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 2024). Based on survey data for the period 2017–2018 (the most recent data available in CDC 2024), the geometric mean total blood mercury (BHg) level in the adult U.S. population was estimated to be 0.730 μg/L (95% confidence interval [CI] 0.620, 0.840). The geometric mean methylmercury blood level was 0.500 μg/L (95% CI 0.420, 0.610). Total and methylmercury blood levels in young children were lower than in adults. For the 2011–2012 period, the detection limits for total mercury were lower, reporting a geometric mean total BHg 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.

1.2 SUMMARY OF HEALTH EFFECTS

The toxicity of mercury compounds has been recognized since ancient times (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.

1. RELEVANCE TO PUBLIC HEALTH

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-duration accidental or intentional exposure to near-fatal or fatal levels. With few exceptions, exposure duration for epidemiological populations is considered to be chronic-duration 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. Mercury in hair or nails can provide a measure of cumulative, long-term exposure because mercury is retained in hair and nails. Mercury levels in blood and urine are much more dynamic (Section 3.1) and more greatly affected by recent exposure history.

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.

1. RELEVANCE TO PUBLIC HEALTH

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. 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). The developing nervous system is more vulnerable to methylmercury exposure than the mature nervous system because maternal-fetal and maternal-child transfer of methylmercury can occur at critical stages of development of the brain and cognition and prior to maturation of the blood-brain barrier to an adult functioning blood-brain barrier.

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 biomarkers indicating increased mercury exposure and markers indicating changes in immune system 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, poisoned by organic mercury consumed in fish. 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-duration 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 (i.e., mg Hg/kg/day), and not in terms of specific mercury compounds, to allow comparison of doses across studies. 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 (Appendix A).

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

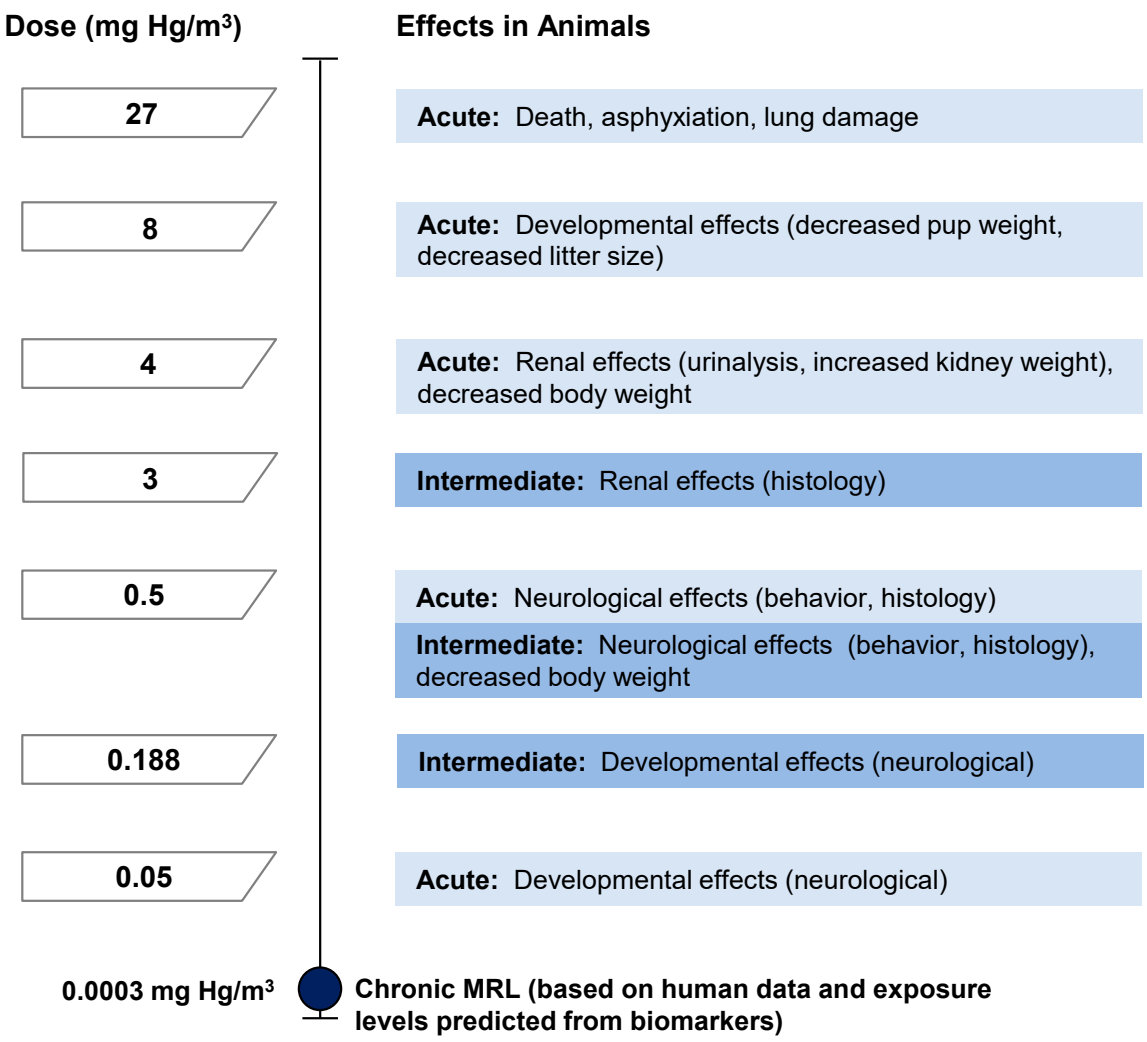
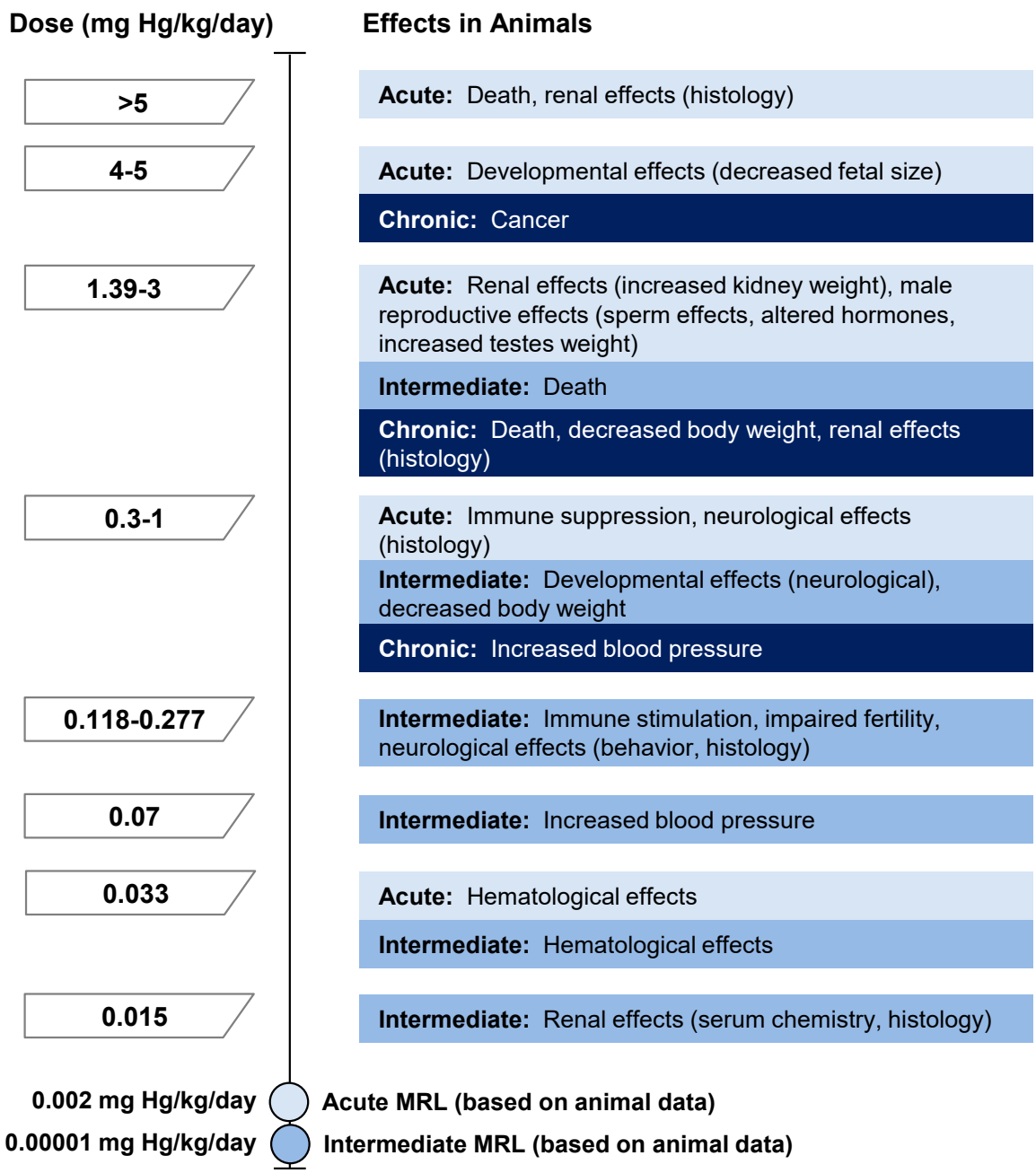
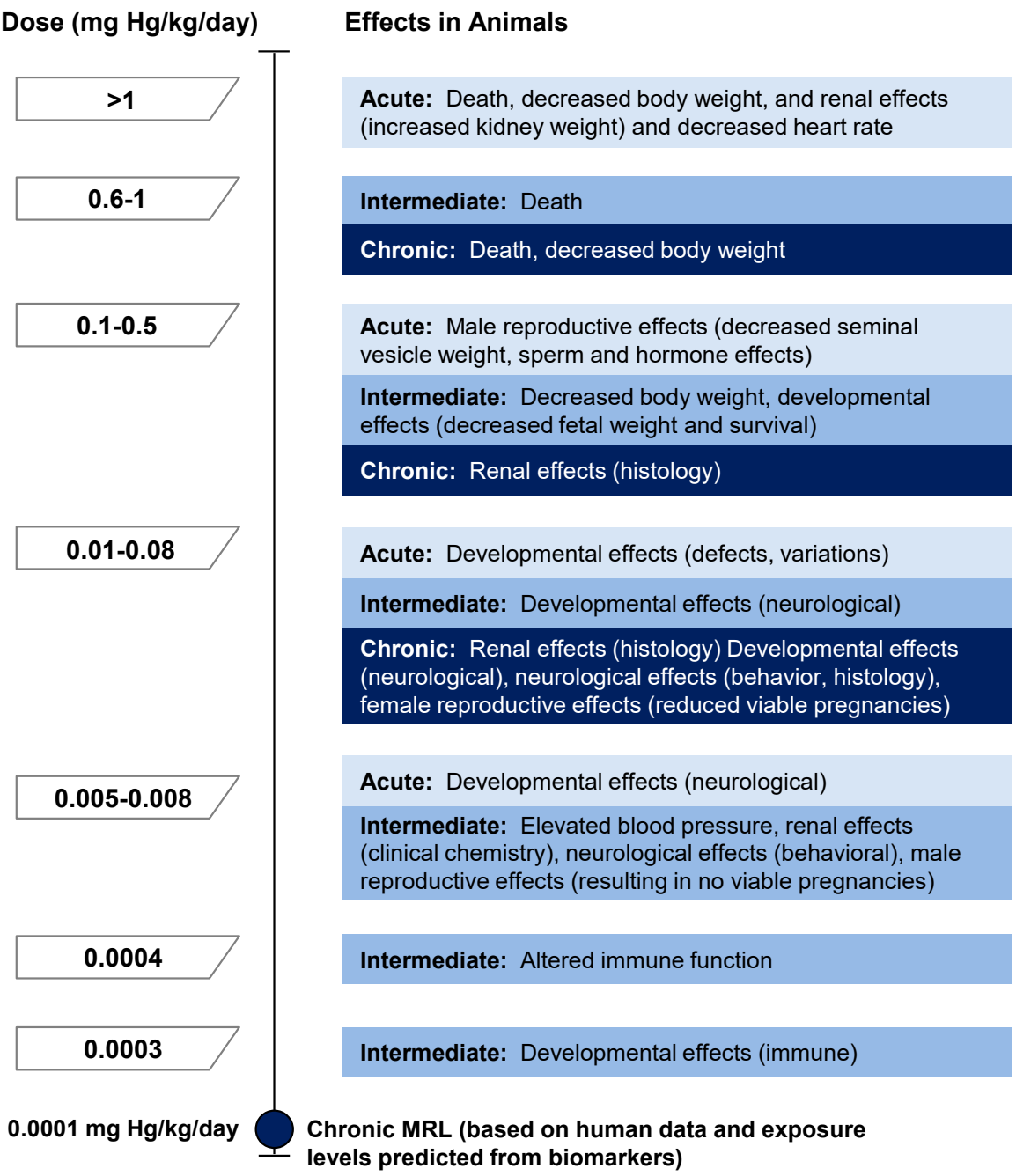


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Inorganic Mercuric Salts*



*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



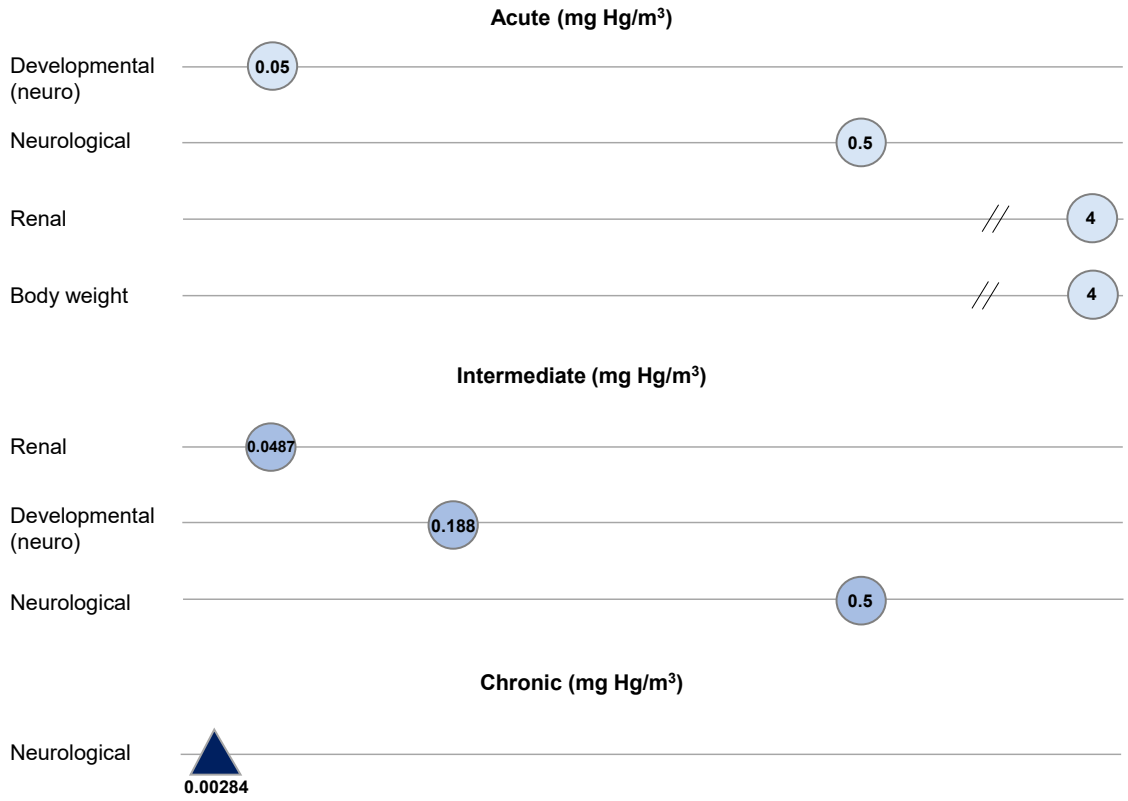
1.3 MINIMAL RISK LEVELS (MRLs)

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

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

Available data indicate that 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*.



*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

Available data indicate that 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.

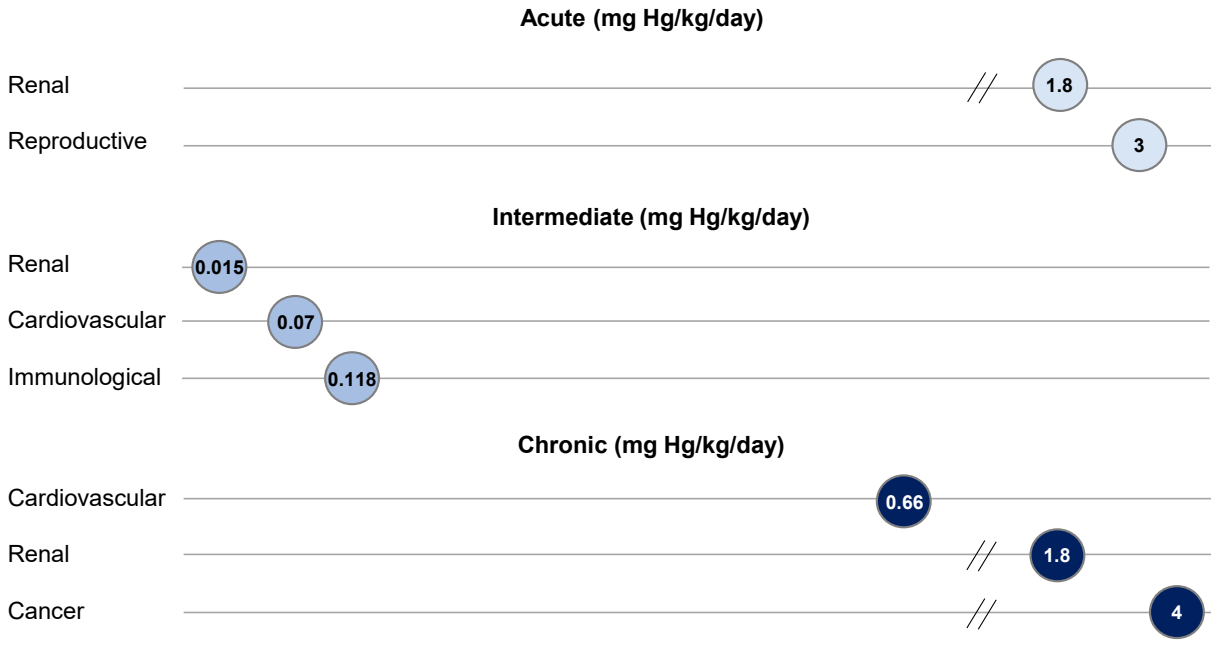
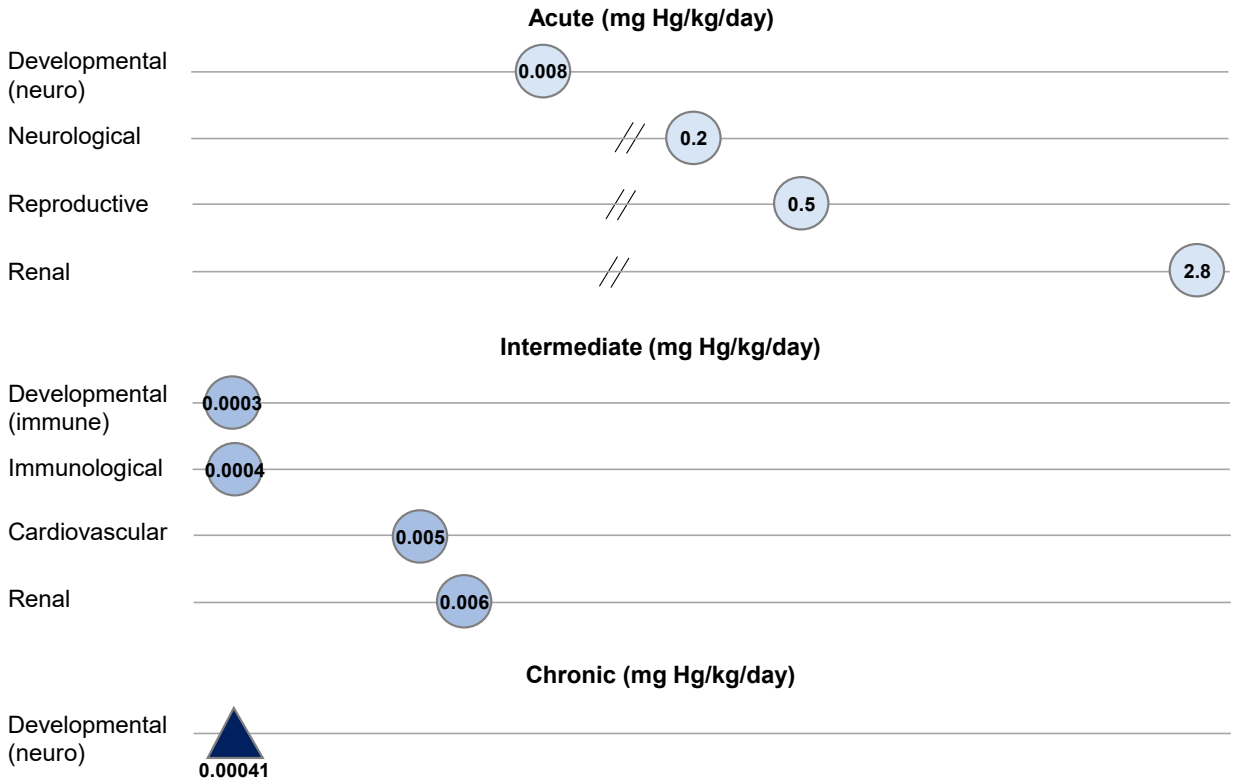


Figure 1-6. Summary of Sensitive Targets of Organic Mercury – Oral

Available data indicate that 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*.



*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 (Axelrad et al. 2007a, 2007b) of three epidemiological studies.

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

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	None	–	–	–	–	–
	Intermediate	None	–	–	–	–	–
	Chronic	**0.3 µg Hg/m^3**	Tremors	95% lower confidence limit of weighted median of seven principal studies	2.84 µg Hg/m^3	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	**No oral MRLs were derived for any duration**						

[a]See Appendix A for additional information.

POD = point of departure; UF = uncertainty factor

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

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	**No inhalation MRLs were derived for any duration**						
Oral	Acute	**0.002 mg Hg/kg/day**	Elevated relative kidney weight	$BMDL_{ADJ}$	0.21 mg Hg/kg/day	UF: 100	Dieter et al. 1992; NTP 1993
	Intermediate	**$1x10^{-5}$ mg Hg/kg/day**	Decreased renal function and histopathological changes	LOAEL	0.015 mg Hg/kg/day	UF: 1,000	Apaydin et al. 2016
	Chronic	None	–	–	–	–	–

[a]See Appendix A for additional information.

ADJ = adjusted; BMDL = 95% lower confidence limit on the BMD; LOAEL = lowest observed adverse effect level; POD = point of departure; UF = uncertainty factor

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

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	**No inhalation MRLs were derived for any duration**						
Oral	Acute	None	–	–	–	–	–
	Intermediate	None	–	–	–	–	–
	Chronic	**0.1 µg Hg/kg/day**	Neurodevelopmental effects (decreased IQ)	NAEL	0.41 µg Hg/kg/day	UF: 3	Axelrad et al. 2007a, 2007b

[a]See Appendix A for additional information.

IQ = intelligence quotient; NAEL = no-adverse-effect level; POD = point of departure; UF = uncertainty factor