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.

- o Oxidation removes Hg^0 from blood, limiting its transfer from blood to exhaled air and its distribution to other tissues.

- *Excretion:*
  - o 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.
  - o 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:*
  - o 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:*
  - o 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.
  - o 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).
  - o Dermal: Inorganic mercuric mercury was absorbed across isolated human and pig skin.

- *Distribution:*
  - o 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.
  - o Inorganic mercury is found in human cord blood, placenta, and breast milk indicating potential routes of transfer to the fetus and nursing infant.

- *Metabolism:*
  - o Exhaled Hg^0 was observed in mice following parenteral doses of mercuric chloride, suggesting that Hg^{2+} had been reduced to Hg^0.

o   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:*

o   The major routes of excretion of absorbed mercuric mercury are feces and urine.

o   Kinetics of elimination of absorbed inorganic mercuric mercury exhibits multiple phases.

o   The terminal half-time has been estimated in humans to range from 49 to 120 days.

- *Toxicokinetics models:*

o   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

o   No studies were located that provide quantitative information on the absorption, distribution, metabolism, or excretion of inorganic mercurous mercury.

o   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.

o   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:*

o   Respiratory tract: No studies were found that have estimated absorption of inhaled organic mercuric mercury.

o   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.

o   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:*

o   Following ingestion of methylmercury, mercury distributes throughout the body, with the highest concentrations occurring in the liver, kidneys, and brain.

- o Methylmercury is found in human cord blood, placenta, and breast milk indicating potential routes of transfer to the fetus and nursing infants.
- *Metabolism:*
  - o 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.
  - o 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:*
  - o The major routes of excretion of absorbed methylmercury are feces, urine, and hair.
  - o Following exposure to phenylmercury, absorbed mercury is eliminated in bile, feces, urine, and hair.
  - o 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:*
  - o 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 (Section 3.1.5 provides a more detailed 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 BHg or UHg 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 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.

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

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

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
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 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

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[a]	Nielsen and Andersen 1990
Mouse	ND	3 months	$HgCl_2$	1 dose	Trace	Gavage (in feed)	Standard diet	2.1[a]	Revis et al. 1990
Mouse	ND	3 months	HgS	1 dose	Trace	Gavage (in feed)	Standard diet	0.4[b]	Revis et al. 1990
Mouse	B	3 months	Soil[c]	1 day	0.002–0.4 mg	5% soil in diet	Standard diet	4–16[b]	Revis et al. 1990
Mouse	B	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; B = both males and females; BW = body weight; EF = exposure frequency; F = female; M = male; ND = no data

[a]Oral/intraperitoneal ratio of whole-body retention.
[b]Dose minus cumulative excretion in feces measured over a period of 96 hours, minus mercury in gastrointestinal tract mercury at termination of exposure.
[c]5% soil in diet.
[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.

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).

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; Li and Wang 2019: 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 methylmercury (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 1.4×10^{-2} cm/hour when the initial mercury concentration was 0.0088 $nmol/cm^3$ (1.8 µg Hg/L) and 3.0×10^{-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 BHg made approximately 5 months following the accident and the estimated half-time of 75 days for HHg 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. (1976) 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 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. Autopsy studies of patients poisoned with mercury vapor found mercury deposited primarily in neuron vascular walls and brainstem and in deep nuclei of the cerebrum and cerebellum (O'Donoghue et al. 2020). Autopsy studies of Parkinson's Disease patients found mercury deposited in neurons of the substantia nigra, motor cortex, striatum, thalamus, and cerebellum (Pamphlett and Bishop 2022). 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, 2019: 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). Following the same exposure protocol, deposits of mercury were found in skeletal connective tissues, including synovial cells, articular chondrocytes, and periosteal and tracheal cartilage cells (Pamphlett and Kum-Jew 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 kidney 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. 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; Højbjerg et al. 1992; Khan et al. 2001; Kostial et al. 1978, 1984; Lu et al. 2020; 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% (Højbjerg 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 have 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).

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; Højbjerg 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% (Højbjerg 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 have 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; Li et al. 2020; 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 (Charette et al. 2021; 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$_3$Hg-S-Cys) and glutathione (CH$_3$Hg-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). BHg 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. Mercury does not uniformly distribute in all areas of the brain following inhalation exposure to methylmercury. Autopsy studies of people exposed to methylmercury found mercury deposited in glial and endothelial cells more prominently than in neurons (O'Donoghue et al. 2020). 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$_3$Hg-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). Following exposure to ethylmercury, mercury has been detected in the brain (reviewed by Kern et al. 2020).

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; Gundacker et al. 2021; Hadavifar et al. 2020; Iwai-Shimada et al. 2015; Kim et al. 2011;
Marques et al. 2013c; Ou et al. 2014; Sakamoto et al. 2018; Stern and Smith 2003; Vahter et al. 2000;
Vollset et al. 2019; 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 BHg 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 blood fraction of the body burden (the fraction of the total amount of methylmercury in the body that is 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 BHg 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 BHg 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 BHg 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 BHg 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 been 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. 2019b; 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; Caito et al. 2018; Farris et al. 1993; Havarinasab et al. 2007; Iverson and Hierlihy 1974; Li et al. 2020; 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). Gastrointestinal 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. 2019b; 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. 2019b). In the liver and gastrointestinal tract, methylmercury can react with reactive sulfur species (e.g., glutathione, hydrogen sulfide and hydrogen persulfide) to form bismethylmercury sulfide ($[MeHg]_2S$) (Abiko et al. 2021;

Yoshida et al. 2011). The reaction in the gastrointestinal tract is thought to be mediated by intestinal bacteria (Abiko et al. 2021; 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; Li et al. 2020; Mottet et al. 1987; Nordenhall et al. 1998; 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. 2019b; 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 HHg 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, HHg 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). Caito et al. (2018) estimated the halftime for elimination of mercury from hair of adults following a fish meal. The estimated mean halftime was 44 days (range: 28–62 days, n=37). 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 HHg 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 HHg (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

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and 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 (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). 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 (Clewell 1995).

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-duration 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, 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}). HHg 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 cessation 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 HHg 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). BHg-time profiles predicted with the model from HHg-time profiles agreed with observed BHg 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 HHg 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 BHg 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 HHg

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 HHg 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 HHg 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 rate 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 (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 (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 (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 (Harari et al. 2012; Medina Pérez et al. 2021; Silva et al. 2023; Wahlberg et al. 2018). 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 BHg 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 HHg 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 2006).

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 from this report are discussed in Section 5.6, General Population Exposure.

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 2006). 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 are discussed in Section 3.3.1.

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 2006). 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 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 Pennings 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 (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; Tuček et al. 2020; 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, 2022). 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 BHg. 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 (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 BHg 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 (Awata et al. 2017; Donohue et al. 2018; McKelvey et al. 2018; Wells et al. 2020; Yin et al. 2021). 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 (Donohue et al. 2018; Lukina et al. 2021; 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). Total HHg concentrations correlate with dietary consumption of mercury from fish and marine mammals (Berglund et al. 2005; Castano et al. 2015; Johnsson et al. 2005; Karatela et al. 2019; Tian et al. 2011; Yaginuma-Sakurai et al. 2012). The correlation between BHg and HHg 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 (5th–95th percentile range: 267–475) and just prior to cessation of exposure, the median ratio was 321 (5th–95th percentile range: 264–451). The mean HHg 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 HHg 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 HHg and BHg 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 (WHO) and United Nations (WHO 1990, 2004) recommend a hair/blood ratio of 250 for interconverting HHg and BHg 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 HHg and neonatal HHg 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 HHg 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; Zhang et al. 2022). 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; Zhang et al. 2022). The total mercury concentration in nails 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 (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; reviewed by Wesolowska et al. 2023).

Fish contain other nutrients that have been shown to be important modifiers of development. These include 3-omega LCPUFAs, folate, iodine, and iron (Cheatham 2008; Choi et al. 2008a; Kim et al. 2020a; Mao et al. 2019; 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 (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 1992).