is renal toxicity in rats, with the lowest LOAEL value of 0.015 mg Hg/kg/day; a NOAEL was not identified as only one dose level was tested in this study (Apaydin et al. 2016). The next lowest LOAEL of 0.033 mg Hg/kg/day was for hematological effects in rats (Mahour and Saxena 2009), and is approximately 2-fold higher than the LOAEL for renal effects. For mercuric sulfide, the lowest LOAEL identified was 6 mg Hg/kg body weight for endocrine effects in mice (Sin and Teh 1992). Available intermediate-duration oral studies on effects of mercuric sulfide did not evaluate renal effects. However, LOAEL values for mercuric sulfide

for endocrine, immunological, and neurological effects are greater than corresponding LOAELs for mercuric chloride by approximately 3-, 144-, and 380-fold, respectively. Therefore, an MRL based on mercuric chloride is expected to be protective for exposure to mercuric sulfide.

Renal effects, long established as a sensitive target for inorganic mercury salts, were selected as basis for derivation of the intermediate-duration oral MRL. Nephrotoxicity of inorganic mercury is characterized primarily by damage to the *pars recta* segment of the proximal tubule, with involvement of proximal convoluted tubules and distal tubule in severe toxicity (Berlin et al. 2015; Zalups and Diamond 2005). Damage to the *pars recta* segment of the proximal tubule is consistent with localized uptake of mercury in the renal cortex and outer stripe of the outer medulla (Section 3.1.2). In the proximal tubule, early changes include loss of the brush border membrane, resulting in urinary excretion of brush border enzymes, such as ALP and GGT. As damage to the proximal tubule becomes more severe and progresses to necrosis, intracellular enzymes, such as AAP and NAG, are excreted in the urine, and renal function declines. Substantial evidence from animal studies shows dose- and duration-dependent related damage to the kidneys. Renal effects observed in intermediate-duration oral studies in laboratory animals are summarized in Table A-11.

Table A-11. Renal Effects in Laboratory Animals Exposed to Oral Mercuric Chloride for Intermediate-Durations

Effect	Species	References
Increased relative kidney weight	Rats and mice	Atkinson et al. 2001; Dieter et al. 1983, 1992; Jonker et al. 1993; Khan et al. 2004; NTP 1993; Takahashi et al. 2000a, 2000b; Wildemann et al. 2015a
Markers of altered renal function or renal damage (increased serum levels of urea, uric acid, and creatinine; elevated urine protein and/or ketones)	Rats	Apaydin et al. 2016; Carmignani et al. 1992; Jonker et al. 1993; Takahashi et al. 2000a, 200b
Histopathological changes (including tubular dilation and glomerular lobulation, tubular damage and degeneration, necrosis)	Rats and mice	Apaydin et al. 2016; Boscolo et al. 1989; Carmignani et al. 1989, 1992; Jonker et al. 1993; NTP 1993
Nephropathy and/or nephrosis	Rats and mice	Dieter et al. 1983, 1992; Jonker et al. 1993; NTP 1993

Selection of the Principal Study: The Apaydin et al. (2016) study provided the lowest LOAEL observed for renal effects in intermediate-duration animal studies and was selected as the principal study.

Summary of the Principal Study:

Apaydin FG, Bas H, Kalender S, et al. 2016. Subacute effects of low dose lead nitrate and mercury chloride on kidney of rats. Environ Toxicol Pharmacol 41:219-224.

Groups of six Wistar rats (90 days old; sex not specified) were administered distilled water or 0.02 mg/kg mercuric chloride in distilled water by gavage daily for 28 days (equivalent to 0.015 mg Hg/kg/day). At the end of the 28-day exposure period, blood samples were obtained and analyzed for serum urea, uric acid, and creatinine levels. Kidneys were examined microscopically, and renal levels of the following

were determined: malondialdehyde, glutathione peroxidase (GPX), glutathione S-transferase (GST), superoxide dismutase (SOD), and catalase.

In rats treated with mercuric chloride, serum levels of urea, uric acid, and creatinine were significantly increased by 28, 54, and 17%, respectively, compared to controls, indicating decreased renal function. Histopathological assessment of the kidneys showed tubular dilation and glomerular lobulation compared to normal appearance in controls. Kidney activity of antioxidant enzymes, GPX, GST, SOD, and catalase were significantly decreased by approximately 31, 25, 32, and 41%, respectively, compared to controls (data presented graphically). Kidney malondialdehyde levels were significantly increased by approximately 69%, compared to controls (data presented graphically). Findings are consistent with oxidative stress and peroxidation of lipid membranes.

Selection of the Point of Departure for the MRL: The LOAEL of 0.015 mg Hg/kg/day for decreased renal function and histopathological alterations in the kidneys was selected as the POD for deriving a provisional MRL for intermediate-duration oral exposure to inorganic mercury salts. BMD modeling was not considered for this dataset, as only one dose level was tested in the study. Existing PBPK models were not suitable for extrapolation of inorganic mercuric mercury dosimetry between rats and humans.

Uncertainty Factor: The LOAEL of 0.015 mg Hg/kg/day was divided by a total uncertainty factor of 1,000:

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

Provisional MRL = LOAEL ÷ UFs
Provisional MRL = 0.015 mg Hg/kg/day ÷ (10x10x10)
Provisional MRL = 0.000015 mg Hg/kg/day ≈ 0.00001 mg Hg/kg/day = 0.01 µg Hg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: See *Selection of the Critical Effect* above for review of supporting evidence from intermediate-duration oral exposure studies in animals. In addition, acute- and chronic-duration oral studies in laboratory animals have observed renal toxicity. Findings in acute-duration studies in rats and mice exposed to mercuric chloride include increased relative kidney weight, proximal tubular damage, and acute renal necrosis (Kim et al. 2003; Lecavalier et al. 1994; Nielsen et al. 1991; NTP 1993). Chronic-duration oral studies in rats and mice observed increased relative kidney weight and degeneration and atrophy of the proximal tubule, and increased incidence and/or severity of renal nephropathy (Dieter et al. 1992; NTP 1993). Kidney toxicity has been observed in human case studies of acute poisoning from ingestion of inorganic mercury compounds (Cappelletti et al. 2019).

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mercury, inorganic salts (mercuric acetate, mercuric chloride, mercuric sulfide)
CAS Numbers: 1600-27-7, 7487-94-7, 1344-48-5
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for inorganic mercury salts.

Rationale for Not Deriving an MRL: Epidemiological studies of chronic oral exposure to inorganic mercury salts were not identified, and few studies have evaluated the effects of chronic-duration oral exposure to inorganic mercury salts in animals (Dieter et al. 1992; NTP 1993; Perry and Erlanger 1974). The lowest LOAELs identified for each study are summarized in Table A-12. The lowest LOAEL identified is 0.66 mg Hg/kg/day for increased systolic blood pressure in rats exposed to mercuric chloride in drinking water for 1 year, with a NOAEL of 0.33 mg Hg/kg/day (Perry and Erlanger 1974). The lowest chronic LOAEL is 44-fold higher than the lowest intermediate LOAEL of 0.015 mg Hg/kg/day that is the basis of the intermediate-duration oral MRL. Studies examining effects of chronic-duration oral exposure at lower levels were not identified. Therefore, a chronic-duration oral MRL was not derived for inorganic mercury.

Table A-12. Summary of LOAELs from Chronic-Duration Oral Studies in Laboratory Animals Exposed to Mercuric Chloride

		NOAEL/LOAEL[a] (mg Hg/kg/day)				
Species	Duration	NOAEL	LOAEL	sLOAEL	Effect	Reference
Rat	1 year	0.33 (F)	0.66 (F)	ND	Increased systolic blood pressure	Perry and Erlanger 1974
Rat	2 years	ND (M)	1.8 (M)	1.8 (M)	LOAEL: Decreased body weight, inflammatory lesions of the nasal mucosa, and epithelial hyperplasia of the forestomach sLOAEL: Decreased survival, degeneration and atrophy of the renal tubular epithelium	Dieter et al. 1992; NTP 1993
Mouse	2 years[b]	ND	4	ND	Nephropathy and increased kidney weight	NTP 1993

[a]Unless otherwise specified, NOAEL and LOAEL values are for both males and females.
[b]Continuous mating study.

F = female; LOAEL = lowest-observed-adverse-effect level; M = male; ND = not determined; NOAEL = no-observed-adverse-effect level; sLOAEL = serious lowest-observed-adverse-effect level

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methylmercury
CAS Number: 22967-92-6
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for methylmercury.

Rationale for Not Deriving an MRL: No human or animal studies evaluating acute-duration inhalation exposure to methylmercury were identified. Therefore, an acute-duration inhalation MRL was not derived.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methylmercury
CAS Number: 22967-92-6
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for methylmercury.

Rationale for Not Deriving an MRL: No human or animal studies evaluating intermediate-duration inhalation exposure to methylmercury were identified. Therefore, an intermediate-duration inhalation MRL was not derived.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methylmercury
CAS Number: 22967-92-6
Date: April 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for methylmercury.

Rationale for Not Deriving an MRL: No human or animal studies evaluating chronic-duration inhalation exposure to methylmercury were identified. Therefore, a chronic-duration inhalation MRL was not derived.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methylmercury
CAS Number: 22967-92-6
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for methylmercury.

Rationale for Not Deriving an MRL: No studies examining effects of acute-duration oral exposure to methylmercury in humans were identified. Numerous studies in laboratory animals have investigated effects of acute-duration oral exposure to methylmercury. Table A-13 lists the lowest reported NOAELs and LOAELs for acute toxicity endpoints. The lowest LOAEL of 0.008 mg Hg/kg/day identified the developing nervous system as the most sensitive target for acute-duration oral exposure (Bornhausen et al. 1980). The associated NOAEL is 0.004 mg Hg/kg/day.

Table A-13. Summary of Lowest NOAELs and LOAELs for Acute-Duration Oral Exposure to Methylmercury

		NOAEL/LOAEL (mg Hg/kg/day)			
Species	Duration	NOAEL	LOAEL	System: Effect	Reference
Rat	4 days (GDs 6–9)	0.004	0.008	***Developmental (neurodevelopmental):*** Impaired operant conditioning at 4 months	Bornhausen et al. 1980
Rat	14 days	ND	0.5	***Reproductive:*** Nonmonotonic sperm effects (decreased count and motility, increased abnormal); inflammatory foci and thickening of epithelium in prostate	Fossato da Silva et al. 2011, 2012
Rat	1–2 weeks	ND	0.7	***Neurological:*** Ultrastructural changes in dorsal root ganglia and cerebellum	Chang and Hartmann 1972a
Mouse	14 days	ND	1.6	***Endocrine:*** Altered glucose homeostasis; apoptosis in pancreatic islet cells	Chen et al. 2012
Rat	14 days	ND	1.9	***Body weight:*** Decreased body weight (~10%)	Chuu et al. 2007
Rat	14 days	0.93	2.8	***Renal:*** Increased relative kidney weight (18%)	Fossato da Silva et al. 2011
Rat	12 days	ND	4	***Musculoskeletal:*** Muscle weakness and wasting	Usuki et al. 1998
Mouse	14 days	ND	5.6	***Hepatic:*** Elevated total cholesterol	Moreira et al. 2012

Table A-13. Summary of Lowest NOAELs and LOAELs for Acute-Duration Oral Exposure to Methylmercury

		NOAEL/LOAEL (mg Hg/kg/day)			
Species	Duration	NOAEL	LOAEL	System: Effect	Reference
Rat	2 days	ND	12	***Cardiovascular:*** Decreased heart rate (10–18%)	Arito and Takahashi 1991

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

Several animal studies provide support for neurodevelopmental effects as the most sensitive target of acute-duration oral exposure to methylmercury. Studies observing neurodevelopmental effects at doses ≤0.5 mg Hg/kg/day (the lowest LOAEL for reproductive effects, the second most sensitive target of acute-duration oral exposure to methylmercury) are summarized in Table A-14. Two neurodevelop-mental studies reported similar LOAELs for neurodevelopmental effects: the Bornhausen et al. (1980) study in rats, with a LOAEL of 0.008 mg Hg/kg/day and the Montgomery et al. (2008) study in mice, with a LOAEL of 0.009 mg Hg/kg/day. The study in rats identified a NOAEL of 0.004 mg Hg/kg/day; however, the study in mice did not identify a NOAEL, as only one dose (0.009 mg Hg/kg/day) was tested.

Table A-14. Neurodevelopmental Effects in Laboratory Animals Exposed to Methylmercury Doses ≤0.5 mg Hg/kg/day for Acute Durations.

		NOAEL/LOAEL (mg Hg/kg/day)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Rat	4 Days, GDs 6–9	0.004	0.008	Impaired operant conditioning at 4 months	Bornhausen et al. 1980
Mouse	11 Days, GDs 8–18	ND	0.009	Impaired learning and memory, decreased motor activity and coordination in adult offspring	Montgomery et al. 2008
Mouse	5 Days, PNDs 29–33	ND	0.2	Impaired balance and motor coordination on PND 38	Bellum et al. 2007
Mouse	Once, PND 10	ND	0.37	Decreased motor activity and impaired learning and memory at 2–6 months of age	Fischer et al. 2008
Rat	4 Days, GDs 6–9	0.04	0.4	Increased startle response in adult offspring Effects at 4 mg Hg/kg/day: impaired swimming, impaired visual discrimination, decreased activity, and decreased habituation	Stoltenburg-Didinger and Markwort 1990

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level PND = postnatal day

The NOAEL of 0.004 mg Hg/kg/day in rats (Bornhausen et al. 1980) and the LOAEL of 0.009 mg Hg/kg/day in mice (Montgomery et al. 2008) were considered as possible PODs for an acute-duration oral MRL, as shown in Table A-15. Based on the NOAEL of 0.004 mg Hg/kg/day in rats and a total uncertainty factor of 100, the MRL would be 0.00004 mg Hg/kg/day (0.04 µg Hg/kg/day). Based on the LOAEL of 0.009 mg Hg/kg/day and a total uncertainty factor of 1,000, the MRL would be 0.000009 mg Hg/kg/day (0.009 µg Hg/kg/day). These acute-duration MRLs are less than the chronic-duration oral MRL for methylmercury of 0.1 µg Hg/kg/day based on data in humans. Therefore, an acute-duration oral MRL for methylmercury was not derived.

Table A-15. Possible Acute-Duration Oral Minimal Risk Levels (MRLs) for Methylmercury Based on Neurodevelopmental Effects

Species	MRL (µg Hg/kg/day)	Critical effect	Point of departure (mg Hg/kg/day)	Uncertainty factors	Reference
Rat	0.04	Impaired operant conditioning at 4 months	NOAEL: 0.004	100[a]	Bornhausen et al. 1980
Mouse	0.009	Impaired learning and memory, and decreased motor activity and coordination in adult offspring	LOAEL: 0.009	1,000[b]	Montgomery et al. 2008

[a]Total uncertainty factor = 100 (10 for extrapolation from rats to humans; 10 for human variability).
[b]Total uncertainty factor = 1,000 (10 for use of LOAEL; 10 for extrapolation from mice to humans; 10 for human variability).

LOAEL = lowest-observed-adverse-effect level; NOAEL = No-observed-adverse-effect level

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methylmercury
CAS Number: 22967-92-6
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for methylmercury.

Rationale for Not Deriving an MRL: In humans, intermediate-duration oral exposure to methylmercury occurred in Iraq in 1972–1973 as a result of widespread consumption of bread made from wheat that had been treated with a methylmercuric fungicide (Al-Mufti et al. 1976; Bakir et al. 1973; Clarkson et al. 1976). Blood mercury levels in poisoning cases measured approximately 65 days after exposure ranged from 10 to 3,000 µg Hg/L (Clarkson et al. 1976). Severe neurological and neurodevelopmental effects were observed in this population; therefore, findings in this population cannot be used to derive an intermediate-duration oral MRL for methylmercury.

Numerous studies in laboratory animals have investigated effects of intermediate-duration oral exposure to methylmercury. The lowest LOAELs for each system are summarized in Table A-16. The lowest dose of methylmercury tested in intermediate-duration oral studies was 0.0003 mg Hg/kg/day in rats exposed during pre-mating through PND 21 (Wild et al. 1997). At this dose, immunodevelopmental effects (enhanced lymphoproliferation in response to mitogens) were observed in offspring assessed on PND 84. This is the lowest LOAEL observed in intermediate-duration oral studies. The next lowest dose tested was 0.0004 mg Hg/kg/day in rats exposed for 8 weeks (Ortega et al. 1997a, 1997b); this dose is a LOAEL for immunological effects in adult rats (immune stimulation). The lowest LOAEL values for renal, neurological, and neurodevelopmental effects were 0.006, 0.0073, and 0.02 mg Hg/kg/day, respectively. Results of these studies indicate that the immune system is a sensitive target for methylmercury. Several animal studies provide support that the developing immunological system is the most sensitive target of methylmercury; studies are summarized in Table A-17. Immunodevelopmental effects have been observed at doses ranging from 0.0003 to 0.37 mg Hg/kg/day.

Table A-16. Summary of Lowest LOAELs for Intermediate-Duration Oral Exposure to Methylmercury

		NOAEL/LOAEL (mg Hg/kg/day)			
Species	Duration	NOAEL	LOAEL	System: Effect	Reference
Rat	14–16 weeks premating to PND 21	ND	0.0003	***Immunodevelopmental:*** Altered functional immune function (enhanced lymphoproliferation in response to mitogens) in PND 84 offspring	Wild et al. 1997
Rat	8 weeks	ND	0.0004	***Immunological:*** Immune stimulation followed by immune suppression at higher doses	Ortega et al.1997a, 1997b
Rat	8 weeks	ND	0.0004	***Endocrine:*** Increase in adrenocorticotrophic hormone	Ortega et al. 1997b

Table A-16. Summary of Lowest LOAELs for Intermediate-Duration Oral Exposure to Methylmercury

Species	Duration	NOAEL/LOAEL (mg Hg/kg/day) NOAEL	LOAEL	System: Effect	Reference
Rat	4 weeks	0.002	0.005	***Cardiovascular:*** Elevated systolic blood pressure and pulse pressure	Wildemann et al. 2015a
Rat	4 weeks	ND	0.006	***Renal:*** Elevated urinary creatinine	Wildemann et al. 2016
Mouse	2 months	0.00046	0.0073	***Neurological:*** Impaired memory	Bourdineaud et al. 2011
Rat	19 weeks[a]	0.0008	0.008	***Reproductive:*** No viable litters produced	Friedmann et al. 1998
Mouse	10–17 weeks premating through PNDs 21–70	ND	0.02	***Neurodevelopmental:*** Decreased motor activity and impaired hearing and motor coordination in offspring	Huang et al. 2011
Rabbit	14 weeks	0.05	0.49	***Body weight:*** Decreased body weight gain	Koller et al. 1977
Mouse	21 days	ND	5.6	***Hepatic:*** Elevated plasma total cholesterol	Moreira et al. 2012

[a]Rats were dosed 2 times/week.

LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day

Table A-17. Summary of LOAELs for Immunodevelopmental Effects in Animals Exposed to Oral Methylmercury for Intermediate Durations

Species	Duration	NOAEL/LOAEL (mg Hg/kg/day) NOAEL	LOAEL	Effect	Reference
Rat	14–16 weeks (premating through PND 21)	ND	0.0003	Altered functional immune endpoints (enhanced lymphoproliferation in response to mitogens) in PND 12 offspring	Wild et al. 1997
Rat	14–16 weeks (premating through PND 21)	ND	0.0006	Altered functional immune endpoints in PND 6–12 offspring (enhanced lymphoproliferation in response to mitogens; decreased NK cell activity)	Wild et al. 1997
Mouse[a]	5 weeks (GD 8 to PND 21)	ND	0.06	Cerebellar inflammation, attributed to autoimmune effects, at PNDs 21 and 70	Zhang et al. 2011

Table A-17. Summary of LOAELs for Immunodevelopmental Effects in Animals Exposed to Oral Methylmercury for Intermediate Durations

Species	Duration	NOAEL/LOAEL (mg Hg/kg/day) NOAEL	LOAEL	Effect	Reference
Rat	26 days (GD 6 to PND 10)	ND	0.08	Altered functional immune endpoints in PND 21–70 offspring (decrease in the primary KLH-specific IgG antibody response on PND 35)	Tonk et al. 2010
Mouse	15–16 weeks (10 weeks premating through PND 15)	ND	0.098	Alterations in functional immune endpoints (increased primary antibody response to a viral antigen) and thymocyte cell populations in PNDs 10–22 offspring	Thuvander et al. 1996
Rat	15 days (PNDs 1–15, via dam)	ND	0.37	13% decrease in relative spleen weight; altered immune function in offspring (decreased splenic lymphoproliferative response to mitogen)	Ilback et al. 1991
Rat	~15 weeks (11 weeks premating through GD 21)	ND	0.37	45% increase in WBCs in offspring on PND 15	Ilback et al. 1991
Rat	~17 weeks (11 weeks premating through PND 15)	ND	0.37	Altered immune function in offspring (increased thymic lymphoproliferative response to mitogen, decreased cell-mediated cytotoxicity)	Ilback et al. 1991

[a]Immune susceptible mouse strain.

GD = gestational day; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NK = natural killer; NOAEL = no-observed-adverse-effect level; PND = postnatal day WBC = white blood cell

If an intermediate-duration oral MRL was derived based on the lowest LOAEL of 0.0003 mg Hg/kg/day (0.3 µg Hg/kg/day) for immunodevelopmental effects and a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), the intermediate-duration oral LOAEL for methylmercury would be 0.0003 µg Hg/kg/day. This value is lower that the provisional chronic-duration oral MRL of 0.1 µg Hg/kg/day; therefore, an intermediate-duration oral MRL for methylmercury was not derived.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methylmercury
CAS Number: 22967-92-6
Date: April 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic
Provisional MRL: 0.1 µg Hg/kg/day
Critical Effect: Neurodevelopmental effects (decreased IQ)
Reference: Axelrad et al. 2007a, 2007b
Point of Departure: NAEL of 0.41 µg Hg/kg/day
Uncertainty Factor: 3
LSE Graph Key: 141
Species: Human

MRL Summary: A provisional chronic-duration oral MRL of 0.0001 mg Hg/kg/day (0.1 µg Hg/kg/day) was derived based on neurodevelopmental effects (decreased full-scale IQ) in humans chronically exposed to methylmercury from consumption of dietary fish (Axelrad et al. 2007a, 2007b). The provisional MRL is based on a NAEL of 0.00041 mg Hg/kg/day (0.41 µg Hg/kg/day) and a total uncertainty factor of 3 for human variability.

Selection of the Critical Effect: Studies conducted in animals (nonhuman primates and rodents) and human epidemiological studies provide strong support for the developing nervous system being the most sensitive target of methylmercury. In humans, severe neurodevelopmental effects (congenital Minamata disease) occurred in association with maternal ingestion of methylmercury in seafood (Harada 1995) and from ingestion of wheat contaminated with a methylmercury fungicide (Iraq outbreak) (Amin-Zaki et al. 1974). In both incidents, exposure levels were sufficient to produce severe neurological effects in adults. Studies of lower levels of prenatal exposures have largely focused on populations that consume large amounts of marine fish. In these populations, the dominant source of the mercury body burden derives from consumption of methylmercury in fish, providing a strong basis for use of blood or hair mercury as a biomarker of methylmercury exposure. Studies of general populations have also relied on biomarkers for assessing exposure; however, in these populations, blood and hair mercury will be more greatly affected by exposures to other forms of mercury, including mercury released from mercury amalgam dental restorations. Therefore, general population studies that estimated oral intake of methylmercury are stronger designs for the purpose of dose-response assessments of methylmercury.

Cognitive and neurosensory effects have been observed in association with prenatal exposures to methylmercury via maternal fish consumption. Consistent findings have been observed at relatively high exposure levels (e.g., Iraq outbreak, Minamata outbreak). However, results of studies that have explored lower exposure levels have been inconsistent. Some studies found improved function or no associations with mercury, and some studies found non-monotonic responses (e.g., declines at lower levels of exposure and improvements at higher levels). Differences in effect estimates may be due to differences in confounders and how they were controlled in models. These variables include fish intake and related nutritional factors (e.g., 3-omega polyunsaturated long-chain fatty acids), co-exposure to other contaminants (e.g., lead, PCBs), and social variables affecting child development. In addition, presence of genetic susceptibility factors (of lack thereof) may act as effect measure modifiers, impacting the associations observed between mercury and a health outcome.

Several high fish consuming populations have been studied to evaluate possible associations between prenatal mercury exposure and neurodevelopment. These include populations in the Amazon River basin,

Arctic Canada, Faroe Islands, North Island New Zealand, and Seychelle Islands. Studies conducted in the Faroe Islands, North Island New Zealand, and Seychelle Islands are particularly important because of several features: (1) prospective design; (2) relatively large sample populations in main cohort (approximately 700–1,000); (3) high quality assurance procedures for biomarker measurements; (4) multiple follow-ups at different ages; (5) multiple tests of cognitive and neurosensory performance that assessed a wide range of cognitive domains; (6) extensive exploration and control of confounding; (7) assessments of biomarker measurement error (Faroe Islands and Seychelle Islands studies); and (8) multiple analyses of the data, which included linear and non-linear regression, cross-sectional and longitudinal analyses, individual and aggregated outcome metrics, and BMD analyses. For each study, observed biomarkers of exposure (e.g., blood mercury) were converted to estimates of oral mercury doses and categorized as either an AEL if an adverse effect was observed or a NAEL if no adverse effect was observed (see Appendix E for definitions of AEL and NAEL).

Selection of the Principal Study: Neurodevelopmental outcomes from studies conducted on populations from the Faroe Islands, North Island New Zealand, and Seychelle Islands are summarized below. A summary of a meta-analysis that includes data from the Faroe Islands, North Island New Zealand, and Seychelle Islands is also described (Axelrad et al. 2007a, 2007b). In addition, detailed summaries of two studies evaluating neurodevelopmental outcomes in a large general population from Norway are included (Vejrup et al. 2016, 2018).

Faroe Islands study. The Faroe Islands study followed a prospective cohort of high fish and marine mammal consumers (n=1,022 mother-infant pairs, recruited 1986–1987) from age 2 weeks to 22 years. The primary methylmercury prenatal exposure metric was total mercury in cord blood, which was predominantly (>80%) methylmercury (Grandjean et al. 1992). The median cord blood mercury concentration was 24 µg Hg/L and the IQR (25^{th} to 75^{th} percentile range) was 13–40 µg Hg/L; approximately 25% of the cord mercury levels were >40 µg Hg/L (Grandjean et al. 1992). Cord blood mercury levels (µg Hg/L) were approximately 5 times maternal hair mercury levels measured at parturition with a median of 4.5 µg Hg/g, and an IQR of 2.5–7.7 (Grandjean et al. 1992). In most studies, depending on the outcome measured, outcome associations were adjusted for covariates: child age, sex, birth weight; breastfeeding; maternal age, alcohol, tobacco use, medical history; and caregiver general intelligence (Raven's Progressive Matrices). Other potential confounders were also explored (e.g., fish consumption, blood selenium, blood PCBs).

The study found associations between prenatal (cord) blood mercury and decreasing performance on tests of cognitive function assessed at age 7 years (Grandjean et al. 1997, 1998, 2003, 2014), 14 years (Debes et al. 2006; Julvez et al. 2010), and 22 years (Debes et al. 2016). The associations were not consistently observed in all tests of cognitive function. The associations tended to cluster into domains of fluid reasoning (e.g., identifying rules for visual similarities and differences), comprehension and knowledge (e.g., naming, word synonyms and antonyms), decision and reaction speed, and motor coordination (Debes et al. 2016). Latencies of brainstem auditory evoked potentials measured at age 7 or 14 years increased in association with increasing prenatal or child hair mercury levels (Grandjean et al. 1997; Murata et al. 2004a).

Exposure measurement error based on estimation of biomarker imprecision was estimated to exceed laboratory measurement error (Grandjean and Budtz-Jorgensen 2007; Grandjean et al. 2004b). The observed associations with cognitive test outcomes persisted after excluding subjects who had large variability in hair mercury levels during pregnancy (Grandjean et al. 2003). Findings from the Faroe Islands included:

- Postnatal hair mercury levels correlated with duration of breastfeeding, although breastfeeding was not a significant explanatory variable for cognitive test outcomes in the cohort (Grandjean et al. 1995; Jensen et al. 2005).

- Blood selenium levels correlated with blood mercury levels and whale consumption (Grandjean et al. 1992); however, prenatal selenium level (cord blood) was not a significant explanatory variable for cognitive test outcomes in the cohort (Choi et al. 2008b).
- Although cord blood PCB concentration correlated with blood mercury levels, associations between cord blood mercury levels and cognitive tests scores persisted after adjustment for cord blood PCB concentrations (Grandjean et al. 1997).
- Adjustment for cord serum omega-3 long-chain polyunsaturated fatty acids (LCPUFA) strengthened associations between prenatal mercury exposure and cognitive test scores or brainstem evoked potential latencies (Choi et al. 2008b; Yorifuji et al. 2013).

Additional details for the Grandjean et al. (1997, 1999) studies are summarized in Table A-18. These studies were included in the Axelrad et al. (2007a, 2007b) meta-analysis.

Table A-18. Summary of the Grandjean et al. (1997) and Grandjean et al. (1999) Studies of the Faroe Islands Population

Study type and population: Prospective study of birth cohort, follow-up at age 7 years (n=917)

Biomarkers:
BHg (geometric mean µg Hg/L, IQR)
Cord: 22.9 (13.4–41.3)
Child (7 years): 8.82 (4.8–18.2)

HHg (geometric mean µg Hg/g, IQR)
Maternal: 4.27 (2.6–7.7)
Child (12 months): 1.12 (0.69–1.88)
Child (7 years): 2.99 (1.7–6.1)

Estimated oral dose[a]: 0.34 µg Hg/kg/day (based on cord BHg)

Analysis: Data were analyzed using multiple regression analysis. Outcome associations were adjusted for age and sex for all analyses. Additional covariates included strabismus (abnormal eye alignment) and eye glasses (VEP); current middle ear infection (BAEP); height (postural sway), maternal cognitive function, maternal smoking and alcohol use, social background, and major medical risk factors such as low birth weight, small-for-date, history of head trauma and meningitis (neuropsychological tests); and child's acquaintance with computers and computer games (computer-assisted tests). Data from neuropsychological tests were also analyzed using the Peters-Belson approach. In this approach, any regression coefficients with p<0.1 in the lowest quartile of cord blood (<15 µg Hg/L) group were included in multiple regressing models for all children. By identifying potential confounders in the lowest quartile blood mercury group, rather than in the full cohort, this approach may provide a less biased estimate of the association between mercury exposure and outcomes in the presence of confounding.

Results[b]:
Adjusted regression coefficients between cord BHg and neurophysiological tests
- BAEPL at 40 Hz
  - I = 0.043, p=0.10
  - III = 0.053, p=0.06
  - V = 0.059, p=0.01
- VEPL at 15 minutes
  - N75 = 0.21, p=0.70
  - P100 = -0.75, p=0.33
  - N145 = -0.99, p=0.37

Peters-Belson regression coefficients between cord BHg and neuropsychological tests
- NES FTT
  - D hand =-1.18, p=0.03
  - ND hand = -0.37, p=0.47
  - Both hands = -1.86, p=0.08
- NES HECT = 0.033, p=0.20
- NES CPT
  - Missed response = 0.14, p=0.007
  - Reaction time = 38.2, p=0.0002

Table A-18. Summary of the Grandjean et al. (1997) and Grandjean et al. (1999) Studies of the Faroe Islands Population

- Postural sway
  - Eyes open = -0.04, p=0.90
  - Eyes closed = -1.54, p=0.09
  - Eyes open, on foam = -0.43, p=0.40
  - Eyes closed, on foam = -0.19, p=0.86
- HRV R-R interval: -0.39, p=0.29

Adjusted regression coefficients between cord BHg and neuropsychological tests

- WISC-R
  - Digit span[c] = -0.27, p=0.05
  - Similarities[c] = -0.05, p=0.90
  - Block design[c] = -0.17, p=0.11
- CVLT
  - Learning = -1.25, p=0.12
  - Short-term[c] = -0.57, p=0.02
  - Long-term = -0.55, p=0.05
  - Recognition = -0.29, p=0.15
- BNT
  - No cues[c] = -1.77, p=0.0003
  - Cues = -1.91, p=0.0001
- BVMGT
  - Copy error[c] = 0.67, p=0.15
  - Reproduction = -0.25, p=0.10
- NES FTT
  - D hand = -1.10, p=0.05
  - ND hand = -0.39, p=0.46
  - Both hands = -1.67, p=0.14
- NES HECT = 0.034, p=0.19
- NES CPT
  - Missed response = 0.12, p=0.02
  - Reaction time = 40.3, p=0.001
- TPT (D hand) = -14.3, p=0.63
- NVAPMS
  - Positive moods = 2.61, p=0.31
  - Negative moods = -0.04, p=0.99
- WISC-R
  - Digit span[c] = -0.27, p=0.05
  - Similarities[c] = 0.14, p=0.70
  - Block design[c] = -0.25, p=0.02
- CVLT
  - Learning = -1.30, p=0.11
  - Short-term[c] = -0.63, p=0.009
  - Long-term = -0.64, p=0.02
  - Recognition = -0.28, p=0.15
- BNT
  - No cues[c] = -1.66, p=0.0007
  - Cues = -1.82, p=0.0002
- BVMGT
  - Copy error[c] = 1.04, p=0.03
  - Reproduction = -0.16, p=0.31
- TPT (D hand) = -18.8, p=0.60
- NVAPMS
  - Positive moods = 2.39, p=0.34
  - Negative moods = 0.17, p=0.94

Adjusted regression coefficients between cord BHg and neuropsychological tests in low exposure children only (maternal HHg <10 µg Hg/g)

- WISC-R
  - Digit span[c] = -0.31, p=0.05
  - Similarities[c] = 0.65, p=0.15
  - Block design[c] = -0.13, p=0.27
- CVLT
  - Learning = -1.55, p=0.10
  - Short-term[c] = -0.74, p=0.009
  - Long-term = -0.56, p=0.08
  - Recognition = -0.22, p=0.34
- BNT
  - No cues[c] = -1.42, p=0.01
  - Cues = -1.57, p=0.005
- BVMGT
  - Copy error[c] = 0.71, p=0.19
  - Reproduction = -0.43, p=0.02
- CBCL
- NES FTT
  - D hand = -0.68, p=0.29
  - ND hand = -0.13, p=0.83
  - Both hands = -0.62, p=0.63
- NES HECT = 0.033, p=0.28
- NES CPT
  - Missed response = 0.21, p=0.0005
  - Reaction time = 46.9, p=0.0003

Table A-18. Summary of the Grandjean et al. (1997) and Grandjean et al. (1999) Studies of the Faroe Islands Population

		• TPT (D hand) = -11.3, p=0.76 • NVAPMS o Positive moods = 3.66, p=0.20 o Negative moods = 1.83, p=0.51

[a]See *Calculations* for how oral mercury doses were calculated.
[b]Interpretation of neurobehavioral test scores:
Age of crawling, sitting, or walking: increase = delay in development
BVMGT: higher score = lower performance
BNT: higher score = higher performance
CTRS: higher score = higher behavioral problems
CVLT: higher score = higher performance
Digit span: higher score = higher performance
NES CPT: longer response time = lower performance
NES FTT: higher score = higher performance
NES HECT: higher score = higher performance
Neurologic optimality score: higher score = higher performance
NVAPMS: higher score = more negative mood
Postural sway: higher score = lower performance
RSPM: higher score = lower performance
Spatial span: higher score = higher performance
ST-BT block design: higher score = higher performance
ST-BI copying: higher score = higher performance
WFRT: higher score = higher performance
WISC-R: higher score = higher performance
WJTA: higher score = higher performance
WMS: higher score = higher performance
[c]Metric included in the meta-analysis by Axelrad et al. (2007a, 2007b).

BAEPL = brain steam auditory evoked potential; BAEPL = brain steam auditory evoked potential latencies; BHg = blood mercury; BNT = Boston Naming Test; BVMGT = Bender Visual Motor Gestalt Test; CBCL = Child Behavior Checklist; CPT = Continuous Performance Task; CVLT = California Verbal Learning Test; FTT = Finger Tapping Test; HECT = Hand-Eye Coordination Test; HHg = hair mercury; HRV R-R = Heart Rate Variability of electrocardiogram RR interval; IQR = interquartile range; NES = Neurobehavioral Evaluation System; NVAPMS = Nonverbal Analogue Profile of Mood States; TPT = Tactual Performance Test; VEPL = visual evoked potential; VEPL = visual evoked potential latencies; WISC-R = Weschler Intelligence Scale for Children, Revised

New Zealand study. The New Zealand study followed a prospective cohort to age 6 years (Kjellstrom et al. 1989). The original cohort consisted of 10,930 children and mother pairs recruited in 1978. Consumption of marine fish was the major contributor to methylmercury exposure in this population. The prenatal exposure metric was the average total mercury in maternal hair during pregnancy. A subset of 935 high consumer subjects was selected based on consumption ≥4 fish meals per week. Hair mercury levels in this group ranged from 6 to 86 µg Hg/g. From the ≥4 fish meals per week group, a subset of 73 high consumers was selected based on hair mercury level >6 µg Hg/g, from which 38 were tested at age 4 years, along with a set of 31 matched referents from mothers who consumed no more than one fish meal per week and matched for maternal ethnic group, age, residence time in New Zealand, tobacco smoking, and child birth date and sex. Assessment of neurodevelopmental outcomes occurred at age 4 and 6 years. At age 4 years, children were assessed for performance on the DDST (function, language, and personal-social behavior), Sheridan-Gardiner Letter Matching Test or Miniature Toy Test (vision), and tactile sensory function (touch, temperature), and parents were surveyed with a questionnaire on child health and neurological signs (Kjellstrom et al. 1986). The OR for abnormal or questionable scores on the DDST at age 4 years (n=31, relative matched referents) was 6.5 ($p<0.005$). Performance of high exposure children on vision and sensory function tests were not different from matched referents.

At age 6 years, 61 children in the high exposure group were re-evaluated, along with a set of three referent groups (n=58–60), each matched with the high exposure group for maternal ethnic group, age, residence time in New Zealand, tobacco smoking, and child birth date and sex (Kjellstrom et al. 1989). The geometric mean maternal hair mercury level was 8.3 µg Hg/g (range 6–86 µg Hg/g) in the high exposure group. Geometric mean hair mercury levels in the three referent groups ranged from 2.0 to 4.5 µg Hg/g. Children were assessed for cognitive performance, academic attainment, language development, motor coordination, intelligence, and behavior. Language development was assessed from performance on the TOLD (phonology, syntax, semantics) and Peabody picture vocabulary test (word knowledge). Intelligence was assessed using the McCarthy Scales for Children's Abilities (MSCA) and WISC. Increased maternal hair mercury was associated with lower scores on the TOLD spoken language quotient and WISC full-scale IQ and McCarthy perceptual scale. When the high exposure group (Group 1) was split into two maternal hair mercury categories, 6–<10 or ≥10 µg Hg/g, a larger fraction of variance in the TOLD and WISC tests was explained by that higher hair mercury category. Performance on the TOLD spoken language quotient was inversely associated with the hair mercury in lower category only (6–<10 µg Hg/g), whereas performance on both the TOLD spoken language quotient and WISC full scale were inversely associated with hair mercury in the higher category (≥10 µg Hg/g). Children scored as having an abnormal DDST at age 4 years had lower WISC full-scale IQ scores at age 6 years. Additional details of the Kjellstrom et al. (1989) study, which is included in the Axelrad et al. (2007a, 2007b) meta-analysis, are provided in Table A-19.

Table A-19. Summary of the Kjellstrom et al. (1989) Study of the North Island, New Zealand Population

Study type and population: Prospective study of birth cohort, follow-up at age 6 (n=238; 61 with high mercury exposure [maternal fish consumption ≥4 meals per week and HHg >6 µg Hg/L]) and matched referents from three referent populations (n=57 per group)

Biomarkers:
Maternal HHg (geometric mean µg Hg/g, range)
High mercury: 8.3 (6–86)
Referent 2 (≥4 fish meals/week): 4.5 (3–5.99)
Referent 3 (≥4 fish meals/week): 2.0 (0.1–2.99)
Referent 4 (≤3 fish meals/week): 2.0 (0.1–2.99)

Estimated oral dose[a]: 0.62 µg Hg/kg/day (based on high mercury group)

Analysis: Data were analyzed using robust weighted multiple regression analysis. This approach can decrease potential bias from outlier observations. Outcome associations were adjusted for significant covariates; variables explored included: maternal ethnic group, age, smoking and alcohol consumption, residence time in New Zealand, social class, language spoken at home, siblings, duration of breastfeeding, and child sex and birth weight, maturity at birth, and Apgar score.

Results[b]:
Adjusted regression coefficients between HHg (>6 µg Hg/g) and measures of intelligence

- WISC-R (FSIQ)[c] = -4.41, p=0.019
- WISC-R (PIQ)[c] = -3.79, p=0.072
- MSCA (perceptual scale)[c] = -4.23, p=0.0034

Adjusted regression coefficients between HHg (>6 µg Hg/g) and measures of language development

- TOLD[c] = -5.48, p=0.0064

Table A-19. Summary of the Kjellstrom et al. (1989) Study of the North Island, New Zealand Population

Adjusted regression coefficients between HHg (>6 µg Hg/g) and measures of motor coordination
• MSCA (motor scale) = -2.36, p=0.074

[a]See *Calculations* for how oral mercury doses were calculated.
[b]Inverse associations indicate declining performance.
[c]Metric included in the meta-analysis by Axelrad et al. 2007a, 2007b.

HHg = hair mercury; FSIQ = Full-Scale Intelligence Quotient; MCSA = McCarthy Scale of Children's Abilities; PIQ = Performance Intelligence Quotient; TOLD = Test of Language Development; WISC-R = Wechsler Intelligence Scales for Children, Revised

Seychelle Islands study. The Seychelle Islands study followed a prospective cohort of high fish consumers (n=779 mother-infant pairs, recruited 1989–1990) from age 6 months to 24 years. The primary methylmercury exposure metric was the average maternal gestational hair mercury level. Methylmercury accounted for >80% of total mercury in hair (Cernichiari et al. 1995). Annual median maternal hair mercury levels measured over the period 1986–1989 ranged from 5.9 to 8.2 µg Hg/g; the highest observed value was 36 µg Hg/g (Cernichiari et al. 1995). The main cohort, followed from age 6 months and later, had a median prenatal maternal level of 5.9 µg Hg/g (range 0.5–26.7 µg Hg/g) (Myers et al. 1995). Approximately half of the maternal hair mercury levels were ≤6 µg Hg/g, while the highest 15% (approximately 95 women) were >12 µg Hg/g; therefore, the power to discern significant associations was higher at hair mercury levels <12 µg Hg/g. Outcome associations were adjusted for covariates that included (in most studies): child sex, birth weight, birth order, gestational age, medical history and breastfeeding; maternal age, alcohol and tobacco use, and medical history; parental education, caregiver general intelligence (Raven's Progressive Matrices), family income, family language, home learning, and social stimulation (HOME score).

The Seychelle Islands has not found consistent evidence for associations between prenatal exposure (maternal hair mercury) and neurodevelopmental outcomes at any age studied thus far. This conclusion is supported by cross-sectional follow-ups of the cohort from ages 6.5 months to 24 years (Davidson et al. 1995, 1998, 1999, 2008a, 2010, 2011; Huang et al. 2005; Myers et al. 1995, 1997, 2000, 2003; Orlando et al. 2014; van Wijngaarden et al. 2009, 2013, 2017), longitudinal analyses of individual outcome metrics (Axtell et al. 1998; Davidson et al. 1998; Myers et al. 1997), and longitudinal analysis of metrics of global cognition based on aggregation of outcome metrics (Davidson et al. 2006a). Accounting for error in measuring hair mercury levels (and other covariates) had no appreciable effect on dose-response models assessed at 66 months (Huang et al. 2003). Although linear regression models consistently found no association between exposure (maternal or child hair mercury) and cognitive development, nonlinear models of cognitive test scores suggested that performance improved or declined in association with prenatal maternal hair mercury or child hair mercury, depending on the hair level (Axtell et al. 1998, 2000; Davidson et al. 1998, 2006a; Huang et al. 2005, 2007, 2018; Myers et al. 1997, 2003). For some outcomes, performance declined at lower hair mercury levels (e.g., ≤7 µg Hg/g), but improved at higher levels, and, for some outcomes, the opposite pattern was observed. At age 66 months, lower performance was not evident in a subgroup of the cohort that had a mean hair mercury level of 15.3 µg Hg/g (>85th percentile) (Davidson et al. 1998). It is uncertain if these nonlinear patterns reflect actual dose-level effects, differential statistical power across the hair mercury range, or, possibly, random outcomes from the numerous (>20) tests evaluated (Axtell et al. 2000; Davidson et al. 2006b; Huang et al. 2005, 2007). Age of walking increased with increasing prenatal maternal hair mercury over the range 1–7 µg Hg/g, however; the effect size was <1 day and the association was not evident at higher levels of hair mercury (Axtell et al. 1998). Aggregating scores of cognitive performance into metrics of global

cognitive function (Davidson et al. 2006a) or dichotomizing test scores into a binomial metric (benchmark response) also revealed no associations in cognitive development and prenatal maternal hair mercury below 20 µg Hg/g (Crump et al. 2000; van Wijngaarden et al. 2006, 2009). Associations between exposure and cognitive function were modified by an interaction with maternal omega-3 fatty acid status, a source of negative confounding through fish consumption (Strain et al. 2008, 2012, 2021). Study details for the Myers et al. (2003) studies are summarized in Table A-20. These studies were included in the Axelrad et al. (2007a, 2007b) meta-analysis.

Table A-20. Summary of the Myers et al. (2003) Study of the Seychelle Islands Population

Study type and population: Prospective study of birth cohort, follow-up at age 9 years (n=643 of 779 in cohort)

Biomarkers:
Maternal HHg (mean µg Hg/g, SD)
6.9 (4.5)

Estimated oral dose[a]: 0.51 µg Hg/kg/day (based on mean maternal HHg)

Analysis: Data were analyzed using multiple regression analysis. Outcome associations were adjusted for sex, examiner, family resource scale, family status (number of biological parents in the home), Henderson early learning process scale, child's age at testing, child's medical history of IUGR or head circumference >2 SD from normal, maternal age, home observation for measurement of the environment (HOME) score, caregiver intelligence, socioeconomic status, and hearing.

Results[b]:

Adjusted regression coefficients (95% CI for a 10 µg Hg/g change in HHg) for measures of general intelligence, cognition and achievement

- WISC-III FSIQ[c] = -0.13 (-3.3, 0.7), p=0.20
- CVLT
  - Short[c] = 0.013 (-0.1, 0.3), p=0.19
  - Long = 0.011 (-0.1, 0.3), p=0.28
- BNT[c] = -0.012 (-1.0, 0.8), p=0.79
- WJTA
  - LWR = 0.19 (-5.8, 9.6), p=0.62
  - AP = -0.057 (-3.5, 2.4), p=0.71

Adjusted regression coefficients (95% CI for a 10 µg Hg/g change in HHg) for measures of motor, perceptual motor, and memory

- VMI[c] = -0.010 (-2.4, 2.2), p=0.93
- BOT = 0.093 (-0.2, 2.0), p=0.10
- HAPDT = -0.010 (-0.5, 0.3), p=0.60
- Grooved peg board
  - D hand = 3.3×10^{-5} (91.4, 98.1), p=0.08
  - ND hand, male = 6.5×10^{-5} (101.7, 112.9), p=0.01
  - ND hand, female = -2.5×10^{-5} (100.0, 111.3), p=0.34

Adjusted regression coefficients (95% CI for a 10 µg Hg/g change in HHg) for measures of attention and behavior

- CPT
  - Reaction time = -0.13 (-4.4, 1.8), p=0.41
  - Attention = -0.0063 (-2.1, 2.0), p=0.95
  - Risk taking = 0.11 (-3.1, 5.4), p=0.60
- CBCL = -0.031 (-2.3, 1.7), p=0.76
- CTRS = -0.0067 (49.4, 54.1), p=0.004

Adjusted regression coefficients (95% CI for a 10 µg Hg/g change in HHg) for measures of motor, perceptual motor, and memory

- Trail making
  - A = 0.0037 (32.5, 37.6), p = 0.33
  - B = 0.0067 (79.1, 96.0), p=0.17
- FTT
  - D hand = -0.050 (-1.5, 0.5), p=0.34
  - ND hand = 0.016 (-0.6, 1.0), p=0.69
- WRAML[c] = -0.021 (-0.8, 0.4), p=0.48

Table A-20. Summary of the Myers et al. (2003) Study of the Seychelle Islands Population

- FTT
  - o D hand = -0.050 (-1.5, 0.5), p=0.34
  - o ND hand = 0.016 (-0.6, 1.0), p=0.69
- WRAML[c] = -0.021 (-0.8, 0.4), p=0.48

[a]See *Calculations* for how oral mercury doses were calculated.
[b]Interpretation of neurobehavioral test scores:
Age of talking or walking: increase = delay in development
Barkley ADHD: higher score = lower performance
BNT: higher score = higher performance
BOT: higher score = higher performance
BVMGT: higher score = lower performance
CANTAB: higher score = higher performance
CVLT: higher score = higher performance
FTII: higher score = higher performance
BSID IBR: higher score = higher performance
BSID MDI: higher score = higher performance
BSID PDI: higher score = higher performance
BVMGT: higher score = lower performance
CBCL: higher score = lower performance
CDI: higher score = higher performance
CELF-5: higher score = higher performance
CTRS: higher score = lower performance
CVLT: higher score = higher performance
DDST: milestones evaluated against a standard; below standard = delayed development
DSA: higher score = higher performance
Finger tapping: higher score = higher performance
GPB: higher score = lower performance
HAPDT: higher score = higher performance
KBIT-2: higher score = higher performance
MSCA: higher score = higher performance
PLS: higher score = higher performance
SCQ: higher score = higher performance
SRS-2: higher score = higher performance
Stroop interference: higher score = higher performance
TSRSS: higher score = higher performance
VEXP: higher score = higher performance
WJTA: higher score = higher performance
WRAML: higher score = higher performance
[c]Metric included in the meta-analysis by Axelrad et al. (2007a, 2007b).

AP = applied problems; BNT = Boston Naming Test; BOT = Bruininks-Oseretsky Test of Motor Proficiency; CBCL = Child Behavior Checklist; CI = confidence interval; CPT = Continuous performance task; CTRS = Connors' Teacher Rating Scale (hyperactivity index); CVLT = California Verbal Learning Test; D = dominant; FSIQ = full-scale intelligence quotient; FTT = Finger Tapping Test; HAPDT = Haptic Discrimination Test; HHg = hair mercury; HOME = Home Observation Measurement of the Environment; IUGR = intrauterine growth retardation; LWR = letter word recognition; ND = non-dominant; SD = standard deviation; VMI = Visual Motor Integration; WJTA = Woodcock-Johnson Test of Achievement; WISC-III = Wechsler Intelligence Scales for Children, 3rd ed.; WRAML = Wide Range Assessment of Memory and Learning

Meta-analysis of Faroe Islands, North Island, New Zealand, and Seychelles Islands studies. Two meta-analyses of the populations from the Faroe Islands, North Island, New Zealand, and Seychelles Islands have been reported (Axelrad et al. 2007a, 2007b; Cohen et al. 2005; Ryan 2008). In the more recent analysis, Axelrad et al. (2007a, 2007b) converted regression slopes for several cognitive test scores measured in each study into an IQ point scale (Axelrad et al. 2007a, 2007b). The meta estimate for the

effect size was -0.18 IQ points per increase of 1 µg Hg/g hair (95% CI -0.378, -0.009). The meta-analysis is described in detail in the *Summary of the Principal Study* section. Ryan (2008) reported a sensitivity analysis of the meta-slope from Axelrad et al. (2007a, 2007b).

Cohen et al. (2005) used a similar analytical approach as Axelrad et al. (2007a, 2007b) in a meta-analysis of the Faroe Islands, North Island, New Zealand, and Seychelles Islands studies. However, Cohen et al. (2005) included results from a wider selection of cognitive tests. The meta estimate from Cohen et al. (2005) was an average decrease of 0.043 SDs in cognitive performance per increase of 1 µg Hg/g maternal hair. For a SD of 15 IQ points, the meta estimate corresponds to an equivalent change in IQ of 0.7 points per 1 µg Hg/g hair, with a plausible range of 0 to 1.5 points per 1 µg Hg/g hair (Cohen et al. 2005).

The Axelrad et al. (2007a, 2007b) meta-analysis was selected as the principal study over the Cohen et al. (2005) because bounds on the meta-estimate from the Cohen et al. (2005) meta-analysis were wider and included zero. A likely contributor to this difference was the inclusion of a wider selection of outcomes in the Cohen et al. (2005) metal-analysis.

Norwegian Mother and Child Cohort Study. In addition to the above studies of high fish consumers, a large prospective study of a general population found associations between dietary fish mercury intake and language proficiency (Vejrup et al. 2016, 2018, Table A-21). This study examined a birth cohort consisting of 46,750 mother-infant pairs recruited during the period 1999–2008 with outcomes measured at age 3 years (Vejrup et al. 2016) and 5 years (Vejrup et al. 2018). Dietary intake of mercury from fish consumption was estimated in each mother based on outcomes of a food frequency questionnaire completed during pregnancy and a survey of mercury levels in fish consumed by Norwegians (Jenssen et al. 2012). Median fish consumption was estimated to be 32 g/day. Median mercury intake from consumption of fish was estimated to be 0.14 µg Hg/kg/week. The 90th percentile was 0.29 µg Hg/kg/week (Vejrup et al. 2016). Estimation of dietary intakes of mercury in fish (which is dominated by methylmercury) precluded reliance on biomarkers as dose metrics for methylmercury exposure. The study evaluated language proficiency and communication skills using parent-reported questionnaires. This study found associations between increasing dietary intake of mercury in fish with decreasing performance on language proficiency tests administered at age 3 and 5 years. These associations persisted after adjustment for known important confounders related to fish consumption, including fish consumption rate (adjustment strengthened the association with mercury), 3-omega LCPUFA consumption, and exposure to PCBs (Vejrup et al. 2016). The language outcomes associated with mercury intake (>0.29 µg Hg/kg/week) were described as "unintelligible speech" on the Dale and Bishop Grammar Rating and "weak communication development" on the Ages and Stages Communication Scale.

In a follow-up at age 5 years, children were assessed with three outcome tests: Ages and Stages Communication Scale, Speech and Language Assessment Scale, and Twenty Statements about Language-Related Difficulties. At age 5 years, in the full cohort (n=38,297) among women who consumed <400 g fish/week, both fish consumption and mercury intake were associated with improvement of scores (negative error scores) in the Ages and Stages Communication Scale and Speech and Language Assessment Scale. When the analysis was confined to matched siblings (n=7,404), dietary fish mercury intake at the 90th percentile level (>3.18 µg Hg/day) was associated with decreasing performance on the Speech and Language Assessment Scale but not on the Ages and Stages Communication Scale or Language-Related Difficulties scale. No associations were observed with mid-pregnancy maternal blood mercury concentrations in a subcohort of the main cohort (2,239 subjects) in which blood mercury levels were measured (median 1.0 µg Hg/L; range 0, 14 µg Hg/L) (Vejrup et al. 2018). These results suggest that fish intake was a confounding variable in this study (correlation between dietary fish mercury intake and dietary seafood intake was 0.88) and may have attenuated associations between dietary methyl-mercury intake and delays in attainment of language skills. The absence of an association with maternal

blood mercury may represent variance in blood mercury levels that is unrelated to dietary methylmercury intake (e.g., mercury from amalgam restorations).

Table A-21. Summary of the Vejrup et al. (2016, 2018) Studies of the Norwegian Population

Study: Vejrup et al. 2016

Study type and population: Prospective cohort of mother-infant pairs, follow-up at age 3 years (n=46,750)

Estimated oral dose: 0.041 µg Hg/kg/day (based on 90th percentile weekly intake)

- Maternal dietary mercury intake from fish (median):
  - 1.3 µg Hg/day
  - 0.14 µg Hg/kg/week
- 90th percentile:
  - 2.6 µg Hg/day
  - 0.29 µg Hg/kg/week

Analysis: Maternal methylmercury was estimated based on fish intake reported in an FFQ administered mid-pregnancy. Outcomes evaluated were performance on the Dale Bishop Grammar Rating and Ages and Stages communication scale (ASQ). ORs were calculated to assess risk in children with high mercury exposure, defined as >90th percentile (>2.64 µg Hg/day, >0.29 µg Hg/kg/week), compared to children with mercury exposure <90th percentile. ORs were adjusted for parity, maternal education, paternal education, pre-pregnancy BMI, bilingual parents, and age of child when reporting language development. Additional models were further adjusted for intake of lean and oily fish, n-3 LCPUFA from diet, n-3 LCPUFA from supplements, and dioxin and PCB exposures.

Results:

Adjusted OR (95% CI) between high prenatal methylmercury exposure (>90th percentile) and language development for Dale and Bishop Grammar rating (n=46,750)

- Complete grammar (reference): 1
- Low grammar: 1.01 (0.93, 1.10)
- Moderate delay: 1.06 (0.88, 1.26)
- Unintelligible speech: 2.22 (1.31, 3.72)
- Severe delay: 1.04 (0.69, 1.57)

Further adjusted for intake of lean and oily fish

- Unintelligible speech: 3.02 (1.47, 6.21)

Adjusted OR (95% CI) between high prenatal MeHg exposure (>90th percentile) and communication development (ASQ, n=45,332)

- Normal skills (reference): 1
- Weak skills: 1.33 (1.03, 1.70)

Further adjusted for intake of lean and oily fish

- Weak skills: 1.46 (1.07, 2.00)

Table A-21. Summary of the Vejrup et al. (2016, 2018) Studies of the Norwegian Population

Study: Vejrup et al. 2018

Study type and population: Prospective cohort of mother-infant pairs, follow-up at age 5 years (n=38,581)

Biomarker: Maternal BHg 1.03 µg Hg/L (median; n=2,239)

Estimated oral dose[a]: 0.049 µg Hg/kg/day (based on 90th percentile adjusted for 65 kg body weight)

- Maternal dietary mercury intake from fish
  - Median: 0.15 µg Hg/kg/week
  - 90th percentile: 3.18 µg Hg/week

Analysis: Outcomes evaluated were performance on the Speech and Language Assessment Scale, Ages and Stages communication scale, and Twenty Statements about Language-Related Difficulties. Data were analyzed using multiple regression analysis. Outcome associations were adjusted for maternal age, education, parity, pre-pregnancy BMI, Hopkins Symptom Checklist-5 (SCL-5), total energy intake, eicosapentaenoic acid and docosahexaenoic acid (DHA) from total diet and/or supplement. A sibling fixed-effect analysis was also conducted.

Results:

Adjusted regression coefficients (95% CI) between maternal BHg and measures of language and communication (n=2239), NS

- ASQ: -0.02 (-0.1, 0.03)
- Language 20: 0.01 (-0.03, 0.05)
- SLAS: -0.01 (-0.1, 0.03)

Adjusted regression coefficients (95% CI) between dietary seafood mercury intake >400 g/week and measures of language and communication (n=4375), NS

- ASQ: 0.1 (-0.1, 0.4)
- Language 20: 0.31 (-0.01, 0.6)
- SLAS: -0.17 (-0.4, 0.1)

Adjusted regression coefficients (95% CI) between maternal seafood intake >400 g/week and measures of language and communication (n=38,297), $p<0.05$

- ASQ: -0.06 (-0.1, -0.01)
- Language 20: -0.05 (-0.1, -0.01)
- SLAS: -0.07 (-0.1, -0.03)

Adjusted regression coefficients (95% CI) between >90th percentile maternal dietary mercury intake and measures of language and communication in sibling fixed effect analysis (n=647)

- ASQ: 0.03 (-0.1, 0.1), NS
- Language 20: 0.02 (-0.1, 0.1), NS
- SLAS: 0.1 (0.01, 0.2), $p<0.05$

[a]See *Calculations* for how oral mercury doses were calculated.

ASQ = Ages and Stages Communication Scale; BHg = blood mercury; BMI = body mass index; CI = confidence interval; DHA = docosahexaenoic acid; FFQ = food frequency questionnaire; Language 20 = Twenty Statements about Language-Related Difficulties; NS = not specified; OR = odds ratio; SLAS = Speech and Language Assessment Scale

Given the variable outcomes within and across the Faroe, New Zealand, and Seychelles studies of high fish consumers, selection of a single population as the basis for the MRL was not considered an ideal approach. Instead, the Axelrad et al. (2007a, 2007b) meta-analysis was considered a better representation of the weight of evidence from the three high fish consumer studies. The meta-analysis was selected over the Norwegian Mother and Child Cohort Study (Vejrup et al. 2016, 2018) as the principal study after weighing strengths and weaknesses of both studies (Table A-22). The key strength of the Axelrad et al. (2007a, 2007b) meta-analysis is that it included outcomes from multiple tests of cognitive performance from three independent prospective studies (approximately 1,800 subjects) after transforming the data into a global metric of full-scale IQ, which can be more readily generalized than individual test scores. The analysis included a test of language proficiency (New Zealand study, Test of Language Development). Language development was also evaluated in the Norwegian Mother and Child Cohort Study, using a different set of tests (Ages and Stages Communication, Dale Bishop Grammar Rating, Speech and Language Assessment Scale) (Vejrup et al. 2016, 2018). The studies included in the meta-analysis also provided biomarkers of exposure in each individual subject, which is likely to have decreased exposure misclassification inherent to using data from dietary recall and national data on mercury concentrations in recalled fish meals, as was used in the Norwegian Mother and Child Cohort Study.

Table A-22. Strengths and Weaknesses of Axelrad et al. (2007a, 2007b) and Vejrup et al. (2016, 2018) for Establishing a Point of Departure for the Chronic Oral MRL for Methylmercury

Study	Strengths	Weaknesses
Axelrad et al. 2007a, 2007b meta-analysis of Faroes, New Zealand, and Seychelles studies of high fish consumers	• Utilized and weighted data from three independent prospective studies (total number ~1,800) • Direct measure of individual subject exposure from biomarker (hair mercury) • Subjects were high fish consumers, which strengthens association between biomarkers and exposure to methylmercury • Included multiple tests of cognitive performance scaled to equivalent IQ points • Language proficiency included as an outcome metric • Sensitivity analysis indicated a narrow range for the effect size estimate • Effect size reported as linear regression β that can be transformed into a *di minimis* change in the biomarker (or equivalent dose); e.g., change in dose above background dietary level associated with a 1 point change in IQ	• Pharmacokinetic model needed to transform biomarkers to equivalent mercury intakes • To derive MRL, must select magnitude of change in IQ that corresponds to an IQ POD • Effect size may have been depressed by negative confounding with nutritional benefits from high fish consumption

Table A-22. Strengths and Weaknesses of Axelrad et al. (2007a, 2007b) and Vejrup et al. (2016, 2018) for Establishing a Point of Departure for the Chronic Oral MRL for Methylmercury

Study	Strengths	Weaknesses
Vejrup et al. 2016, 2018 Norwegian Mother and Child Cohort Study of general population	• Large prospective study • Larger size of cohort (~47,000 subjects) of general population, with lower fish consumption than high consumption studies	• Associations with dietary methylmercury intake were based on a semi-quantitative food survey and national data on fish mercury concentrations, rather than biomarkers of mercury exposure in individual subjects • The association with dietary methylmercury intake predicted lower language proficiency at age 3 years, whereas the association predicted higher proficiency at age 5 years • In a subset of the cohort with measurements of individual subject blood mercury levels, there was no association between language proficiency and blood mercury • Outcome evaluation was limited language proficiency, which was assessed using a parental self-report survey of their children and not by unbiased experts

CI = confidence interval; FFQ = food frequency questionnaire; IQ = intelligence quotient; MRL = Minimal Risk Level; POD = point of departure

Summary of the Principal Study:

Axelrad DA, Bellinger DC, Ryan LM, et al. 2007a. Dose-response relationship of prenatal mercury exposure and IQ: An integrative analysis of epidemiologic data. Environ Health Perspect 115(4):609-615. http://doi.org/10.1289/ehp.9303.

Axelrad DA, Bellinger DC, Ryan LM, et al. 2007b. Supplemental material: Dose-response relationship of prenatal mercury exposure and IQ: An integrative analysis of epidemiologic data. Environmental health perspectives. https://ehp.niehs.nih.gov/action/downloadSupplement?doi=10.1289%2Fehp.9303&file=9303_suppl.pdf. March 18, 2021.

Ryan L. 2008. Combining data from multiple sources, with applications to environmental risk assessment. Statist Med 27:698-710. http://doi.org/10.1002/sim.3053.

The meta-analysis included outcomes from the Faroe Islands study at age 7 years, New Zealand study at age 6 years, and Seychelles Islands study at age 9 years (Axelrad et al. 2007a, 2007b). Outcomes

included in the analysis are summarized in Table A-23. Additional study details are provided in Table A-24.

Table A-23. Cognitive Performance Tests[a] Included in Meta-analysis of Faroe Islands, New Zealand, and Seychelle Islands Studies

Cognitive domain	Faroe Islands	New Zealand	Seychelles Islands
General intelligence	WISC-R (full-scale IQ)	WISC-R (full-scale IQ) WISC-R (performance IQ)	WISC-III (full-scale IQ)
Verbal learning and memory	CVLT (short term)	NE	CVLT (short term)
Visual-motor integration	BGT	NE	VMI
Visual memory	NE	NE	WRAML (design memory)
Confrontational naming	BNT (no cues)	NE	BNT (total score)
General development	NE	MSCA (perceptual)	NE
General verbal skills	NE	TOLD (spoken language coefficient)	NE
Visual memory	NE	NE	WRAML (design memory)

[a]Regression slopes derived in these tests were rescaled to full-scale IQ.

BGT= Bender Gestalt Test; BNT = Boston Naming Test; CVLT = California Verbal Learning Test; IQ = intelligence quotient; MSCA = McCarthy Scales of Children's Abilities; NE = not evaluated; TOLD = Test of Language Development; VMI = Visual–Motor Integration; WISC-R = Wechsler Intelligence Scales for Children, Revised; WISC-III = Wechsler Intelligence Scales for Children, 3rd ed.; WRAML = Wide Range Assessment of Memory and Learning

Table A-24. Summary of the Axelrad et al. (2007a, 2007b) Meta-Analysis Study

Study type and population: Meta-analysis of prospective birth cohorts in Faroe Islands (N=917), Seychelles Islands (N=643), and New Zealand (N=237; Grandjean et al. 1997, 1999; Kjellstrom et al. 1989; Myers et al. 2003) with follow-up at age 7, 9, and 6 years, respectively

Estimated oral dose: 0.41 µg Hg/kg/day (based on 1 IQ point per 5.56 µg Hg/kg/day; -0.18 IQ points per µg Hg/g hair)

Analysis: Bayesian hierarchical modeling integrated data from the three study populations. A primary mercury-IQ dose-response analysis model was built using metrics with coefficients that were rescaled to be interpretable in the same scale as FSIQ estimates. FSIQ for the Faroe Islands data was estimated by combining three WISC subsets (Digit Span, Similarities, Block Design), which Axelrad et al. (2005) concluded would provide valid estimates of full-scale IQ.

Table A-24. Summary of the Axelrad et al. (2007a, 2007b) Meta-Analysis Study

Results:

Rescaled regression coefficients (SE) for cognitive endpoints from the Faroe Islands

- WISC-R (FSIQ) = -0.124 (0.057)
- BGT = -0.104 (0.083)
- BNT = -0.260 (0.086)
- CVLT = -0.169 (0.093)

Rescaled regression coefficients (SE) for cognitive endpoints from the Seychelle Islands

- WISC-III (FSIQ) = -0.17 (0.130)
- CVLT = 0.19 (0.144)
- BNT = -0.038 (0.144)
- WRAML = -0.109 (0.15)
- VMI = -0.013 (0.15)

Rescaled regression coefficients (SE) for cognitive endpoints from New Zealand

- WISC-R (FSIQ) = -0.50 (0.268)
- WISC-R (PIQ) = -0.51 (0.310)
- TOLD = -0.56 (0.282)
- MSCA = -0.80 (0.315)

Estimated IQ decrement per µg Hg/g maternal hair mercury (95% CI), at different *R* levels (ratio of study-to-study variability relative to end point-to-endpoint variability)

- 4.0 = -0.188 (-0.398, -0.010)
- 3.5 = -0.182 (-0.390, -0.007)
- 3.0 = -0.180 (-0.378, -0.009)
- 2.5 = -0.183 (-0.384, -0.017)
- 2.0 = -0.178 (-0.371, -0.012)
- 1.5 = -0.168 (-0.360, -0.003)
- 1.0 = -0.165 (-0.338, -0.015)
- 0.5 = -0.160 (-0.321, -0.026)
- 0.25 = -0.151 (-0.283, -0.033)

BGT= Bender Gestalt Test; BNT = Boston naming test; CVLT = California Verbal Learning Test; FSIQ = Full-Scale Intelligence Quotient; IQ = intelligence quotient; MSCA = McCarthy Scales of Children's Abilities; PIQ = performance intelligence quotient; SE = standard error; TOLD = Test of Language Development; VMI = Visual Motor Integration; WISC-R = Wechsler Intelligence Scales for Children, Revised; WISC-III = Wechsler Intelligence Scales for Children, 3rd ed.

Linear regression parameters, slope (β) and intercept (Int) for associations between mercury and scores on tests of cognitive performance were rescaled to IQ by adjusting the parameters by a scaling factor. The scaling factor was the ratio of the SDs for the full-scale IQ (SD_{IQ}) and the test (SD_{test}), $SD_{IQ}/SDtest$, where SD_{IQ} was assigned a value of 15. The adjusted parameters were calculated as follows:

$$\beta^* = \beta \times SD_{IQ}/SD_{test}$$
$$Int^* = Int \times SD_{IQ}/SD_{test}$$
$$SE^* = SE \times SD_{IQ}/SD_{test}$$

where β^* and Int^* are the rescaled values for the slope and intercept, respectively.

The Faroe Islands parameters required additional factors. A factor of 10 adjusted the Faroe Islands log-normal model to a normal model (Budtz-Jorgensen et al. 2004). A factor of 200 µg Hg/kg per µg Hg/L was used to convert Faroe Islands cord blood mercury levels to hair mercury (Budtz-Jorgensen et al. 2004).

Meta-β estimates were weighted by study-to-study variance (σ^2) in β and endpoint-to-endpoint variance endpoint outcomes, using a Bayesian approach with exploratory values for the variance ratio R ($\sigma^2_{study}/\sigma^2_{endpoint}$). The meta estimate for the effect size was -0.18 IQ points per µg Hg/g hair (95% CI -0.378, -0.009). Ryan (2008) conducted a sensitivity analysis of the Axelrad et al. (2007a, 2007b) meta-β to varying correlations between error (standard errors) of different outcomes measured in the same

study. The analysis supports the estimate of the meta-β estimated by Axelrad et al. (2007a, 2007b). Increasing error correlation was predicted to decrease the estimated β. The range in the estimated β was -0.18 to -0.20 IQ points per µg Hg/g hair. The low end of the range, -0.18, was predicted when correlation of within study outcome error was ignored.

To determine the change in hair mercury levels, one IQ point is divided by the meta estimate of 0.18 µg Hg/g hair (as seen in Equation 6, below). Because the meta-β is a parameter of a linear regression equation, the change in IQ points is predicted to be proportional to the change in hair mercury levels near the center of the distribution of the hair mercury scale. The central estimates of hair mercury levels for the three contributing studies ranged from approximately 4 to 9 µg Hg/g hair. Therefore, the proportional relationship can be expected for hair mercury levels within this range. The corresponding estimates of the change in hair mercury level corresponding to a specific change in IQ are shown in Table A-25 (see the Calculations section for equation used to convert change in IQ or change in hair mercury). As can be ascertained from Table A-25, a change in hair mercury of 5.56 ug Hg/g hair is predicted to result in a 1-point decrease in IQ.

Table A-25. Estimates of the Change in Hair Mercury Level Corresponding to a Specific Change in IQ

Change in IQ (points)	Change in hair mercury (µg Hg/g)
-1	5.56
-2	11.1
-3	16.7
-4	22.2
-5	27.8

Selection of the Point of Departure for the MRL: The POD selected for derivation of the chronic-duration oral MRL for methylmercury is 5.56 µg Hg/g hair. This value is the change in hair mercury level that corresponds to a decrease of 1 point in full-scale IQ, based on the meta-β of -0.18 IQ points per 1 µg Hg/g hair (see *Calculations*). A decrease in full-scale IQ of ≤1 point is considered to be a NAEL.

Loss of IQ has been used as a metric for assessing the health burden of neurotoxicants, including methylmercury (Bellanger et al. 2013; Bellinger 2012; Bellinger et al. 2019). While IQ losses ranging from 1 to 5 points are not significant for most children (the SD associated with IQ tests is approximately 5 points), these small decrements may represent meaningful intellectual and economic achievement at a population level (Bellanger et al. 2013, Bellinger et al. 2019; EPA 1998; Griffiths et al. 2007; Trasande et al. 2005). Based on the meta-β of -0.18 IQ points per µg Hg/g hair (Axelrad et al. 2007a, 2007b) and regional data on maternal hair mercury levels, the global disability life years attributed to methylmercury exposure was estimated to range from 7 per 100,000 to 44 per 100,000 (Bellinger et al. 2019). The neurological impact of IQ score decrements (≥1, ≥2, and ≥3 IQ points) was used for the risk assessment of lead in paint, dust, and soil (EPA 1998) and estimates of the economic impact per 1-point decrease in IQ was used to estimate benefits of revisions of the National Ambient Air Quality Standards for Lead (EPA 2008). Risk assessments of fluoride exposure have been conducted based on IQ point losses of both 1 and 5 points (Hirzy et al. 2016).

Calculations:

Conversion of meta-β to hair mercury POD. The linear regression model predicts a proportional relationship between the change in IQ points and change in hair mercury. Therefore, the conversion of the meta-β to a mercury POD in units of hair mercury (POD_{hair}) is as follows (Equation 8):

$$POD_{hair} = \frac{1\ IQ\ point}{0.18\ IQ\ points\ per\ \mu g\ Hg/g\ hair} \quad \text{Eq. (8)}$$

The *POD* in units of hair mercury from Equation 1 is 5.56 µg Hg/g hair.

Conversion of hair mercury level to oral mercury dose. Hair mercury levels were converted to equivalent oral doses by applying a steady-state mass balance model, which did the following: (1) converted the hair level (µg Hg/g, assumed to represent steady state) to an equivalent steady-state blood mercury level (µg Hg/L) and (2) converted the steady-state blood mercury level to an equivalent steady-state oral dose (µg Hg/kg/day). Steady-state mass balance models have been used to reconstruct methylmercury intakes in human populations (Sirot et al. 2008). The assumption of steady state requires that the exposures were relatively constant (or intermittent with a constant frequency) for periods >300 days. This is the exposure duration that would achieve 95% of steady-state body burden, assuming a terminal elimination half-time of 65 days (Albert et al. 2010; Equation 9):

$$Time\ to\ steady\ state = \frac{\ln(1-0.95)}{k_e} \quad \text{Eq. (9)}$$

where 0.95 is the fraction of steady state and k_e is ln(2)/half-time.

The steady-state model is based on Albert et al. (2010) and is given in Equation 10:

$$Hg_{bl} = \frac{Hg_{dose} \cdot AF \cdot f_{bl} \cdot BW}{k_e \cdot V_{bl}} \quad \text{Eq. (10)}$$

where Hg_{bl} is the steady-state blood mercury level (µg Hg/L), Hg_{dose} is the steady-state dose (µg Hg/kg/day) *AF* is the gastrointestinal absorption fraction, f_{bl} is the blood fraction of the mercury body burden, *BW* is body weight (kg), k_e is the terminal elimination rate constant for mercury and V_{bl} is the blood volume (L).

The corresponding steady-state hair mercury level was calculated assuming a hair/blood ratio (Equation 11):

$$Hg_{hair} = Hg_{bl} \cdot HBR \quad \text{Eq (11)}$$

where Hg_{hair} is the hair mercury level (µg Hg/g hair) *HBR* is the hair/blood ratio (µg Hg/g per µg/L blood).

Parameter values for Equations 8 and 9 are presented in Table A-26. With these parameter values, the conversion factors for hair and blood mercury are as follows (Equations 12 and 13):

$$Dose = \frac{Hg_{bl}}{66.51} \quad \text{Eq. (12)}$$

$$Dose = \frac{Hg_{hair}}{13.50} \quad \text{Eq. (13)}$$

where the dose is in units of µg Hg/kg/day, blood mercury in units of µg Hg/L and hair mercury in units of µg Hg/g.

Table A-26. Parameter Values for the Methylmercury Dose Equivalence Model[a]

Parameter	Unit	Value
Blood elimination half-time	Day	65.4
Blood elimination rate constant	Day^{-1}	0.0106
Steady-state external dose	µg Hg/kg/day	1.00
Gastrointestinal absorption fraction	Fraction	0.94
Blood fraction of body burden	Fraction	0.060
Body weight	kg	60
Blood fraction of body weight	L/kg	0.080
Hair/blood ratio	µg Hg/kg per µg Hg/L	203

[a]Parameter values from Albert et al. (2010).

Basis for parameter values. Albert et al. (2010) was used as the basis for parameter values in the dose equivalence model because it provided estimates for the full set model parameters in a sample of the critical population represented in the MRL, pregnant females. Albert et al. (2010) estimated values for parameters in Equations 8 and 9 based on hair mercury levels and dietary seafood mercury intakes in 125 pregnant women. Scalp and hair mercury levels were measured at weeks 12 and 32 of pregnancy. Dietary mercury intakes were estimated in each subject from a food frequency questionnaire with seafood items paired to a national (France) database on methylmercury content of foods (Verger et al. 2007). Values for parameters were assigned prior distributions based on various sources (Albert et al. 2010) and posterior distributions were estimated in Markov Chain Monte Carlo simulations. Studies similar to Albert et al. (2010) have also estimated the full set of parameters for the model in other adult populations (Jenssen et al. 2012; Jo et al. 2015).

Additional support for the individual parameter values in the dose equivalence model derive from a variety of sources summarized below.

*Gastrointestinal absorption fraction. T*he value for the gastrointestinal absorption fraction used in the dose equivalence model is 0.94 (Albert et al. 2010). Studies conducted in humans, monkeys, and rodents have shown that gastrointestinal absorption of mercury is close to 100% following ingestion of methylmercury as the chloride salt or when incorporated into fish or other ingested protein (Aberg et al. 1969; Berlin et al. 1975; Clarkson 1971; Clarkson and Shapiro 1971; Miettinen et al. 1971; Mori et al. 2012; Nielsen 1992; Nielsen and Andersen 1991, Nielsen et al. 1992; Sundberg et al. 1999; Yannai and Sachs 1993).

Blood fraction of mercury body burden. The value for the blood fraction of the body burden used in the dose equivalence model is 0.06 (Albert et al. 2010). In clinical studies of known doses of methylmercury, blood mercury accounted for approximately 5–7% of the absorbed dose (Kershaw et al. 1980; Miettinen et al. 1971; Sherlock et al. 1984; Smith et al. 1994).

Blood mercury elimination half-time. The value for the terminal blood elimination half-time used in the dose equivalence model is 65.4 days (Albert et al. 2010). The corresponding elimination rate constant used in Equation 8 is 0.0106 day^{-1}. Population-based estimates of the blood half-time for methylmercury

have relied on fitting biokinetics models to data on blood or hair mercury levels to dietary methylmercury intakes (Albert et al. 2010; Jo et al. 2015). Albert et al. (2010) estimated half-times in 125 pregnant women from measurements of hair mercury and dietary methylmercury intake estimated from a dietary survey. When estimated assuming a point estimate for the population dietary intake, the mean half-time was 65.4 days (SD 6.0; 95% CI 54, 78). When interindividual variability in dietary mercury intake was included in the estimation of the half-time, the population mean half-time was 103 days (SD 9.5; 95% CI 83, 121). Jo et al. (2015) estimated half-times in 304 adults who were randomly selected from blood mercury quartiles of the KRIEFS cohort. The estimated population mean half-time (with interindividual variability in dietary intake included in the estimation) was 80.2 days (2.5–97.5 percentile range 64.0–97.4 days). The estimated mean half-time for males (n=167) was 81.6 days (range 66.0–98.8 days) and, for females (n=137), the estimated mean half-time was 78.9 days (range 62.8–96.4 days).

Hair/blood ratio. The value for the hair/blood ratio used in the dose equivalence model is 203 µg Hg/kg hair per µg Hg/L blood (Albert et al. 2010). The Faroe Islands study collected individual subject data on cord blood and parental hair at parturition (Budtz-Jorgensen et al. 2004). The median ratio (µg Hg/kg hair per µg Hg/L blood) was 190 (5^{th}–95^{th} percentile: 74–442) for full-length hair and 201 (5^{th}–95^{th} percentile: 89–439) for proximal hair (2-cm scalp segment). The hair/blood concentration ratio has been measured in numerous other studies and shows high inter-individual variability, with population means ranging from 100 to 400 (Akagi et al. 1995; Albert et al. 2010; Birke et al. 1972; Clarkson et al. 1988; Kershaw et al. 1980; Liberda et al. 2014; Muckle et al. 2001; Phelps et al. 1980; Sherlock et al. 1982; Yaginuma-Sakurai et al. 2012).

Blood volume. The value for the blood volume used in the dose equivalence model is 0.08 L/kg body weight (Albert et al. 2010). Data on blood volume in humans have been extensively reviewed (e.g., Brown et al. 1962; ICRP 1981; Stern 1997). These sources provide estimates that range from 0.06 to 0.08 L/kg. The upper end of the range is appropriate for the expanded blood volume that occurs during pregnancy (Hytten 1985).

Body weight. The value for body weight used in the dose equivalence model is 60 kg, based on ICRP (1981) and EPA (2011).

Evaluation of the dose equivalence model. The dose equivalence model was evaluated by comparing predicted doses with observed blood or hair mercury levels in populations of pregnant women in which individual dietary methylmercury intakes were known or estimated (Pouzaud et al. 2010; Vejrup et al. 2018). The results of these comparisons are summarized below. The close agreement between the observed methylmercury intakes and dose equivalents predicted from blood or hair mercury levels supports use of the model in derivation of the chronic oral MRL.

Pouzaud et al. (2010) measured dietary scalp hair mercury levels in 137 pregnant women during weeks 12 and 32 of pregnancy and paired these data with estimates of dietary methylmercury intake from a dietary survey. The group mean hair level was 0.82 µg Hg/g at week 12 and 0.79 µg Hg/g at week 32. The corresponding mean dietary intakes were 0.56 µg Hg/kg/week (0.080 µg Hg/kg/day) and 0.67 µg Hg/kg/week (0.096 µg Hg/kg/day). The observed and predicted mercury doses for this study are as follows:

Observed mean hair mercury: 0.82, 0.79 µg Hg/kg
Observed mean mercury intake: 0.080, 0.096 µg Hg/kg/day
Predicted mean dose equivalent: 0.061, 0.059 µg Hg/kg/day
Predicted minus observed: -0.019, -0.037 µg Hg/kg/day

The differences between the predicted and observed mercury intakes ranged from 0.02 to 0.04 µg Hg/kg/day. Good agreement between the predicted and observed dietary methylmercury intakes are expected for this dataset, since it included data from 123 subjects used to estimate parameters for the dose equivalence model.

Vejrup et al. (2018) estimated median dietary fish mercury intakes and measured blood mercury levels for a subset of the full cohort of the Norwegian Mother and Child Cohort Study (n=2,239). The median maternal blood mercury level was 1.0 µg Hg/L (SD 0.9) and the median estimated dietary fish mercury intake was 0.15 µg Hg/kg/week (0.021 µg Hg/g/day). The observed and predicted mercury doses for this study are as follows:

Observed median blood mercury: 1.0 µg Hg/L (SD 0.9)
Observed median mercury intake: 0.021 µg Hg/kg/day
Predicted median dose equivalent: 0.015 µg Hg/kg/day
Predicted minus observed: -0.006 µg Hg/kg/day

The difference between the predicted and observed mercury intake was 0.006 µg Hg/kg/day.

Conversion of meta-β (IQ points per µg Hg/g hair) to POD_{dose} (µg/kg/day per 1 IQ point).

Calculate POD_{hair} (µg Hg/g hair per 1 IQ point) from meta-β (IQ points per µg Hg/g hair; Equation 8):

$$POD_{hair} = (IQ\ points)/(meta\beta)$$

$$POD_{hair} = \frac{1}{0.18} = 5.56$$

Calculate ratio of blood mercury to dose (µg/L blood per µg Hg/kg/day; Equation 10):

$$Ratio\ blood{:}\ dose = (AF \times f_{blood} \times BW)/(k_e \times V_{blood})$$

$$Ratio\ blood{:}\ dose = \frac{0.94\ \times 0.060\ \times 60\ kg}{0.0106\ day^{-1}\ \times 4.80\ L} = 66.51$$

where *AF* is the absorption fraction, f_{blood} is the fraction of the dose transferred to blood, *BW* is body weight, k_e is the elimination rate constant ($\ln(2)/t_{1/2}$) and V_{blood} is the blood volume (0.080 × body weight).

Calculate ratio of hair mercury to dose (µg Hg/g hair per µg Hg/kg/day; Equations 11 and 13):

$$Ratio\ hair{:}\ dose = (Ratio\ blood{:}\ dose \times Ratio\ hair{:}\ blood)/1000$$

$$Ratio\ hair{:}\ dose = 66.51\ \times \frac{203}{1000} = 13.50$$

Calculate POD_{dose} (µg Hg/kg/day) from POD_{hair} (µg Hg/g hair):

$$POD_{dose} = POD_{hair}\ /\ Ratio\ hair{:}\ dose$$

$$POD_{dose} = \frac{5.56}{13.50} = 0.41$$

Uncertainty Factor: An uncertainty factor of 3 was applied to the POD of 0.41 µg Hg/kg/day to account for expected human variability in pharmacokinetics and dynamics. The uncertainty factor was reduced from the standard factor for 10 for the following reasons: (1) the principal study examined a highly sensitive target population, the fetus and (2) a well-supported biokinetic model was used to calculate the equivalent maternal dose from a well-supported biomarker of exposure to methylmercury in high fish consuming populations.

- 3 for human variability

Provisional MRL = POD ÷ UF
Provisional MRL = 0.41 µg Hg/kg/day ÷ 3
Provisional MRL = 0.1 µg Hg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The chronic oral MRL based on the meta-analysis of the Faroe Islands, North Island New Zealand, and Seychelle Islands is 0.1 µg Hg/kg/day. The MRL is lower than the equivalent doses predicted in the individual contributing studies, which were 0.34 µg Hg/kg/day for the Faroe Islands cohort, 0.61 µg Hg/kg/day for the North Island New Zealand cohort, and 0.41 µg Hg/kg/day for the Seychelle Islands cohort. The equivalent doses from the Faroe Islands and North Island New Zealand cohorts are AELs, while the equivalent dose from the Seychelle Island cohort is a NAEL.

In addition to the epidemiological studies conducted in the Faroe Islands, North Island New Zealand, and Seychelle Islands, studies of other populations have found associations between exposures to methylmercury and neurodevelopmental outcomes (see Chapter 2, Section 2.16, Neurological). These include studies of high fish consumers in the Amazon River basin (Chevrier et al. 2009; Cordier et al. 2002), Arctic Canada (Boucher et al. 2012a, 2012b, 2014, 2016; Despres et al. 2005; Ethier et al. 2012; Jacobson et al. 2015), fishing villages on the Mediterranean coast (Murata et al. 1999a, 2004b), and populations residing in the vicinity of artisanal gold mining operations (Counter 2003; Counter et al. 1998, 2002, 2006, 2012; Ramirez et al. 2000, 2003; Reuben et al. 2020).

The MRL is approximately 2 times higher than the dietary fish methylmercury intakes in the Norwegian Mother and Child Cohort Study that were associated with effects on language proficiency. However, a POD based on the dietary intakes estimated in this study would have lower confidence than the POD used in the derivation of the MRL for several reasons: (1) the associations with dietary methylmercury intake were based on a semi-quantitative food survey and national data on fish mercury concentrations, rather than biomarkers of mercury exposure in individual subjects; (2) the association with dietary methylmercury intake predicted lower language proficiency at age 3 years, whereas the association predicted higher proficiency at age 5 years (Vejrup et al. 2016, 2018); (3) in a subset of the cohort for which measurements of individual subject blood mercury levels were available, there was no association between language proficiency and blood mercury (Vejrup et al. 2018); and (4) language proficiency assessment was assessed from results of a parental self-report survey of their children rather than an assessment made by professional, non-biased observers.

Studies conducted in animals (nonhuman primates and rodents) provide strong support for the developing nervous system being most sensitive target of methylmercury (see Chapter 2, Section 2.16.1, Neurodevelopmental Effects for references and additional details). Studies conducted in monkeys have shown that gestational exposure to methylmercury resulted in sensorimotor dysfunction, and vision and hearing deficits. Gestational exposures in rodents produced sensorimotor dysfunction, vision and hearing deficits, impaired learning and memory, and neuropathological changes in the central and peripheral nervous systems.

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APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR MERCURY

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to mercury.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for mercury. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of mercury have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of mercury are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects
    - Developmental effects
    - Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the 1999 toxicological profile for mercury; thus, the literature search was restricted to studies published between January 1998 and January 2019. The following main databases were searched in January 2019:

- PubMed
- National Library of Medicine's Toxline
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for mercury. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures

and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to mercury were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
1/2019	(("mercury/toxicity"[mh] OR "mercury/adverse effects"[mh] OR "mercury/poisoning"[mh] OR "mercury/pharmacokinetics"[mh] OR ("mercury"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury/blood"[mh] OR "mercury/cerebrospinal fluid"[mh] OR "mercury/urine"[mh] OR "mercury/antagonists and inhibitors"[mh]) OR ("mercury/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury"[majr] AND cancer[sb]) OR "mercury/pharmacology"[majr])) OR ("phenylmercuric acetate/toxicity"[mh] OR "phenylmercuric acetate/adverse effects"[mh] OR "phenylmercuric acetate/poisoning"[mh] OR "phenylmercuric acetate/pharmacokinetics"[mh] OR ("phenylmercuric acetate"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("phenylmercuric acetate"[mh] AND toxicokinetics[mh:noexp]) OR ("phenylmercuric acetate/blood"[mh] OR "phenylmercuric acetate/cerebrospinal fluid"[mh] OR "phenylmercuric acetate/urine"[mh] OR "phenylmercuric acetate/antagonists and inhibitors"[mh]) OR ("phenylmercuric acetate/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("phenylmercuric acetate"[majr] AND cancer[sb]) OR "phenylmercuric

Table B-2. Database Query Strings

Database search date	Query string
	acetate/pharmacology"[majr])) OR ("mercuric chloride/toxicity"[mh] OR "mercuric chloride/adverse effects"[mh] OR "mercuric chloride/poisoning"[mh] OR "mercuric chloride/pharmacokinetics"[mh] OR ("mercuric chloride"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercuric chloride"[mh] AND toxicokinetics[mh:noexp]) OR ("mercuric chloride/blood"[mh] OR "mercuric chloride/cerebrospinal fluid"[mh] OR "mercuric chloride/urine"[mh] OR "mercuric chloride/antagonists and inhibitors"[mh]) OR ("mercuric chloride/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercuric chloride"[majr] AND cancer[sb]) OR "mercuric chloride/pharmacology"[majr])) OR ("cinnabar"[tw] OR "mercuric sulfide"[tw] OR "mercuric sulphide"[tw] OR "mercury (ii) sulfide"[tw] OR "mercury monosulfide"[tw] OR "mercury sulfide"[tw] OR "mercury sulphide"[tw] OR "mercury(2+) sulfide"[tw] OR "mercury(ii) sulfide"[tw] OR "monomercury sulfide"[tw] OR "Mercury poisoning"[mh])) AND 1998:3000[mhda] ("mercury compounds/toxicity"[mh] OR "mercury compounds/adverse effects"[mh] OR "mercury compounds/poisoning"[mh] OR "mercury compounds/pharmacokinetics"[mh] OR ("mercury compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury compounds/blood"[mh] OR "mercury compounds/cerebrospinal fluid"[mh] OR "mercury compounds/urine"[mh] OR "mercury compounds/antagonists and inhibitors"[mh]) OR ("mercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury compounds"[majr] AND cancer[sb]) OR "mercury compounds/pharmacology"[majr])) OR ("methylmercury compounds/toxicity"[mh] OR "methylmercury compounds/adverse effects"[mh] OR "methylmercury compounds/poisoning"[mh] OR "methylmercury compounds/pharmacokinetics"[mh] OR ("methylmercury compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	"medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("methylmercury compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("methylmercury compounds/blood"[mh] OR "methylmercury compounds/cerebrospinal fluid"[mh] OR "methylmercury compounds/urine"[mh] OR "methylmercury compounds/antagonists and inhibitors"[mh]) OR ("methylmercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("methylmercury compounds"[majr] AND cancer[sb]) OR "methylmercury compounds/pharmacology"[majr])) OR ("mercury isotopes/toxicity"[mh] OR "mercury isotopes/adverse effects"[mh] OR "mercury isotopes/poisoning"[mh] OR "mercury isotopes/pharmacokinetics"[mh] OR ("mercury isotopes"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury isotopes"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury isotopes/blood"[mh] OR "mercury isotopes/cerebrospinal fluid"[mh] OR "mercury isotopes/urine"[mh] OR "mercury isotopes/antagonists and inhibitors"[mh]) OR ("mercury isotopes/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury isotopes"[majr] AND cancer[sb]) OR "mercury isotopes/pharmacology"[majr])) OR ("organomercury compounds/toxicity"[mh] OR "organomercury compounds/adverse effects"[mh] OR "organomercury compounds/poisoning"[mh] OR "organomercury compounds/pharmacokinetics"[mh] OR ("organomercury compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene

Table B-2. Database Query Strings

Database search date	Query string
	expression profiling"[mh])) OR ("organomercury compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("organomercury compounds/blood"[mh] OR "organomercury compounds/cerebrospinal fluid"[mh] OR "organomercury compounds/urine"[mh] OR "organomercury compounds/antagonists and inhibitors"[mh]) OR ("organomercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("organomercury compounds"[majr] AND cancer[sb]) OR "organomercury compounds/pharmacology"[majr])) ((("(acetato)phenylmercury"[tw] OR "(acetato-kappao)phenylmercury"[tw] OR "(acetato-o)phenylmercury"[tw] OR "(acetoxymercuri)benzene"[tw] OR "(acetoxymercurio)benzene"[tw] OR "acetic acid, mercuridi-"[tw] OR "acetic acid, mercury(2+) salt"[tw] OR "acetic acid, phenylmercury deriv."[tw] OR "acetic acid, phenylmercury(ii) salt"[tw] OR "acetoxyphenylmercury"[tw] OR "benzene, (acetoxymercuri)-"[tw] OR "benzene, (acetoxymercurio)-"[tw] OR "bis(acetyloxy)mercury"[tw] OR "calochlor"[tw] OR "calomel"[tw] OR "chloromethylmercury"[tw] OR "cinnabar"[tw] OR "cinnabarite"[tw] OR "diacetoxymercury"[tw] OR "dichloromercury"[tw] OR "dimercury dichloride"[tw] OR "dimethylmercury"[tw] OR "fungche"[tw] OR "hydrargyrum"[tw] OR "mercuriacetate"[tw] OR "mercuric acetate"[tw] OR "mercuric bichloride"[tw] OR "mercuric chloride"[tw] OR "mercuric diacetate"[tw] OR "mercuric nitrate"[tw] OR "mercuric sulfide"[tw] OR "mercuric sulphide"[tw] OR "mercuridiacetic acid, "[tw] OR "mercuriphenyl acetate"[tw] OR "mercurius 6a"[tw] OR "mercurous chloride"[tw] OR "mercury"[tw] OR "mercury(1+), methyl-"[tw] OR "mercury(2+) acetate"[tw] OR "mercury(2+) chloride"[tw] OR "mercury(2+) nitrate"[tw] OR "mercury(2+) sulfide"[tw] OR "mercury(i) chloride"[tw] OR "mercury(ii) acetate"[tw] OR "mercury(ii) acetate, phenyl-"[tw] OR "mercury(ii) chloride"[tw] OR "mercury(ii) nitrate"[tw] OR "mercury(ii) sulfide"[tw] OR "mercury, (acetato)phenyl-"[tw] OR "mercury, (acetato-kappao)phenyl-"[tw] OR "mercury, (acetato-o)phenyl-"[tw] OR "mercury, acetoxyphenyl-"[tw] OR "mercury, chloromethyl-"[tw] OR "mercury, dimethyl-"[tw] OR "mercuryl acetate"[tw] OR "mercurymethylchloride"[tw] OR "methyl mercuric chloride"[tw] OR "methyl mercuric(ii) chloride"[tw] OR "methyl meruric chloride"[tw] OR "methylmercuric chloride"[tw] OR "methylmercury"[tw] OR "methylmercury chloride"[tw] OR "methylmercury monochloride"[tw] OR "methylmercury(1+)"[tw] OR "methylmercury(ii) cation"[tw] OR "millon's reagent"[tw] OR "monomercury sulfide"[tw] OR "monomethylmercury cation"[tw] OR "nitric acid, mercury(2+) salt"[tw] OR "nitric acid, mercury(ii) salt"[tw] OR "phenomercuric acetate"[tw] OR "phenyl mercuric acetate"[tw] OR "phenylmercuriacetate"[tw] OR "phenylmercuric acetate"[tw] OR "phenylmercury acetate"[tw] OR "phenylmercury(ii) acetate"[tw] OR "Anticon"[tw] OR "Celmer"[tw] OR "Femma"[tw] OR "Hexasan"[tw] OR "Hostaquick"[tw] OR "Kwiksan"[tw] OR "Lorophyn"[tw] OR "Parasan"[tw] OR "Phix"[tw] OR "Samtol"[tw] OR "Sanitol"[tw] OR "Sc-110"[tw] OR "Verdasan"[tw] OR "Volpar"[tw] OR "Caspan"[tw] OR "Liquid silver"[tw] OR "Quick silver"[tw] OR "Quicksilver"[tw] OR "Sulem"[tw] OR "Agrosan D"[tw] OR "Agrosan GN 5"[tw] OR "Algimycin 200"[tw] OR "Antimucin WBR"[tw] OR "Antimucin WDR"[tw] OR "Bufen"[tw] OR "Bufen 30"[tw] OR "Cekusil"[tw] OR "Ceresol"[tw] OR "Contra Creme"[tw] OR "Dyanacide"[tw] OR "Fungicide R"[tw] OR "Fungitox OR"[tw] OR "Gallotox"[tw] OR "Hl-331"[tw] OR "Hong nien"[tw] OR "Hostaquik"[tw] OR "Intercide 60"[tw] OR "Intercide PMA 18"[tw] OR "Liquiphene"[tw] OR "Meracen"[tw] OR "Mercron"[tw] OR "Mercuron"[tw] OR "Mergal A 25"[tw] OR "Mersolite"[tw] OR "Metasol 30"[tw] OR "Neantina"[tw] OR "Norforms"[tw] OR "Nuodex PMA 18"[tw] OR "Nylmerate"[tw] OR "PMA (fungicide)"[tw] OR "Pamisan"[tw] OR "Panomatic"[tw] OR "Parasan (bactericide)"[tw] OR "Phenmad"[tw] OR "Programin"[tw] OR "Purasan-SC-10"[tw] OR "Puraturf 10"[tw] OR "Quicksan"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"Quicksan 20"[tw] OR "Riogen"[tw] OR "Ruberon"[tw] OR "Sanitized SPG"[tw] OR "Sanmicron"[tw] OR "Scutl"[tw] OR "Seed Dressing R"[tw] OR "Seedtox"[tw] OR "Setrete"[tw] OR "Shimmerex"[tw] OR "Spor-Kil"[tw] OR "Spruce Seal"[tw] OR "Tag (VAN)"[tw] OR "Tag 331"[tw] OR "Tag HL 331"[tw] OR "Tag fungicide"[tw] OR "Trigosan"[tw] OR "Troysan 30"[tw] OR "Troysan PMA 30"[tw] OR "Zaprawa Nasienna R"[tw] OR "Ziarnik"[tw] OR "Hydraargyrum bichloratum"[tw] OR "Calo-Clor"[tw] OR "Calocure"[tw] OR "Calogreen"[tw] OR "Calotab"[tw] OR "Abavit B"[tw] OR "Citrine ointment"[tw] OR "Ethiops mineral"[tw] OR "Mercurius vivus"[tw] OR "beta-Mercuric sulfide"[tw] OR "Phenylquecksilberacetate"[tw] OR "Quecksilber(II)-sulfid, rotes"[tw] OR "Rotes Quecksilbersulfid"[tw] OR "Paragite"[tw] OR "TL 898"[tw]) NOT medline[sb])) AND (1998:3000[crdat] OR 1998:3000[edat]) ((7546-30-7[rn] OR 10031-18-2[rn] OR 7789-47-1[rn] OR 15385-58-7[rn] OR 628-86-4[rn] OR 7783-30-4[rn] OR 15385-57-6[rn] OR 7774-29-0[rn] OR 10415-75-5[rn] OR 14836-60-3[rn] OR 15829-53-5[rn] OR 21908-53-2[rn] OR 20601-83-6[rn] OR 11138-42-4[rn] OR 7783-36-0[rn] OR 7783-35-9[rn] OR 12068-90-5[rn] OR 592-04-1[rn] OR 631-60-7[rn] OR 14302-87-5[rn] OR 22542-11-6[rn]) AND (("mercury/toxicity"[mh] OR "mercury/adverse effects"[mh] OR "mercury/poisoning"[mh] OR "mercury/pharmacokinetics"[mh] OR ("mercury"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury/blood"[mh] OR "mercury/cerebrospinal fluid"[mh] OR "mercury/urine"[mh] OR "mercury/antagonists and inhibitors"[mh]) OR ("mercury/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury"[majr] AND cancer[sb]) OR "mercury/pharmacology"[majr])) OR ("phenylmercuric acetate/toxicity"[mh] OR "phenylmercuric acetate/adverse effects"[mh] OR "phenylmercuric acetate/poisoning"[mh] OR "phenylmercuric acetate/pharmacokinetics"[mh] OR ("phenylmercuric acetate"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("phenylmercuric acetate"[mh] AND

Table B-2. Database Query Strings

Database search date	Query string
	toxicokinetics[mh:noexp]) OR ("phenylmercuric acetate/blood"[mh] OR "phenylmercuric acetate/cerebrospinal fluid"[mh] OR "phenylmercuric acetate/urine"[mh] OR "phenylmercuric acetate/antagonists and inhibitors"[mh]) OR ("phenylmercuric acetate/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("phenylmercuric acetate"[majr] AND cancer[sb]) OR "phenylmercuric acetate/pharmacology"[majr])) OR ("mercuric chloride/toxicity"[mh] OR "mercuric chloride/adverse effects"[mh] OR "mercuric chloride/poisoning"[mh] OR "mercuric chloride/pharmacokinetics"[mh] OR ("mercuric chloride"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercuric chloride"[mh] AND toxicokinetics[mh:noexp]) OR ("mercuric chloride/blood"[mh] OR "mercuric chloride/cerebrospinal fluid"[mh] OR "mercuric chloride/urine"[mh] OR "mercuric chloride/antagonists and inhibitors"[mh]) OR ("mercuric chloride/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercuric chloride"[majr] AND cancer[sb]) OR "mercuric chloride/pharmacology"[majr])) OR ("cinnabar"[tw] OR "mercuric sulfide"[tw] OR "mercuric sulphide"[tw] OR "mercury (ii) sulfide"[tw] OR "mercury monosulfide"[tw] OR "mercury sulfide"[tw] OR "mercury sulphide"[tw] OR "mercury(2+) sulfide"[tw] OR "mercury(ii) sulfide"[tw] OR "monomercury sulfide"[tw] OR "Mercury poisoning"[mh])))) OR ((7546-30-7[rn] OR 10031-18-2[rn] OR 7789-47-1[rn] OR 15385-58-7[rn] OR 628-86-4[rn] OR 7783-30-4[rn] OR 15385-57-6[rn] OR 7774-29-0[rn] OR 10415-75-5[rn] OR 14836-60-3[rn] OR 15829-53-5[rn] OR 21908-53-2[rn] OR 20601-83-6[rn] OR 11138-42-4[rn] OR 7783-36-0[rn] OR 7783-35-9[rn] OR 12068-90-5[rn] OR 592-04-1[rn] OR 631-60-7[rn] OR 14302-87-5[rn] OR 22542-11-6[rn]) AND (("mercury compounds/toxicity"[mh] OR "mercury compounds/adverse effects"[mh] OR "mercury compounds/poisoning"[mh] OR "mercury compounds/pharmacokinetics"[mh] OR ("mercury compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury compounds/blood"[mh] OR "mercury compounds/cerebrospinal fluid"[mh] OR "mercury compounds/urine"[mh] OR "mercury compounds/antagonists and inhibitors"[mh]) OR

Table B-2. Database Query Strings

Database search date	Query string
	("mercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury compounds"[majr] AND cancer[sb]) OR "mercury compounds/pharmacology"[majr])) OR ("methylmercury compounds/toxicity"[mh] OR "methylmercury compounds/adverse effects"[mh] OR "methylmercury compounds/poisoning"[mh] OR "methylmercury compounds/pharmacokinetics"[mh] OR ("methylmercury compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("methylmercury compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("methylmercury compounds/blood"[mh] OR "methylmercury compounds/cerebrospinal fluid"[mh] OR "methylmercury compounds/urine"[mh] OR "methylmercury compounds/antagonists and inhibitors"[mh]) OR ("methylmercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("methylmercury compounds"[majr] AND cancer[sb]) OR "methylmercury compounds/pharmacology"[majr])) OR ("mercury isotopes/toxicity"[mh] OR "mercury isotopes/adverse effects"[mh] OR "mercury isotopes/poisoning"[mh] OR "mercury isotopes/pharmacokinetics"[mh] OR ("mercury isotopes"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury isotopes"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury isotopes/blood"[mh] OR "mercury isotopes/cerebrospinal fluid"[mh] OR "mercury isotopes/urine"[mh] OR "mercury isotopes/antagonists and inhibitors"[mh]) OR ("mercury isotopes/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury isotopes"[majr] AND cancer[sb]) OR "mercury isotopes/pharmacology"[majr])) OR ("organomercury compounds/toxicity"[mh] OR "organomercury compounds/adverse effects"[mh] OR "organomercury compounds/poisoning"[mh] OR "organomercury compounds/pharmacokinetics"[mh] OR ("organomercury compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("organomercury compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("organomercury compounds/blood"[mh] OR "organomercury compounds/cerebrospinal fluid"[mh] OR "organomercury compounds/urine"[mh] OR "organomercury compounds/antagonists and inhibitors"[mh]) OR ("organomercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("organomercury compounds"[majr] AND cancer[sb]) OR "organomercury compounds/pharmacology"[majr]))) ("Cyclosan"[tw] OR "Mercurous iodide"[tw] OR "Mercury telluride"[tw] OR "Mercury hydride"[tw] OR "Mercurane"[tw] OR "Mercury bromide"[tw] OR "Mercury iodide"[tw] OR "Mercury oxide"[tw] OR "Mercuric selenide"[tw] OR "Mercury cyanide"[tw] OR ("Mercury chloride"[tw] NOT "mercuric chloride"[mh])) OR (("Cyclosan"[tw] OR "Mercury chloride"[tw] OR "Mercury bromide"[tw] OR "Mercuric bromide"[tw] OR "Mercuric dibromide"[tw] OR "Mercury dibromide"[tw] OR "Mercury(II) bromide"[tw] OR "Mercury fulminate"[tw] OR "Mercurous iodide"[tw] OR "Mercuric iodide"[tw] OR "Mercury iodide"[tw] OR "Mercury(II) iodide"[tw] OR "Mercuric oxide"[tw] OR "Mercury oxide"[tw] OR "Red Precipitate"[tw] OR "Yellow precipitate"[tw] OR "Mercuric selenide"[tw] OR "Mercury selenide"[tw] OR "Mercury-selenium complex"[tw] OR "Mercurous sulfate"[tw] OR "Mercury(I) sulfate"[tw] OR "Mercuric sulfate"[tw] OR "Mercuric sulphate"[tw] OR "Mercury sulfate"[tw] OR "Mercury sulphate"[tw] OR "Mercury telluride"[tw] OR "Mercuric cyanide"[tw] OR "Mercurius cyanatus"[tw] OR "Mercury cyanide"[tw] OR "Mercury hydride"[tw] OR "Mercurane"[tw] OR "Mercuric cation"[tw] OR "Mercuric cations"[tw] OR "Mercuric ion"[tw] OR "Mercuric ions"[tw]) NOT medline[sb])
Toxline	
1/2019	((10112-91-1 [rn] OR 115-09-3 [rn] OR 1344-48-5 [rn] OR 1600-27-7 [rn] OR 593-74-8 [rn] OR 62-38-4 [rn] OR 7439-97-6 [rn] OR 7487-94-7 [rn])) AND 1998:2018 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] ("(acetato)phenylmercury" OR "(acetato-kappao)phenylmercury" OR "(acetato-o)phenylmercury" OR "(acetoxymercuri)benzene" OR "(acetoxymercurio)benzene" OR "acetic acid, mercuridi-" OR "acetic acid, mercury(2+) salt" OR "acetic acid, phenylmercury deriv." OR "acetic acid, phenylmercury(ii) salt" OR "acetoxyphenylmercury" OR "benzene, (acetoxymercuri)-" OR "benzene, (acetoxymercurio)-" OR "bis(acetyloxy)mercury" OR "calochlor" OR "calomel" OR "chloromethylmercury" OR "cinnabar" OR "cinnabarite" OR "diacetoxymercury" OR "dichloromercury" OR "dimercury dichloride" OR "dimethylmercury" OR "fungche" OR "hydrargyrum" OR "mercuriacetate" OR "mercuric acetate" OR "mercuric bichloride" OR "mercuric chloride" OR "mercuric diacetate" OR "mercuric nitrate" OR "mercuric sulfide" OR "mercuric sulphide" OR "mercuridiacetic acid, " OR "mercuriphenyl acetate" OR "mercurius 6a" OR "mercurous chloride" OR "mercury" OR "mercury(1+),

Table B-2. Database Query Strings

Database search date	Query string
	methyl-" OR "mercury(2+) acetate" OR "mercury(2+) chloride" OR "mercury(2+) nitrate" OR "mercury(2+) sulfide" OR "mercury(i) chloride" OR "mercury(ii) acetate" OR "mercury(ii) acetate, phenyl-") AND 1998:2018 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] ("mercury(ii) chloride" OR "mercury(ii) nitrate" OR "mercury(ii) sulfide" OR "mercury, (acetato)phenyl-" OR "mercury, (acetato-kappao)phenyl-" OR "mercury, (acetato-o)phenyl-" OR "mercury, acetoxyphenyl-" OR "mercury, chloromethyl-" OR "mercury, dimethyl-" OR "mercuryl acetate" OR "mercurymethylchloride" OR "methyl mercuric chloride" OR "methyl mercuric(ii) chloride" OR "methyl meruric chloride" OR "methylmercuric chloride" OR "methylmercury" OR "methylmercury chloride" OR "methylmercury monochloride" OR "methylmercury(1+)" OR "methylmercury(ii) cation" OR "millon's reagent" OR "monomercury sulfide" OR "monomethylmercury cation" OR "nitric acid, mercury(2+) salt" OR "nitric acid, mercury(ii) salt" OR "phenomercuric acetate" OR "phenyl mercuric acetate" OR "phenylmercuriacetate" OR "phenylmercuric acetate" OR "phenylmercury acetate" OR "phenylmercury(ii) acetate" OR "Anticon" OR "Celmer" OR "Femma" OR "Hexasan" OR "Hostaquick" OR "Kwiksan" OR "Lorophyn" OR "Parasan" OR "Phix" OR "Samtol" OR "Sanitol" OR "Sc-110" OR "Verdasan" OR "Volpar" OR "Caspan" OR "Liquid silver" OR "Quick silver" OR "Quicksilver" OR "Sulem") AND 1998:2018 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] ("Agrosan D" OR "Agrosan GN 5" OR "Algimycin 200" OR "Antimucin WBR" OR "Antimucin WDR" OR "Bufen" OR "Bufen 30" OR "Cekusil" OR "Ceresol" OR "Contra Creme" OR "Dyanacide" OR "Fungicide R" OR "Fungitox OR" OR "Gallotox" OR "Hl-331" OR "Hong nien" OR "Hostaquik" OR "Intercide 60" OR "Intercide PMA 18" OR "Liquiphene" OR "Meracen" OR "Mercron" OR "Mercuron" OR "Mergal A 25" OR "Mersolite" OR "Metasol 30" OR "Neantina" OR "Norforms" OR "Nuodex PMA 18" OR "Nylmerate" OR "PMA (fungicide)" OR "Pamisan" OR "Panomatic" OR "Parasan (bactericide)" OR "Phenmad" OR "Programin" OR "Purasan-SC-10" OR "Puraturf 10" OR "Quicksan" OR "Quicksan 20" OR "Riogen" OR "Ruberon" OR "Sanitized SPG" OR "Sanmicron" OR "Scutl" OR "Seed Dressing R" OR "Seedtox" OR "Setrete" OR "Shimmerex" OR "Spor-Kil" OR "Spruce Seal" OR "Tag (VAN)" OR "Tag 331" OR "Tag HL 331" OR "Tag fungicide" OR "Trigosan" OR "Troysan 30" OR "Troysan PMA 30" OR "Zaprawa Nasienna R" OR "Ziarnik" OR "Hydraargyrum bichloratum" OR "Calo-Clor" OR "Calocure" OR "Calogreen" OR "Calotab" OR "Abavit B" OR "Citrine ointment" OR "Ethiops mineral" OR "Mercurius vivus" OR "beta-Mercuric sulfide" OR "Phenylquecksilberacetate" OR "Quecksilber(II)-sulfid, rotes" OR "Rotes Quecksilbersulfid" OR "Paragite" OR "TL 898") AND 1998:2018 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]

Table B-2. Database Query Strings

Database search date	Query string
	(22967-92-6 [rn] OR 10045-94-0 [rn] OR 19122-79-3 [rn]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("Mercury(1+), methyl-" OR "Methyl mercury" OR "Methylmercury" OR "Methylmercury(1+)" OR "Methylmercury(II) cation" OR "Monomethylmercury cation" OR "Citrine ointment" OR "Mercuric nitrate" OR "Mercury dinitrate" OR "Mercury nitrate" OR "Mercury pernitrate" OR "Mercury(2+) nitrate" OR "Mercury(II) nitrate" OR "Millon's reagent" OR "Nitric acid, mercury(2+) salt" OR "Nitric acid, mercury(II) salt" OR "Cinnabar" OR "Cinnabarite" OR "Mercurius 6a" OR "Paragite") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	(7546-30-7[rn] OR 10031-18-2[rn] OR 7789-47-1[rn] OR 15385-58-7[rn] OR 628-86-4[rn] OR 7783-30-4[rn] OR 15385-57-6[rn] OR 7774-29-0[rn] OR 10415-75-5[rn] OR 14836-60-3[rn] OR 15829-53-5[rn] OR 21908-53-2[rn] OR 20601-83-6[rn] OR 11138-42-4[rn] OR 7783-36-0[rn] OR 7783-35-9[rn] OR 12068-90-5[rn] OR 592-04-1[rn] OR 631-60-7[rn] OR 14302-87-5[rn] OR 22542-11-6[rn]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("Cyclosan" OR "Mercury chloride" OR "Mercury monochloride" OR "Mercury protochloride" OR "Precipite blanc" OR "Mercurous bromide" OR "Mercury bromide" OR "Mercury monobromide" OR "Mercury(I) bromide" OR "Dibromomercury" OR "Mercuric bromide" OR "Mercuric dibromide" OR "Mercury dibromide" OR "Mercury(II) bromide" OR "dibromodimercury" OR "Mercury, dibromodi-, (Hg-Hg)" OR "Mercury(I) fulminate" OR "Fulminate of mercury" OR "Fulminating mercury" OR "Fulminic acid, mercury(2+) salt" OR "Fulminic acid, mercury(II) salt" OR "Mercuric cyanate" OR "Mercury difulminate" OR "Mercury fulminate" OR "mercury fulminic acid" OR "Mercury(II) fulminate" OR "Mercury, bis(fulminato)-" OR "Mercury, bis(fulminato-kappaC)-") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("Mercurous iodide" OR "Mercury protoiodide" OR "Mercury(I) iodide" OR "Dimercury diiodide" OR "Diiodomercury" OR "Hydrargyrum diodatum" OR "Mercuric iodide" OR "Mercurius bijodatus" OR "Mercury biniodide" OR "Mercury diiodide" OR "Mercury iodide" OR "Mercury(2+) diiodide" OR "Mercury(2+) iodide" OR "Mercury(II) iodide" OR "Dimercury dinitrate" OR "Mercurous nitrate" OR "Mercury protonitrate" OR "Mercury(1+) nitrate" OR "Mercury(I) nitrate" OR "Monomercury nitrate" OR "Nitric acid, mercury(1+) salt" OR "Nitric acid, mercury(I) salt" OR "Mercurous oxide" OR "Mercury(I) oxide") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org]

Table B-2. Database Query Strings

Database search date	Query string
	OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] ("Hydrargyrum oxid flav" OR "Hydrargyrum oxydatum rubrum" OR "Mercuric monooxide" OR "Mercuric oxide" OR "Mercury monoxide" OR "Mercury oxide" OR "Mercury(2+) oxide" OR "Mercury(II) oxide" OR "Natural montroydite" OR "Red oxide of mercury" OR "Red Precipitate" OR "Santar" OR "Yellow oxide of mercury" OR "Yellow precipitate" OR "Mercury(I) selenide" OR "Mercurous selenide" OR "Mercuric selenide" OR "Mercury monoselenide" OR "Mercury selenide" OR "Mercury(2+) selenide" OR "Mercury(II) selenide" OR "Mercury-selenium complex" OR "Dimercury sulfate" OR "Dimercury sulphate" OR "Mercurous sulfate" OR "Mercurous sulphate" OR "Mercury(I) sulfate" OR "Sulfuric acid, dimercury(1+) salt" OR "Sulfuric acid, dimercury(1++) salt" OR "Mercuric bisulphate" OR "Mercuric sulfate" OR "Mercuric sulphate" OR "Mercurous bisulphate" OR "Mercury bisulfate" OR "Mercury bisulphates" OR "Mercury disulfate" OR "Mercury persulfate" OR "Mercury sulfate" OR "Mercury sulphate" OR "Mercury(II) sulfate" OR "Sulfuric acid, mercury(2+) salt") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] ("Mercuric telluride" OR "Mercury monotelluride" OR "Mercury telluride" OR "Mercury(2+) telluride" OR "mercury(II) telluride" OR "Mercury(I) cyanide" OR "Mercurous cyanide" OR "Cianurina" OR "Dicyanomercury" OR "Hydrargyrum cyanatum" OR "Mercuric cyanide" OR "Mercurius cyanatus" OR "Mercury cyanide" OR "Mercury dicyanide" OR "Mercury(II) cyanide" OR "Dimercurane" OR "Mercurous hydride" OR "Mercury hydride" OR "Mercury monohydride" OR "Mercury(I) hydride" OR "Mercurane" OR "Mercuric hydride" OR "Mercury(II) hydride" OR "Acetic acid, mercury (1+) salt" OR "Dimercury di(acetate)" OR "Mercurous acetate" OR "Mercury monoacetate" OR "Mercuric cation" OR "Mercuric cations" OR "Mercuric ion" OR "Mercuric ions") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
4/2018	FILE 'TOXCENTER' ENTERED AT 14:09:59 ON 16 APR 2018 CHARGED TO COST=MERCURYRFP TSD18.015TE ACT DATE1/A --------- L1 (128290)SEA 7439-97-6 OR 7487-94-7 OR 1344-48-5 OR 10112-91-1 OR 1600-27-7 OR 115-09-3 OR 593-74-8 OR 62-38-4 L2 (76310)SEA L1 AND PY>1997 L3 (67121)SEA L2 NOT PATENT/DT L4 (67121)SEA L3 NOT TSCATS/FS L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)

Table B-2. Database Query Strings

Database search date	Query string
	L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L20 QUE (ENDOCRIN? AND DISRUPT?) L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L27 QUE (NEPHROTOX? OR HEPATOTOX?) L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)

Table B-2. Database Query Strings

Database search date	Query string
	L33 QUE L30 OR L31 OR L32 L34 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L35 QUE L33 OR L34 L36 (33977)SEA L4 AND L35 L37 (19296)SEA L36 AND PY>2008 L38 (3992)SEA L37 AND MEDLINE/FS L39 (4778)SEA L37 AND BIOSIS/FS L40 (10511)SEA L37 AND CAPLUS/FS L41 (15)SEA L37 NOT (L38 OR L39 OR L40) L42 (14309)DUP REM L38 L39 L41 L40 (4987 DUPLICATES REMOVED) L43 (3992)SEA L42 L44 (3167)SEA L42 L45 (7137)SEA L42 L46 (13)SEA L42 L47 2794 SEA (L43 OR L44 OR L45 OR L46) AND PY>2015 --------- ACT DATE2/A --------- L48 (128290)SEA 7439-97-6 OR 7487-94-7 OR 1344-48-5 OR 10112-91-1 OR 1600-27-7 OR 115-09-3 OR 593-74-8 OR 62-38-4 L49 (76310)SEA L48 AND PY>1997 L50 (67121)SEA L49 NOT PATENT/DT L51 (67121)SEA L50 NOT TSCATS/FS L52 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L53 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L54 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L55 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L56 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L57 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L58 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L59 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L60 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L61 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L62 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L63 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L64 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR

Table B-2. Database Query Strings

Database search date	Query string
	SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L65 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR
	SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L66 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L67 QUE (ENDOCRIN? AND DISRUPT?)
	L68 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L69 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L70 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L71 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR
	NEOPLAS?)
	L72 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L73 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L74 QUE (NEPHROTOX? OR HEPATOTOX?)
	L75 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L76 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L77 QUE L52 OR L53 OR L54 OR L55 OR L56 OR L57 OR L58 OR L59 OR L60 OR L61 OR L62 OR L63 OR L64 OR L65 OR L66 OR L67 OR L68 OR L69 OR L70 OR L71 OR L72 OR L73 OR L74 OR L75 OR L76
	L78 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE
	OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE
	OR PORCINE OR MONKEY? OR MACAQUE?)
	L79 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L80 QUE L77 OR L78 OR L79
	L81 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L82 QUE L80 OR L81
	L83 (33977)SEA L51 AND L82
	L84 (19296)SEA L83 AND PY>2008
	L85 (3992)SEA L84 AND MEDLINE/FS
	L86 (4778)SEA L84 AND BIOSIS/FS
	L87 (10511)SEA L84 AND CAPLUS/FS
	L88 (15)SEA L84 NOT (L85 OR L86 OR L87)
	L89 (14309)DUP REM L85 L86 L88 L87 (4987 DUPLICATES REMOVED)
	L90 (3992)SEA L89
	L91 (3167)SEA L89
	L92 (7137)SEA L89
	L93 (13)SEA L89
	L94 4451 SEA (L90 OR L91 OR L92 OR L93) AND PY<2012

Table B-2. Database Query Strings

Database search date	Query string
	L95 1952 SEA L47 NOT MEDLINE/FS L96 1108 SEA L95 AND CAPLUS/FS L97 844 SEA L95 NOT CAPLUS/FS L98 3274 SEA L94 NOT MEDLINE/FS L99 2408 SEA L98 AND CAPLUS/FS L100 866 SEA L98 NOT CAPLUS/FS L101 1710 SEA L97 OR L100 D SCAN L101 DIS COST ACT DATE3/A --------- L102(128290)SEA FILE=TOXCENTER 7439-97-6 OR 7487-94-7 OR 1344-48-5 OR 10112 L103(76310)SEA FILE=TOXCENTER L102 AND PY>1997 L104(67121)SEA FILE=TOXCENTER L103 NOT PATENT/DT L105(67121)SEA FILE=TOXCENTER L104 NOT TSCATS/FS L106 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L107 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L108 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L109 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L110 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L111 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L112 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L113 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L114 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L115 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L116 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L117 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L118 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L119 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L120 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L121 QUE (ENDOCRIN? AND DISRUPT?)

Table B-2. Database Query Strings

Database search date	Query string
	L122 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L123 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L124 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L125 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L126 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L127 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L128 QUE (NEPHROTOX? OR HEPATOTOX?)
	L129 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L130 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L131 QUE L106 OR L107 OR L108 OR L109 OR L110 OR L111 OR L112 OR L113 OR L114 OR L115 OR L116 OR L117 OR L118 OR L119 OR L120 OR L121 OR L122 OR L123 OR L124 OR L125 OR L126 OR L127 OR L128 OR L129 OR L130
	L132 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L133 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L134 QUE L131 OR L132 OR L133
	L135 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L136 QUE L134 OR L135
	L137(33977)SEA FILE=TOXCENTER L105 AND L136
	L138(19296)SEA FILE=TOXCENTER L137 AND PY>2008
	L139(3992)SEA FILE=TOXCENTER L138 AND MEDLINE/FS
	L140(4778)SEA FILE=TOXCENTER L138 AND BIOSIS/FS
	L141(10511)SEA FILE=TOXCENTER L138 AND CAPLUS/FS
	L142(15)SEA FILE=TOXCENTER L138 NOT (L139 OR L140 OR L141)
	L143(14309)DUP REM L139 L140 L142 L141 (4987 DUPLICATES REMOVED)
	L144(3992)SEA FILE=TOXCENTER L143
	L145(3167)SEA FILE=TOXCENTER L143
	L146(7137)SEA FILE=TOXCENTER L143
	L147(13)SEA FILE=TOXCENTER L143
	L148(2794)SEA FILE=TOXCENTER (L144 OR L145 OR L146 OR L147) AND PY>2015
	L149(3992)SEA FILE=TOXCENTER L143
	L150(3167)SEA FILE=TOXCENTER L143
	L151(7137)SEA FILE=TOXCENTER L143
	L152(13)SEA FILE=TOXCENTER L143
	L153(4451)SEA FILE=TOXCENTER (L149 OR L150 OR L151 OR L152) AND PY<2012

Table B-2. Database Query Strings

Database search date	Query string
	L154(3992)SEA FILE=TOXCENTER L143 L155(3167)SEA FILE=TOXCENTER L143 L156(7137)SEA FILE=TOXCENTER L143 L157(13)SEA FILE=TOXCENTER L143 L158 7064 SEA (L154 OR L155 OR L156 OR L157) NOT (L148 OR L153) --------- L159 5091 SEA L158 NOT MEDLINE/FS L160 3621 SEA L159 AND CAPLUS/FS L161 1470 SEA L159 NOT CAPLUS/FS D SCAN L161 DIS COST ACT DATE4/A --------- L162(128290)SEA FILE=TOXCENTER 7439-97-6 OR 7487-94-7 OR 1344-48-5 OR 10112 L163(76310)SEA FILE=TOXCENTER L162 AND PY>1997 L164(67121)SEA FILE=TOXCENTER L163 NOT PATENT/DT L165(67121)SEA FILE=TOXCENTER L164 NOT TSCATS/FS L166 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L167 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L168 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L169 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L170 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L171 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L172 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L173 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L174 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L175 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L176 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L177 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L178 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L179 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L180 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)

Table B-2. Database Query Strings

Database search date	Query string
	L181 QUE (ENDOCRIN? AND DISRUPT?)
	L182 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L183 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L184 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L185 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L186 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L187 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L188 QUE (NEPHROTOX? OR HEPATOTOX?)
	L189 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L190 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L191 QUE L166 OR L167 OR L168 OR L169 OR L170 OR L171 OR L172 OR L173 OR L174 OR L175 OR L176 OR L177 OR L178 OR L179 OR L180 OR L181 OR L182 OR L183 OR L184 OR L185 OR L186 OR L187 OR L188 OR L189 OR L190
	L192 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L193 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L194 QUE L191 OR L192 OR L193
	L195 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L196 QUE L194 OR L195
	L197(33977)SEA FILE=TOXCENTER L165 AND L196
	L198(19296)SEA FILE=TOXCENTER L197 AND PY>2008
	L199(14681)SEA FILE=TOXCENTER L197 NOT L198
	L200(3235)SEA FILE=TOXCENTER L199 AND MEDLINE/FS
	L201(3669)SEA FILE=TOXCENTER L199 AND BIOSIS/FS
	L202(7631)SEA FILE=TOXCENTER L199 AND CAPLUS/FS
	L203(146)SEA FILE=TOXCENTER L199 NOT (L200 OR L201 OR L202)
	L204(11087)DUP REM L200 L201 L203 L202 (3594 DUPLICATES REMOVED)
	L205(3227)SEA FILE=TOXCENTER L204
	L206(2511)SEA FILE=TOXCENTER L204
	L207(5233)SEA FILE=TOXCENTER L204
	L208(116)SEA FILE=TOXCENTER L204
	L209 7860 SEA (L205 OR L206 OR L207 OR L208) NOT MEDLINE/FS ---
	L210 7860 SEA L209 NOT MEDLINE/FS
	L211 5233 SEA L209 AND CAPLUS/FS
	L212 2627 SEA L210 NOT CAPLUS/FS D SCAN L212

Table B-2. Database Query Strings

Database search date	Query string
	DIS COST ACT NODATE1/A ---
	L213(8637)SEA FILE=TOXCENTER 22967-92-6 OR 10045-94-0 OR 19122-79-3
	L214 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L215 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L216 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L217 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L218 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L219 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L220 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L221 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L222 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L223 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L224 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L225 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L226 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L227 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L228 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L229 QUE (ENDOCRIN? AND DISRUPT?)
	L230 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L231 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L232 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L233 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L234 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L235 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L236 QUE (NEPHROTOX? OR HEPATOTOX?)
	L237 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)

Table B-2. Database Query Strings

Database search date	Query string
	L238 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L239 QUE L214 OR L215 OR L216 OR L217 OR L218 OR L219 OR L220 OR L221 OR L222 OR L223 OR L224 OR L225 OR L226 OR L227 OR L228 OR L229 OR L230 OR L231 OR L232 OR L233 OR L234 OR L235 OR L236 OR L237 OR L238 L240 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L241 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L242 QUE L239 OR L240 OR L241 L243 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L244 QUE L242 OR L243 L245(7765)SEA FILE=TOXCENTER L213 NOT PATENT/DT L246(7765)SEA FILE=TOXCENTER L245 NOT TSCATS/FS L247(5195)SEA FILE=TOXCENTER L246 AND L244 L248(100)SEA FILE=TOXCENTER L247 AND MEDLINE/FS L249(2536)SEA FILE=TOXCENTER L247 AND BIOSIS/FS L250(2019)SEA FILE=TOXCENTER L247 AND CAPLUS/FS L251(540)SEA FILE=TOXCENTER L247 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/ L252(4358)DUP REM L248 L249 L251 L250 (837 DUPLICATES REMOVED) L253(100)SEA FILE=TOXCENTER L252 L254(2500)SEA FILE=TOXCENTER L252 L255(1221)SEA FILE=TOXCENTER L252 L256(537)SEA FILE=TOXCENTER L252 L257 4258 SEA (L253 OR L254 OR L255 OR L256) NOT MEDLINE/FS --------- L258 1221 SEA L257 AND CAPLUS/FS L259 3037 SEA L257 NOT CAPLUS/FS L260 3541 SEA L257 AND PY>1997 L261 2518 SEA L260 NOT CAPLUS/FS L262 519 SEA L259 NOT L261 SAVE TEMP L258 NODATECAPLUS/A L263 12370 SEA L96 OR L99 OR L160 OR L211 SAVE TEMP L263 DATECAPLUS/A D SCAN L262 D SCAN L261
1/2019	FILE 'TOXCENTER' ENTERED AT 11:00:42 ON 09 JAN 2019 CHARGED TO COST=EH038.01.01.LB.01 L1 137232 SEA FILE=TOXCENTER 7439-97-6 OR 7487-94-7 OR 1344-48-5 OR 10112-91-1 OR 1600-27-7 OR 115-09-3 OR 593-74-8 OR 62-38-4 OR 22967-92-6 OR 10045-94-0 OR 19122-79-3 L2 137137 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 123895 SEA FILE=TOXCENTER L2 NOT PATENT/DT

Table B-2. Database Query Strings

Database search date	Query string
	L4 2641 SEA FILE=TOXCENTER L3 AND ED>=20180401 L5 2640 SEA FILE=TOXCENTER L4 AND PY>1997 ACT TOXQUERY/Q --------- L6 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L7 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L8 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L9 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L10 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L18 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L19 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L20 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L21 QUE (ENDOCRIN? AND DISRUPT?) L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L28 QUE (NEPHROTOX? OR HEPATOTOX?) L29 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L30 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)

Table B-2. Database Query Strings

Database search date	Query string
	L31 QUE L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30
	L32 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L33 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L34 QUE L31 OR L32 OR L33
	L35 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L36 QUE L34 OR L35

	L37 1631 SEA FILE=TOXCENTER L5 AND L36
	L38 442 SEA FILE=TOXCENTER L37 AND MEDLINE/FS
	L39 792 SEA FILE=TOXCENTER L37 AND BIOSIS/FS
	L40 394 SEA FILE=TOXCENTER L37 AND CAPLUS/FS
	L41 3 SEA FILE=TOXCENTER L37 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L42 1325 DUP REM L38 L39 L41 L40 (306 DUPLICATES REMOVED) ANSWERS '1-1325' FROM FILE TOXCENTER
	L*** DEL 442 S L37 AND MEDLINE/FS
	L*** DEL 442 S L37 AND MEDLINE/FS
	L43 442 SEA FILE=TOXCENTER L42
	L*** DEL 792 S L37 AND BIOSIS/FS
	L*** DEL 792 S L37 AND BIOSIS/FS
	L44 606 SEA FILE=TOXCENTER L42
	L*** DEL 394 S L37 AND CAPLUS/FS
	L*** DEL 394 S L37 AND CAPLUS/FS
	L45 274 SEA FILE=TOXCENTER L42
	L*** DEL 3 S L37 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L*** DEL 3 S L37 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L46 3 SEA FILE=TOXCENTER L42
	L47 883 SEA FILE=TOXCENTER (L43 OR L44 OR L45 OR L46) NOT MEDLINE/FS
	L48 442 SEA FILE=TOXCENTER L43 NOT CAPLUS/FS
	L49 609 SEA FILE=TOXCENTER L47 NOT CAPLUS/FS
	L50 274 SEA FILE=TOXCENTER L47 AND CAPLUS/FS D SCAN L49
	L51 739 SEA FILE=TOXCENTER 7546-30-7 OR 10031-18-2 OR 7789-47-1 OR 15385-58-7 OR 628-86-4 OR 7783-30-4 OR 15385-57-6 OR 7774-29-0 OR 10415-75-5 OR 14836-60-3
	L52 5609 SEA FILE=TOXCENTER 15829-53-5 OR 21908-53-2 OR 20601-83-6 OR 11138-42-4 OR 7783-36-0 OR 7783-35-9 OR 12068-90-5 OR 592-04-1 OR 631-60-7 OR 14302-87-5 OR 22542-11-6
	L53 6209 SEA FILE=TOXCENTER L51 OR L52
	L54 6206 SEA FILE=TOXCENTER L53 NOT TSCATS/FS

Table B-2. Database Query Strings

Database search date	Query string
	L55 5086 SEA FILE=TOXCENTER L54 NOT PATENT/DT
	L56 1729 SEA FILE=TOXCENTER L55 AND L36
	L57 101 SEA FILE=TOXCENTER L56 AND MEDLINE/FS
	L58 606 SEA FILE=TOXCENTER L56 AND BIOSIS/FS
	L59 941 SEA FILE=TOXCENTER L56 AND CAPLUS/FS
	L60 81 SEA FILE=TOXCENTER L56 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L61 1622 DUP REM L57 L58 L60 L59 (107 DUPLICATES REMOVED)
	ANSWERS '1-1622' FROM FILE TOXCENTER
	L*** DEL 101 S L56 AND MEDLINE/FS
	L*** DEL 101 S L56 AND MEDLINE/FS
	L62 101 SEA FILE=TOXCENTER L61
	L*** DEL 606 S L56 AND BIOSIS/FS
	L*** DEL 606 S L56 AND BIOSIS/FS
	L63 592 SEA FILE=TOXCENTER L61
	L*** DEL 941 S L56 AND CAPLUS/FS
	L*** DEL 941 S L56 AND CAPLUS/FS
	L64 850 SEA FILE=TOXCENTER L61
	L*** DEL 81 S L56 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L*** DEL 81 S L56 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L65 79 SEA FILE=TOXCENTER L61
	L66 1521 SEA FILE=TOXCENTER (L62 OR L63 OR L64 OR L65) NOT MEDLINE/FS
	L67 671 SEA FILE=TOXCENTER L66 NOT CAPLUS/FS
	L68 850 SEA FILE=TOXCENTER L66 AND CAPLUS/FS
	L69 442 SEA FILE=TOXCENTER L67 AND PY>1997
	L70 17 SEA FILE=TOXCENTER L67 AND ED>=20180401
	L71 466 SEA FILE=TOXCENTER L67 NOT L1
	L72 471 SEA FILE=TOXCENTER L70 OR L71
	L73 334 SEA FILE=TOXCENTER L72 AND PY>1997
	L74 137 SEA FILE=TOXCENTER L72 NOT L73
	L75 229 SEA FILE=TOXCENTER L67 NOT L69
	D SCAN L69
	D SCAN L75
	L76 1 SEA FILE=TOXCENTER "MERCURY(I) FULMINATE" OR "MERCURY(I) SELENIDE" OR "MERCUROUS SELENIDE" OR "MERCURY(I) CYANIDE" OR "MERCUROUS CYANIDE"
	L77 54 SEA FILE=TOXCENTER "DIMERCURANE" OR "MERCUROUS HYDRIDE" OR
	"MERCURY HYDRIDE" OR "MERCURY MONOHYDRIDE" OR "MERCURY(I) HYDRIDE" OR "MERCURANE" OR "MERCURIC HYDRIDE" OR "MERCURY(II) HYDRIDE"
	L78 55 SEA FILE=TOXCENTER L76 OR L77
	L79 54 SEA FILE=TOXCENTER L78 NOT PATENT/DT
	L80 54 SEA FILE=TOXCENTER L79 NOT TSCATS/FS
	L81 52 SEA FILE=TOXCENTER L80 NOT L53
	L82 26 SEA FILE=TOXCENTER L81 AND L36
	L83 6 SEA FILE=TOXCENTER L82 AND MEDLINE/FS
	L84 10 SEA FILE=TOXCENTER L82 AND BIOSIS/FS
	L85 9 SEA FILE=TOXCENTER L82 AND CAPLUS/FS
	L86 1 SEA FILE=TOXCENTER L82 NOT (L83 OR L84 OR L85)

Table B-2. Database Query Strings

Database search date	Query string
	L87 18 DUP REM L83 L84 L86 L85 (8 DUPLICATES REMOVED) ANSWERS '1-18' FROM FILE TOXCENTER
	L*** DEL 6 S L82 AND MEDLINE/FS
	L*** DEL 6 S L82 AND MEDLINE/FS
	L88 6 SEA FILE=TOXCENTER L87
	L*** DEL 10 S L82 AND BIOSIS/FS
	L*** DEL 10 S L82 AND BIOSIS/FS
	L89 6 SEA FILE=TOXCENTER L87
	L*** DEL 9 S L82 AND CAPLUS/FS
	L*** DEL 9 S L82 AND CAPLUS/FS
	L90 5 SEA FILE=TOXCENTER L87
	L*** DEL 1 S L82 NOT (L83 OR L84 OR L85)
	L*** DEL 1 S L82 NOT (L83 OR L84 OR L85)
	L91 1 SEA FILE=TOXCENTER L87
	L92 12 SEA FILE=TOXCENTER (L88 OR L89 OR L90 OR L91) NOT MEDLINE/FS
	L93 59014 SEA FILE=TOXCENTER 92 NOT CAPLUS/FS
	L94 7 SEA FILE=TOXCENTER L92 NOT CAPLUS/FS D SCAN L94

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
1/2019	Compounds searched: 7439-97-6; 7487-94-7; 1344-48-5; 10112-91-1; 1600-27-7; 115-09-3; 593-74-8; 62-38-4; 22967-92-6; 10045-94-0; 19122-79-3; 7546-30-7; 10031-18-2; 7789-47-1; 15385-58-7; 628-86-4; 7783-30-4; 15385-57-6; 7774-29-0; 10415-75-5; 14836-60-3; 15829-53-5; 21908-53-2; 20601-83-6; 11138-42-4; 7783-36-0; 7783-35-9; 12068-90-5; 592-04-1; 631-60-7; 14302-87-5; 22542-11-6
NTP	
1/2019	Terms searched individually: 7439-97-6; 7487-94-7; 1344-48-5; 10112-91-1; 1600-27-7; 115-09-3; 593-74-8; 62-38-4; 22967-92-6; 10045-94-0; 19122-79-3; mercuric; mercurous; mercury; methylmercury; methylmercuric; phenylmercury; phenylmercuric; ethylmercury; ethylmercuric; calomel; cinnabar; 7546-30-7; 10031-18-2; 7789-47-1; 15385-58-7; 628-86-4; 7783-30-4; 15385-57-6; 7774-29-0; 10415-75-5; 14836-60-3; 15829-53-5; 21908-53-2; 20601-83-6; 11138-42-4; 7783-36-0; 7783-35-9; 12068-90-5; 592-04-1; 631-60-7; 14302-87-5; 22542-11-6
Regulations.gov	
1/2019	Compounds searched: 7439-97-6; 7487-94-7; 1344-48-5; 10112-91-1; 1600-27-7; 115-09-3; 593-74-8; 62-38-4; 22967-92-6; 10045-94-0; 19122-79-3; 7546-30-7; 10031-18-2; 7789-47-1; 15385-58-7; 628-86-4; 7783-30-4; 15385-57-6; 7774-29-0; 10415-75-5; 14836-60-3; 15829-53-5; 21908-53-2; 20601-83-6; 11138-42-4; 7783-36-0; 7783-35-9; 12068-90-5; 592-04-1; 631-60-7; 14302-87-5; 22542-11-6
NIH RePORTER	
11/2020	**Text Search:** mercury OR mercuric OR mercurous OR dimercury (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	Text Search: "Mercuric dibromide" OR "Mercury dibromide" OR "Mercury(II) bromide" OR "Mercury fulminate" OR "Mercurous iodide" OR "Mercuric iodide" OR "Mercury iodide" OR "Mercury(II) iodide" OR "Mercuric oxide" OR "Mercury oxide" OR "Red Precipitate" OR "Yellow precipitate" OR "Mercuric selenide" OR "Mercury selenide" OR "Mercury-selenium complex" OR "Mercurous sulfate" OR "Mercury(I) sulfate" OR "Mercuric sulfate" OR "Mercuric sulphate" OR "Mercury sulfate" OR "Mercury sulphate" OR "Mercury telluride" OR "Mercuric cyanide" OR "Mercurius cyanatus" OR "Mercury cyanide" OR "Mercury hydride" OR "Mercurane" OR "Mercuric cation" OR "Mercuric cations" OR "Mercuric ion" OR "Mercuric ions" OR "Agrosan D" OR "Agrosan GN 5" OR "Algimycin 200" OR "Antimucin WBR" OR "Antimucin WDR" OR "Bufen" OR "Bufen 30" OR "Cekusil" OR "Ceresol" OR "Contra Creme" OR "Dyanacide" OR "Fungicide R" OR "Fungitox OR" OR "Gallotox" OR "Hl-331" OR "Hong nien" OR "Hostaquik" OR "Intercide 60" OR "Intercide PMA 18" OR "Liquiphene" OR "Meracen" OR "Mercron" OR "Mercuron" OR "Mergal A 25" OR "Mersolite" OR "Metasol 30" OR "Neantina" OR "Norforms" OR "Nuodex PMA 18" OR "Nylmerate" OR "PMA (fungicide)" OR "Pamisan" OR "Panomatic" OR "Parasan (bactericide)" OR "Phenmad" OR "Programin" OR "Purasan-SC-10" OR "Puraturf 10" OR "Quicksan" OR "Quicksan 20" OR "Riogen" OR "Ruberon" OR "Sanitized SPG" OR "Sanmicron" OR "Scutl" OR "Seed Dressing R" OR "Seedtox" OR "Setrete" OR "Shimmerex" OR "Spor-Kil" OR "Spruce Seal" OR "Tag (VAN)" OR "Tag 331" OR "Tag HL 331" OR "Tag fungicide" OR "Trigosan" OR "Troysan 30" OR "Troysan PMA 30" OR "Zaprawa Nasienna R" OR "Ziarnik" OR "Hydraargyrum bichloratum" OR "Calo-Clor" OR "Calocure" OR "Calogreen" OR "Calotab" OR "Abavit B" OR "Citrine ointment" OR "Ethiops mineral" OR "Mercurius vivus" OR "beta-Mercuric sulfide" OR "Phenylquecksilberacetate" OR "Quecksilber(II)-sulfid, rotes" OR "Rotes Quecksilbersulfid" OR "Paragite" OR "TL 898" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects **Text Search:** "(acetato)phenylmercury" OR "(acetato-kappao)phenylmercury" OR "(acetato-o)phenylmercury" OR "(acetoxymercuri)benzene" OR "(acetoxymercurio)benzene" OR "acetic acid, mercuridi-" OR "acetic acid, mercury(2) salt" OR "acetic acid, phenylmercury deriv." OR "acetic acid, phenylmercury(ii) salt" OR "acetoxyphenylmercury" OR "benzene, (acetoxymercuri)-" OR "benzene, (acetoxymercurio)-" OR "bis(acetyloxy)mercury" OR "calochlor" OR "calomel" OR "chloromethylmercury" OR "cinnabar" OR "cinnabarite" OR "diacetoxymercury" OR "dichloromercury" OR "dimercury dichloride" OR "dimethylmercury" OR "fungche" OR "hydrargyrum" OR "mercuriacetate" OR "mercuric acetate" OR "mercuric bichloride" OR "mercuric chloride" OR "mercuric diacetate" OR "mercuric nitrate" OR "mercuric sulfide" OR "mercuric sulphide" OR "mercuridiacetic acid, " OR "mercuriphenyl acetate" OR "mercurius 6a" OR "mercurous chloride" OR "mercury(1), methyl-" OR "mercury(2) acetate" OR "mercury(2) chloride" OR "mercury(2) nitrate" OR "mercury(2) sulfide" OR "mercury(i) chloride" OR "mercury(ii) acetate" OR "mercury(ii) acetate, phenyl-" OR "mercury(ii) chloride" OR "mercury(ii) nitrate" OR "mercury(ii) sulfide" OR "mercury, (acetato)phenyl-" OR "mercury, (acetato-kappao)phenyl-" OR "mercury, (acetato-o)phenyl-" OR "mercury, acetoxyphenyl-" OR "mercury, chloromethyl-" OR "mercury, dimethyl-" OR "mercuryl acetate" OR "mercurymethylchloride" OR "methyl mercuric chloride" OR "methyl mercuric(ii) chloride" OR "methyl meruric chloride" OR "methylmercuric chloride" OR "methylmercury" OR "methylmercury chloride" OR "methylmercury monochloride" OR "methylmercury(1)" OR "methylmercury(ii) cation" OR "millon's reagent" OR "monomercury sulfide" OR "monomethylmercury cation" OR "nitric acid, mercury(2) salt" OR "nitric acid, mercury(ii) salt" OR "phenomercuric acetate" OR "phenyl mercuric acetate" OR "phenylmercuriacetate" OR "phenylmercuric acetate" OR "phenylmercury acetate" OR "phenylmercury(ii) acetate"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	OR "Anticon" OR "Celmer" OR "Femma" OR "Hexasan" OR "Hostaquick" OR "Kwiksan" OR "Lorophyn" OR "Parasan" OR "Phix" OR "Samtol" OR "Sanitol" OR "Sc-110" OR "Verdasan" OR "Volpar" OR "Caspan" OR "Liquid silver" OR "Quick silver" OR "Quicksilver" OR "Sulem" OR "Cyclosan" OR "Mercury chloride" OR "Mercury bromide" OR "Mercuric bromide" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects **Text Search:** "Mercury monochloride" OR "Mercury protochloride" OR "Precipite blanc" OR "Mercurous bromide" OR "Mercury monobromide" OR "Mercury(I) bromide" OR "Dibromomercury" OR "dibromodimercury" OR "Mercury, dibromodi-,(Hg-Hg)" OR "Mercury(I) fulminate" OR "Fulminate of mercury" OR "Fulminating mercury" OR "Fulminic acid, mercury(2) salt" OR "Fulminic acid, mercury(II) salt" OR "Mercuric cyanate" OR "Mercury difulminate" OR "mercury fulminic acid" OR "Mercury(II) fulminate" OR "Mercury, bis(fulminato)-" OR "Mercury, bis(fulminato-kappaC)-" OR "Mercury protoiodide" OR "Mercury(I) iodide" OR "Dimercury diiodide" OR "Diiodomercury" OR "Hydrargyrum diodatum" OR "Mercurius bijodatus" OR "Mercury biniodide" OR "Mercury diiodide" OR "Mercury(2) diiodide" OR "Mercury(2) iodide" OR "Dimercury dinitrate" OR "Mercurous nitrate" OR "Mercury protonitrate" OR "Mercury(1) nitrate" OR "Mercury(I) nitrate" OR "Monomercury nitrate" OR "Nitric acid, mercury(1) salt" OR "Nitric acid, mercury(I) salt" OR "Mercurous oxide" OR "Mercury(I) oxide" OR "Hydrargyrum oxid flav" OR "Hydrargyrum oxydatum rubrum" OR "Mercuric monooxide" OR "Mercury monoxide" OR "Mercury(2) oxide" OR "Mercury(II) oxide" OR "Natural montroydite" OR "Red oxide of mercury" OR "Santar" OR "Yellow oxide of mercury" OR "Mercury(I) selenide" OR "Mercurous selenide" OR "Mercury monoselenide" OR "Mercury(2) selenide" OR "Mercury(II) selenide" OR "Dimercury sulfate" OR "Dimercury sulphate" OR "Mercurous sulphate" OR "Sulfuric acid, dimercury(1) salt" OR "Sulfuric acid, dimercury(1) salt" OR "Mercuric bisulphate" OR "Mercurous bisulphate" OR "Mercury bisulfate" OR "Mercury bisulphates" OR "Mercury disulfate" OR "Mercury persulfate" OR "Mercury(II) sulfate" OR "Sulfuric acid, mercury(2) salt" OR "Mercuric telluride" OR "Mercury monotelluride" OR "Mercury(2) telluride" OR "mercury(II) telluride" OR "Mercury(I) cyanide" OR "Mercurous cyanide" OR "Cianurina" OR "Dicyanomercury" OR "Hydrargyrum cyanatum" OR "Mercury dicyanide" OR "Mercury(II) cyanide" OR "Dimercurane" OR "Mercurous hydride" OR "Mercury monohydride" OR "Mercury(I) hydride" OR "Mercuric hydride" OR "Mercury(II) hydride" OR "Acetic acid, mercury (1) salt" OR "Dimercury di(acetate)" OR "Mercurous acetate" OR "Mercury monoacetate" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2019 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 35,856
- Number of records identified from other strategies: 418
- Total number of records to undergo literature screening: 36,274

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on mercury:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

- Number of titles and abstracts screened: 36,274
- Number of studies considered relevant and moved to the next step: 1,793

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 1,793
- Number of studies cited in the pre-public draft of the toxicological profile: 502
- Total number of studies cited in the profile: 1,595

Prioritization of Human Data. Due to the extent of the literature database, it is not practical or realistic to cite all, or even most, of the studies on health effects of mercury. This profile is not to provide a comprehensive review of all literature; instead, the purpose and scope of this profile is to summarize the major lines of evidence regarding health effects associated with environmental and occupational exposure to mercury compounds. Therefore, human data were prioritized for inclusion as follows:

- Epidemiological studies of environmental and occupational exposures were only considered for inclusion if they were well-conducted and reported and included the following: measurements of mercury intakes or biomarker data, measures of variance for outcome metrics, and reported methods for addressing confounding.
  - Exception: Studies of mercury poisoning outbreaks that lacked biomonitoring data but provided critical hazard identification information (e.g., Minamata disease)
- Human studies reporting health effects associated with consumer or medicinal products containing mercury (e.g., vaccines) were excluded, as these studies are not focused on sources of environmental or occupational exposure.
- Case reports were not included in the profile due to the extensive number of available epidemiological studies.
  - Exception 1: Case reports that included discussion of acute accidental or intentional exposure to near-fatal or fatal levels of mercury
  - Exception 2: Case reports that described portal-of-entry effects following acute exposures

Quality criteria were considered in selecting studies to include in the mercury profile and, in particular, for consideration as support for MRLs. In general, epidemiological studies that attempted dose-response assessments (e.g., regression models) were included in the profile if the following criteria were met: (1) reported estimates of variance in the dose-response metrics (e.g., SE, CL); (2) included adjustments for confounding; and (3) reported biomarker data. For studies used to derive MRLs, reporting of quality assurance of analytical methods was also required.

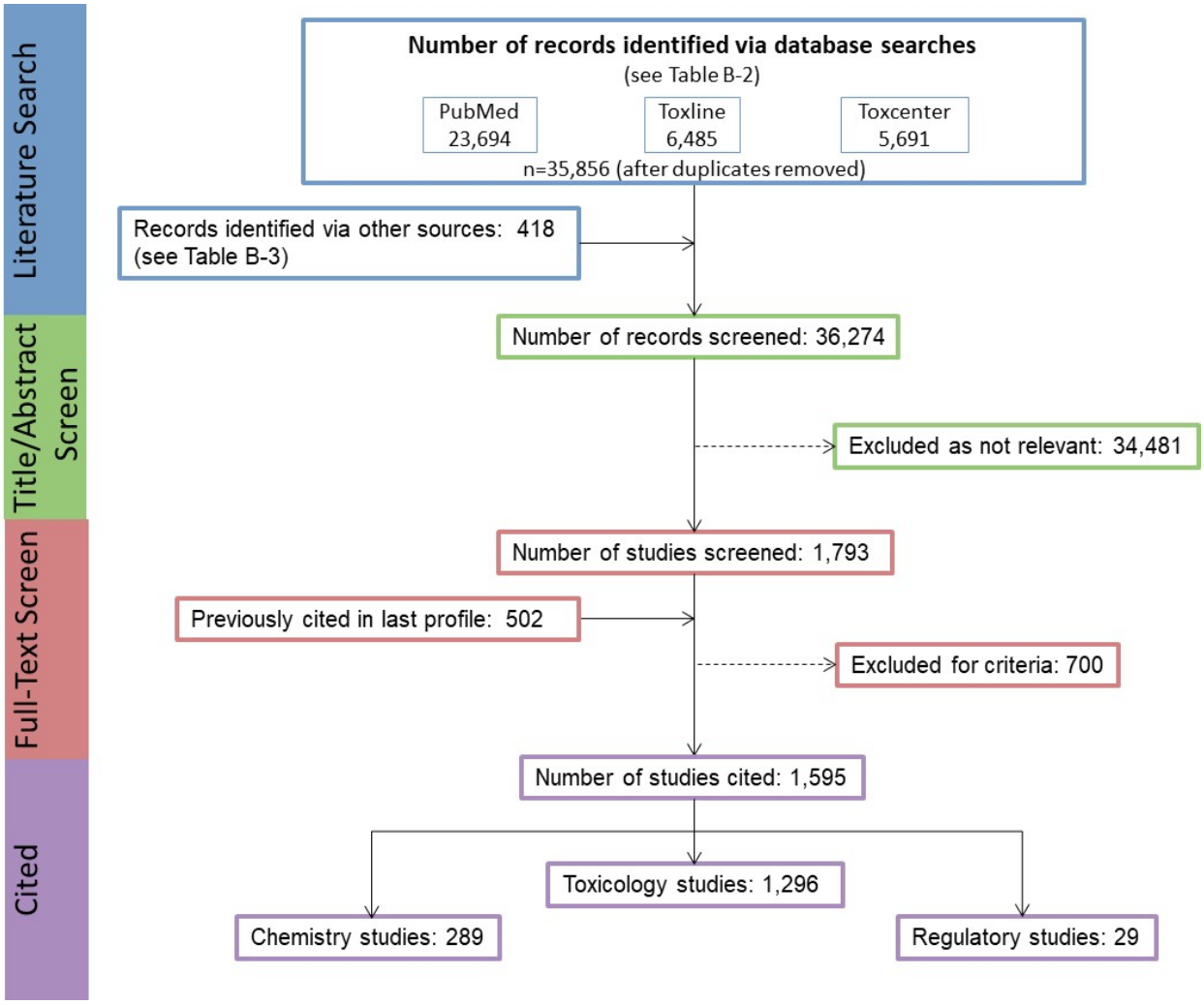
Prioritization of Animal Data

- All well-conducted and reported studies were considered for inclusion with a focus on routes of exposure most relevant to environmental exposure of humans (inhalation, oral, dermal).
- Parenteral studies were included only when needed to support understanding of mechanisms, but not for exposure-response relationships (since dose-response relationships observed following parenteral dosing may not accurately reflect exposure-response relationships).

- Animal studies focused on toxicity of traditional medicine or cultural uses of mercury-containing compounds (e.g., cinnabar) were excluded as not relevant to environmental exposures.

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. January 2019 Literature Search Results and Screen for Mercury



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

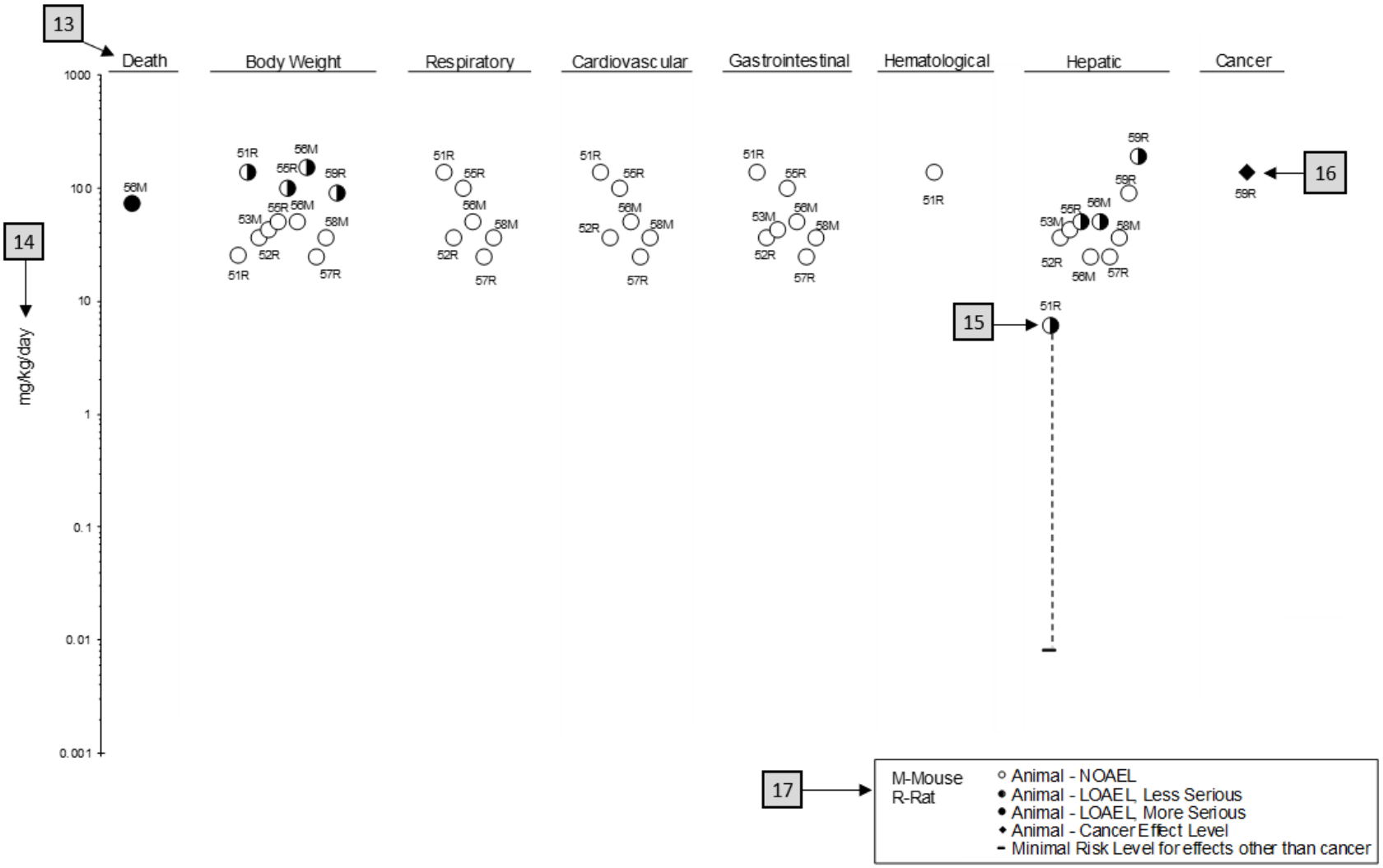
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Adverse-Effect Level (AEL)—An estimate of an exposure concentration or dose at which an adverse outcome was observed. For example, in the derivation of the chronic-duration inhalation MRL for elemental mercury, urine mercury levels were converted to equivalent exposure concentrations at which tremor was observed. Unlike a LOAEL, an AEL is not a point of departure from a dose-response relationship and may not represent the LOAEL.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Confounding—The confusion, or mixing, of effects; this definition implies that the effect of exposure, if mixed together with the effect of another variable, leads to bias. A confounder:

1. must be associated with the disease (as a cause or as a proxy for a cause but not as an effect of the disease);
2. must be associated with exposure, and
3. must not be an effect of the exposure.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Effect Measure Modification—In epidemiology, effect measure modification occurs when the measure of an effect or association (e.g., risk ratio) for an exposure of interest changes over the values of some other variable. This other variable results in a departure from the underlying statistical model.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Adverse-Effect Level (NAEL)—An estimate of an exposure concentration or dose at which an adverse outcome was not observed. For example, in the derivation of the chronic-duration inhalation MRL for elemental mercury, urine mercury levels were converted to equivalent exposure concentrations at which tremors were not observed. Unlike a NOAEL, a NAEL is not a point of departure from a dose-response relationship and may not represent the highest NOAEL.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AEL	adverse-effect level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act

FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAEL	no-adverse-effect level
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram

NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States

USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result