APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substances than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Elemental mercury
CAS Number: 7439-97-6
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for elemental mercury.

Rationale for Not Deriving an MRL: No epidemiological studies investigating effects of acute-duration exposure to inhaled elemental mercury were identified. Acute-duration inhalation studies in humans are limited to accidental or intentional exposure to fatal or near-fatal levels of elemental mercury vapor.

Studies in rats and mice have identified several targets of toxicity including neurological alterations, neurodevelopmental effects, and renal effects. Acute-duration studies have also reported developmental outcome effects and reproductive effects in rats; however, given the limited number of studies reporting these effects, the data are insufficient to draw conclusions as to whether reproductive and developmental outcome effects are sensitive targets for elemental mercury. It is noted that the reported developmental and reproductive effects occur at higher elemental mercury concentrations than the neurological effects. Summaries of the lowest LOAELs for neurological, neurodevelopmental, renal, developmental, and reproductive endpoints are presented in Table A-1.

Table A-1. Selected NOAEL and LOAEL Values in Animals Acutely Exposed to Inhaled Elemental Mercury

		NOAEL/LOAEL (mg Hg/m^3)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Neurodevelopmental					
Rat	7 days PNDs 11–17 1 hour/day (WB)	ND	0.05	Increased spontaneous locomotion and total activity and decreased rearing counts at 4 months of age; impaired spatial learning at 6 months of age	Fredriksson et al. 1992
Rat	7 days PNDs 11–17 4 hours/day (WB)	ND	0.05	Increased spontaneous locomotion and total activity and decreased rearing counts at 2 months of age; decreased spontaneous locomotion, total activity, and rearing counts at 4 months of age; and impaired spatial learning at 6 months of age	Fredriksson et al. 1992
Rat	6 days GDs 14–19 1.5 hours/day (WB)	ND	1.8	Increased spontaneous locomotion, rearing, and total activity at 4 months of age; impaired spatial learning	Fredriksson et al. 1996

Table A-1. Selected NOAEL and LOAEL Values in Animals Acutely Exposed to Inhaled Elemental Mercury

		NOAEL/LOAEL ($mg\ Hg/m^3$)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Rat	8 days GDs 11–14 + GDs 17–20 1 or 3 hours/day (WB)	ND	1.8	Decreased spontaneous locomotion, rearing, and total activity at 3 months; reduced novel environment habituation at 7 months	Danielsson et al. 1993
Neurological					
Mouse	4 hours (WB)	ND	0.5	Reduced grip strength 4–7 months post-exposure, decreased motor axon diameter 7 months post-exposure	Stankovic 2006
Rat	GDs 6–15 2 hours/day (N)	4	8	Mild tremor, lethargy, unsteady gait	Morgan et al. 2002
Reproductive					
Rat	11 days 2 hours/day (N)	1	2	Prolonged estrous cycle	Davis et al. 2001
Rat	1–8 days 2 hours/day (N)	ND	2	Prolonged estrous cycle after 6–8 days exposure; immature corpora lutea during estrus and metestrus phases	Davis et al. 2001
Renal					
Rat	GDs 6–15 2 hours/day (N)	2	4	Elevated maternal relative kidney weight (32% on GD 15); increased urinary protein (80%) and ALP (943%)	Morgan et al. 2002
Developmental					
Rat	GDs 6–15 2 hours/day (N)	4	8	Increased resorptions, decreased litter size, decreased pup weight	Morgan et al. 2002

ALP = alkaline phosphatase; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; (N) = nose-only exposure; ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day; (WB) = whole-body exposure

The lowest LOAEL is 0.05 mg Hg/m^3 for neurodevelopmental effects in rats exposed on PNDs 11–17 for 1 or 4 hours/day (Fredriksson et al. 1992). When the animals exposed for 4 hours/day were examined at 2 months of age, increased spontaneous locomotion and total activity and decreased rearing were observed. At 4 months of age, spontaneous locomotion and total activity were decreased in the group exposed for 4 hours/day and increased in the group exposed for 1 hour/day. At 6 months of age, impaired spatial learning was observed in the groups exposed for 1 and 4 hours/day. Similar effects were also observed in offspring of rats exposed to 1.8 mg Hg/m^3 for 1.5 hours/day on GDs 14–19 and tested at 4 months of age (Fredriksson et al. 1996). Neurological effects consisting of reduced grip strength and

decreased motor axon diameter were reported in adult mice 4–7 months after a single 4-hour exposure (Stankovic 2006). At higher concentrations, non-neurological effects such as prolonged estrus cycle (Davis et al. 2001), increased resorptions and decreased pup weight (Morgan et al. 2002), and evidence of renal damage (Morgan et al. 2002) were observed.

Although there is strong evidence from epidemiological studies involving chronic exposure and acute- and intermediate-duration animal studies supporting the identification of neurotoxicity/ neuro-developmental toxicity as the critical effect, the acute-duration inhalation database was not considered adequate for derivation of an MRL. The Fredriksson et al. (1992) study, which identified the lowest LOAEL was not considered a suitable principal study for several reasons: (1) the daily exposure was short (1 or 4 hours/day) and there is uncertainty that the observed effects may not be predictive of continuous exposure; (2) the control group treatment was not identical to the exposed groups (i.e., the controls were placed in exposure chamber for 2 hours/day compared to 1 or 4 hours/day for the exposed groups); and (3) animals received whole-body exposure and no measures were taken to prevent mercury ingestion during preening or inhalation exposure from volatilization of mercury deposited on fur/skin.

Agency Contacts (Chemical Manager): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Elemental mercury
CAS Number: 7439-97-6
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for elemental mercury.

Rationale for Not Deriving an MRL: No intermediate-duration epidemiological studies were identified for elemental mercury. A number of animal studies have evaluated the toxicity of elemental mercury following intermediate-duration inhalation exposure. The results of these studies suggest that neurological and/or neurodevelopmental effects are the most sensitive outcomes. At higher concentrations, renal and male reproductive effects have also been reported. Neurological and/or neurodevelopmental effects observed in monkeys, rats, mice, and rabbits include decreased motor activity, impairments in learning and memory, and tremors (Fukuda 1971; Kishi et al. 1978; Newland et al. 1996; Yoshida et al. 2018). Renal effects include slight degenerative changes in the renal tubular epithelium (Kishi et al. 1978). The male reproductive effects included seminiferous tubule atrophy, and decreased spermatocyte and spermatids (Altunkaynak et al. 2015); it is noted that this is the only reproductive toxicity study on elemental mercury that examined male reproductive effects and the database is considered insufficient to draw conclusions.

Selected NOAEL and LOAEL values are presented in Table A-2. The lowest LOAEL is 0.188 mg Hg/m^3 for decreased motor activity on PND 77 in the offspring of mice continuously exposed to elemental mercury on PNDs 2–28 (Yoshida et al. 2018); the study only tested one concentration (in addition to a control group). The study did not find alterations in passive avoidance tests or working memory tests. Earlier studies by this group found no alterations in motor activity, learning, or memory in the offspring of mice exposed to 0.03 mg Hg/m^3 during GDs 0–18 (Yoshida et al. 2011) or in mice exposed to 0.057 mg Hg/m^3 on PNDs 1–20 (Yoshida et al. 2013).

Table A-2. Selected NOAEL and LOAEL Values in Animals Exposed to Inhaled Elemental Mercury for Intermediate Durations

		NOAEL/LOAEL (mg Hg/m^3)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Neurodevelopmental					
Mouse	PNDs 2–28 24 hours/day (WB)	ND	0.188	Decreased motor activity at PND 77	Yoshida et al. 2018
Monkey	15–17 weeks gestational exposure 5 days/week 4 or 7 hours/day (WB)	ND	0.5	Impaired operant training in offspring tested at 0.8–4 years of age	Newland et al. 1996

Table A-2. Selected NOAEL and LOAEL Values in Animals Exposed to Inhaled Elemental Mercury for Intermediate Durations

Species	Duration	NOAEL/LOAEL (mg Hg/m^3) NOAEL	LOAEL	Effect	Reference
Mouse	GDs 0–18 6 hours/day (WB)	0.03	ND	No effect on motor activity, learning, or memory assessed on PND56	Yoshida et al. 2011
Mouse	PNDs 1–20 24 hours/day (WB)	0.057	ND	No effect on motor activity, learning, or memory assessed at 3 or 15 months of age	Yoshida et al. 2013
Neurological					
Rat	8 weeks 4–5 days/week 5 hours/day (WB)	ND	0.5	Irritability, aggressiveness; loss of Purkinje and granular cells in cerebellum	Sørensen et al. 2000
Reproductive					
Rat	6 weeks 7 days/week 9 hours/day (WB)	ND	1	Seminiferous tubule atrophy; damage to spermatogenic cells; decreased testicular and seminiferous tubule volume, decreased seminiferous tubule diameter; decreased Sertoli cells, spermatogonia, spermatocytes, and spermatids	Altunkaynak et al. 2015
Renal					
Rat	12–42 weeks 5 days/week 3 hour/day (WB)	ND	3	Slight degenerative changes (i.e., dense deposits in tubule cells and lysosomal inclusions) in the renal tubular epithelium	Kishi et al. 1978

GD = gestation day; LOAEL = lowest-observed-adverse-effect level ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day; (WB) = whole-body exposure

The intermediate-duration inhalation database for elemental mercury was not considered adequate for MRL derivation. Although several studies have identified NOAELs and LOAELs for neuro-developmental effects (the presumed critical effect), most of the studies only tested a single concentration and the database was considered insufficient for establishing concentration-response relationships. It should also be noted that the highest NOAEL (0.057 mg Hg/m^3) for the intermediate-duration database is similar to the lowest LOAEL (0.05 mg Hg/m^3) identified for neurodevelopmental effects in the acute-duration inhalation database; this may be due to, but not limited to, species differences (mice versus rats) and/or differences in the study design (e.g., age at dosing and assessment, exposure duration, total exposure concentration, etc.).

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Elemental mercury
CAS Number:	7439-97-6
Date:	October 2024
Profile Status:	Final
Route:	Inhalation
Duration:	Chronic
MRL	0.3 μg Hg/m^3 (3x10^{-4} mg Hg/m^3)
Critical Effect:	Tremors
Reference:	Bast-Pettersen et al. 2005; Boogaard et al. 1996; Chapman et al. 1990; Ellingsen et al. 2001; Fawer et al. 1983; Langworth et al. 1992a; Wastensson et al. 2006, 2008
Point of Departure:	2.84 μg Hg/m^3 (95% lower confidence limit of weighted median of seven
principal	studies)
Uncertainty Factor:	10
LSE Graph Key:	29
Species:	Human

MRL Summary: A chronic-duration inhalation MRL of 0.3 μg Hg/m^3 was derived for elemental mercury based on tremors reported in several occupational exposure studies. The MRL is based on 2.84 μg Hg/m^3, which is the 95% lower confidence limit of the weighted median of 4.92 μg Hg/m^3 calculated using estimated air concentrations from seven studies, reported in eight publications (Bast-Pettersen et al. 2005; Boogaard et al. 1996; Chapman et al. 1990; Ellingsen et al. 2001; Fawer et al. 1983; Langworth et al. 1992a; Wastensson et al. 2006, 2008) and a total uncertainty factor of 10 for human variability.

Selection of the Critical Effect: The available information on the toxicity of elemental mercury vapor comes from numerous epidemiological studies of workers in the chloralkali, fluorescent lamp, lithium-6 purification, natural gas production, gold mining and processing, and thermometer industries and of dental workers. Most epidemiological studies used urinary mercury levels (expressed as μg Hg/L or μg Hg/g creatinine) as a biomarker of exposure, and some studies also provided work area or breathing zone mercury levels. Reported UHg levels were converted to equivalent exposure concentrations by applying a steady-state mass balance model (see the *Calculation of Estimated Air Concentration* section below for additional information). No reliable chronic-duration animal studies were identified.

The epidemiological studies provide consistent evidence of neurological effects, specifically alterations in color vision, tremor, nerve conduction velocity, and cognitive function. There is also suggestive evidence of renal effects, particularly glomerular function decrements and tubular injury from epidemiological studies. Neurotoxicity was selected as the critical effect based on the stronger weight of evidence supporting an association with elemental mercury exposure.

Over 35 epidemiological studies have evaluated neurological outcomes among workers exposed to mercury vapor; the most commonly assessed endpoints were decrements or loss in color vision, tremors, and alterations in motor speed and fine motor coordination, and cognitive function (memory, and integrative function), typically compared to a reference group. A list of the studies examining these neurological effects is presented in Table A-3. For each study, observed biomarkers of exposure (e.g., UHg) were converted to estimates of exposure air concentrations and categorized as either an adverse-effect level (AEL) if an adverse effect was observed or a no-adverse-effect level (NAEL) if no adverse effect was observed (Appendix E has for definitions of AEL and NAEL). The aggregate median AEL estimated air concentrations for the types of effects observed are similar, ranging from 8.8 to 13.9 μg

Hg/m^3 (for more details on how air concentrations were estimated, see the *Calculation of Estimated Air Concentration* section below).

Table A-3. Summary of Adverse Effect Levels for Neurological Effects Reported in Epidemiological Studies of Elemental Mercury

	Median (range) estimated air concentrations (µg Hg/m^3)	Number of exposed workers examined in each study	References
Color vision			
NAEL	ND (2.58)	21	Cavalleri and Gobba 1998
AEL	8.76 (0.914–8.74)	15–40	Barboni et al. 2008, 2009; Canto-Pereira et al. 2005; Cavalleri and Gobba 1998; Urban et al. 2003; Ventura et al. 2005
Tremor			
NAEL	4.75 (0.914–8.74)	43–200	Bast-Pettersen et al. 2005; Boogaard et al. 1996; Ellingsen et al. 2001; Harari et al. 2012; Langworth et al. 1992a; Wastensson et al. 2006, 2008
AEL	11.72 (0.422–63.1)	15–13,905	Albers et al. 1988; Anglen et al. 2015; Bittner et al. 1998; Chapman et al. 1990; Echeverria et al. 2005; Fawer et al. 1983; Frumkin et al. 2001; Harari et al. 2012; Iwata et al. 2007; Langolf et al. 1978; Letz et al. 2000; Miller et al. 1975; Roels et al. 1982; Tang and Li 2006; Verberk et al. 1986
Cognitive function			
NAEL	1.44 (0.072–4.57)	49–550	Bast-Pettersen et al. 2005; Factor-Litvak et al. 2003; Ritchie et al. 2002; Sletvold et al. 2012
AEL	13.9 (0.405–30.5)	26–426	Bluhm et al. 1992; Echeverria et al. 1998, 2005; Mathiesen et al. 1999; Ngim et al. 1992; Piikivi and Hanninen 1989; Piikivi et al. 1984; Sletvold et al. 2012; Smith et al. 1983

AEL = adverse-effect level; NAEL = no-adverse-effect level

The tremor endpoint was selected as the critical effect because more studies (20 studies) with larger populations have evaluated tremor compared to color vision (5 studies). Alterations in cognitive function was not selected as the critical effect because the studies evaluated various domains of cognitive function and the number of studies evaluating similar domains is small, as compared to the number of studies evaluating tremors. The NAELs and AELs for the epidemiological studies evaluating tremors are presented in Table A-4.

Table A-4. NAEL and AEL Values for Epidemiological Studies Evaluating Tremor

Study	Population	Number of subjects	Estimated air concentration (µg Hg/m^3) NAEL	AEL
Albers et al. 1988	Lithium 6 workers	247		42.6
Anglen et al. 2015	Dental workers	13,906		1.00
Bast-Pettersen et al. 2005	Chloralkali workers	49	4.57	
Bittner et al. 1998	Dental workers	230		11.7
Boogaard et al. 1996	Gas production	40	8.74	
Chapman et al. 1990	Chloralkali workers	18		4.92
Echeverria et al. 2005	Dental workers	427		0.422
Ellingsen et al. 2001	Chloralkali workers	47	4.43	
Fawer et al. 1983	Lamp and chloralkali workers	26		5.57
Frumkin et al. 2001	Chloralkali workers	139		18.7
Harari et al. 2012	Gold miners	200	0.914	
Harari et al. 2012	Gold merchants	37		10.2
Iwata et al. 2007	Cinnabar miners and smelters	27		63.1
Langolf et al. 1978	Chloralkali workers	79		51.1
Langworth et al. 1992a	Chloralkali workers	85	7.03	
Letz et al. 2000	Lithium 6 workers	104		38.4
Miller et al. 1975	Chloralkali workers	77		27.5
Roels et al. 1982	Chloralkali workers	43		13.8
Tang and Li 2006	Thermometer workers	143		10.7
Verberk et al. 1986	Lamp workers	20		9.88
Wastensson et al. 2006, 2008	Chloralkali workers	43	4.90	

AEL = adverse-effect level; NAEL = no-adverse-effect level

Selection of the Principal Study: Rather than selecting an individual study as the principal study, a group of seven studies, reported in eight publications, that provide information on the NAEL/AEL boundary were selected as the principal studies (see the *Selection of the Point of Departure* section for information on criteria for selecting these studies). Citations for the principal studies are listed below; summaries of these studies are included in Table A-5.

Bast-Pettersen R, Ellingsen DG, Efskind J, et al. 2005. A neurobehavioral study of chloralkali workers after the cessation of exposure to mercury vapor. Neurotoxicology 26(3):427-437.

Boogaard PJ, Houtsma A-T AJ, Journée HL, et al. 1996. Effects of exposure to elemental mercury on the nervous system and the kidneys of workers producing natural gas. Arch Environ Health 51(2):108-115.

Chapman LJ, Sauter SL, Henning RA, et al. 1990. Differences in frequency of finger tremor in otherwise asymptomatic mercury workers. Br J Ind Med 47(12):838-843.

Ellingsen DG, Bast-Pettersen R, Efskind J, et al. 2001. Neuropsychological effects of low mercury vapor exposure in chloralkali workers. Neurotoxicology 22(2):249-258.

Fawer RF, DeRibaupierre Y, Guillemin M, et al. 1983. Measurement of hand tremor induced by industrial exposure to metallic mercury. Br J Ind Med 40:204-208.

Langworth S, Almkvist O, Soderman E, et al. 1992a. Effects of occupational exposure to mercury vapour on the central nervous system. Br J Ind Med 49(8):545-555.

Wastensson G, Lamoureux D, Sällsten G, et al. 2006. Quantitative tremor assessment in workers with current low exposure to mercury vapor. Neurotoxicol Teratol 28(6):681-693.

Wastensson, G, Lamoureux, D, Sallsten G, et al. 2008. Quantitative assessment of neuromotor function in workers with current low exposure to mercury vapor. Neurotoxicol 29(4):596-604.

Table A-5. Summary of the Principal Studies Examining Tremor in Workers Exposed to Elemental Mercury

Reference: Bast-Pettersen et al. 2005

Study type and population: Retrospective cohort of 49 former chloralkali workers and 49 referents from Norway. Average duration of exposure of workers was 13.1 years. Average time elapsed since exposure ceased was 4.8 years.

Biomarkers:

UHg working (average µg Hg/g Cr/year, range)
Referent: NA
Exposed: 16.5 (7.1–45)

UHg at testing (mean µg Hg/g Cr, range)
Referent: 2.0 (0.6–5.7)
Exposed: 2.9 (0.4–9.2)

Estimated air concentration[a]: 4.57 µg Hg/m^3 (based on exposed working average)

Analysis: Subjects were excluded for history of alcohol abuse, major head injuries; or metabolic, major psychiatric or neurological disease that caused severe disability. Data were analyzed using ANOVA for comparison of means between exposure groups and referents.

Results:

Mean (range) of tremor intensity (m/s^2)
- Dominant hand, NS
  - Exposed: 0.12 (0.07–0.33)
  - Referent: 0.13 (0.07–0.40)
  - Mean ratio: 0.96 (95% CI 0.85, 1.10)
- Non-dominant hand, NS
  - Exposed: 0.12 (0.07–0.31)
  - Referent: 0.12 (0.06–0.51)
  - Mean ratio: 1.01 (95% CI 0.87, 1.17)

Mean (range) of frequency dispersion (Hz)
- Dominant hand, NS
  - Exposed: 2.9 (1.2–4.4)

Mean (range) of center frequency (Hz)
- Dominant hand, NS
  - Exposed: 7.4 (6.0–9.6)
  - Referent: 7.5 (5.8–10.6)
  - Mean difference: -0.1 (95% CI -0.5, 0.3)
- Non-dominant hand, NS
  - Exposed: 7.6 (5.9–10.8)
  - Referent: 7.4 (2.4–9.9)
  - Mean difference: 0.2 (95% CI -0.3, 0.6)

Mean (range) of harmonic index
- Dominant hand, NS
  - Exposed: 0.92 (0.80–0.97)
  - Referent: 0.91 (0.82–0.98)
  - Mean difference: 0.01 (95% CI -0.01, 0.02)

Table A-5. Summary of the Principal Studies Examining Tremor in Workers Exposed to Elemental Mercury

- Referent: 2.8 (0.9–4.3)
- Mean difference: 0.1 (95% CI -0.2, 0.4)

- Non-dominant hand, NS
  - Exposed: 3.3 (1.0–4.9)
  - Referent: 3.3 (1.1–6.4)
  - Mean difference: 0 (95% CI -0.3, 0.3)

- Non-dominant hand, NS
  - Exposed: 0.89 (0.82–0.98)
  - Referent: 0.89 (0.78–0.97)
  - Mean difference: 0 (95% CI -0.02, 0.02)

Interpretation: Tremor was not significantly different between exposed and referent groups; therefore, the working mean UHg in the exposed group (16.5 µg/g Cr) was considered to be a NAEL for tremor. The equivalent air mercury concentration (4.57 µg Hg/m^3) was weighted by the number of subjects in the exposed group (49).

Reference: Boogaard et al. 1996

Study type and population: Retrospective cohort of 40 natural gas workers (18 with "high" exposure; 22 with "low" exposure) and 19 referents from the Netherlands. Median (range) exposure time for high- and low-exposure workers was 9 years (1–15 years) and 10 years (3–20 years), respectively. Time elapsed since exposure ceased was not reported.

Biomarkers:

UHg working (median µg Hg/L, range)
Referent: 3 (1–8)
High exposure: 41 (7–72)
Low exposure: 12 (7–53)

UHg at testing (median µg Hg/L, range)
Referent: 2 (0.5–6.8)
High exposure: 17 (3.5–71.9)
Low exposure: 5 (0.6–8.8)

Estimated air concentration[a]: 8.74 µg Hg/m^3 (based on high working median)

Analysis: Subjects were excluded for history of nonoccupational neuropathies or disorders with potential renal sequelae. Data were analyzed using MANOVA for comparison of means between exposure groups and referents. Multivariate regression analysis was performed for the entire population (referents plus exposed).

Results:

Mean (median; range) of resting tremor

- Right hand, NS
  - High exposed: 6.49 (6.5; 1.4–10.3)
  - Low exposed: 6.45 (5.95; 2.3–10.2)
  - Referent: 6.34 (6.0; 3.9–9.2)
- Left hand, NS
  - High exposed: 5.94 (4.9; 2.9–10.4)
  - Low exposed: 6.60 (6.8; 2.9–10.5)
  - Referent: 6.64 (6.8; 3.6–10.1)

Mean (median; range) of intention tremor

- Right hand, NS
  - High exposed: 5.09 (4.85; 3.9–8.0)
  - Low exposed: 5.38 (5.2; 3.7–10.8)
  - Referent: 5.22 (5.2; 3.9–6.7)
- Left hand, NS
  - High exposed: 5.15 (4.9; 4.2–8.0)
  - Low exposed: 5.50 (5.3; 4.2–10.6)
  - Referent: 5.39 (5.6; 3.9–6.2)

No significant correlation between tremor measures and present or historical UHg levels (data not shown).

Table A-5. Summary of the Principal Studies Examining Tremor in Workers Exposed to Elemental Mercury

Mean (median; range) of action tremor

- Right hand, NS
  - High exposed: 6.61 (7.05; 2.2–10.3) (lower end of range reported as 97.05)
  - Low exposed: 7.39 (7.4; 2.0–12.3)
  - Referent: 6.67 (7.5; 2.4–9.0)
- Left hand, NS
  - High exposed: 6.76 (6.8; 2.3–12.0
  - Low exposed: 7.75 (7.55; 1.6–11.4)
  - Referent: 7.00 (7.7; 2.5–9.5)

Interpretation: No significant association between UHg and tremor; therefore, the working median UHg in the high exposure group (41 µg/L) is a NAEL for tremor. The equivalent air mercury concentration (8.74 µg Hg/m^3) was weighted by the number of subjects in the high exposure group (40).

Reference: Chapman et al. 1990

Study type and population: Cross-sectional cohort of 18 mercury battery workers and 18 referents from the United States. Average exposure time (range) for workers was 5.3 (0.3–32) years.

Biomarkers:
UHg at testing (mean µg Hg/L, SD)
Exposed: 23.1 (28.3)
Referent: Not measured

Estimated air concentration[a]: 4.92 µg Hg/m^3

Analysis: Subjects were excluded for previous or current injuries or illnesses with neuropathic potential and neurotoxic drug or chemical exposures. Data were analyzed using non-parametric Mann-Whitney test to compare means between exposed and referent subjects, adjusted for the four comparison metrics.

Results:
Mean (SD) of hand tremor amplitude, NS

- Exposed: 35.6 (2.5)
- Referent: 23.0 (6.5)

Mean (SD) of hand tremor power, p<0.01

- Exposed: 315.0 (37.0)
- Referent: 68.0 (5.0)

Mean (SD) of hand tremor half power frequency, NS

- Exposed: 7.8 (0.9) Hz
- Referent: 7.5 (0.6) Hz

Mean (SD) of tremor highest band power (5–15 Hz), p<0.001

- Exposed: 2.6 (2.3)
- Referent: 1.5 (0.6)

Interpretation: Tremor was significantly higher in the exposed group; therefore, the mean UHg in the exposed group (23.1 µg/L) is an AEL for tremor. The equivalent air mercury concentration (4.92 µg Hg/m^3) was weighted by the number of subjects in the exposed group (18).

Table A-5. Summary of the Principal Studies Examining Tremor in Workers Exposed to Elemental Mercury

Reference: Ellingsen et al. 2001

Study type and population: Retrospective cohort of 47 former chloralkali workers exposed for at least one year, and 47 referents; from Norway. Average exposure duration of 13.3 years.

Biomarkers:
UHg working (average µg Hg/g Cr/year, range)
Referent: NA
Exposed: 16.0 (7.1–35)

UHg at testing (mean µg Hg/g Cr, range)
Referent: 2.3 (0.4–8.9)
Exposed: 10.5 (2.0–30)

Estimated air concentration[a]: 4.43 µg Hg/m^3 (exposed)

Analysis: Subjects were excluded for alcohol abuse, major heads injuries; or metabolic, psychiatric, neurologic or other diseases causing severe disability. Data on intentional hand steadiness were analyzed by ANOVA of means between exposed and referents.

Results:
Mean (SD) of static steadiness (number of hits)

- Dominant hand, NS
  - Exposed: 126.5 (113.3)
  - Referent: 123.4 (117.0)
- Non-dominant hand, NS
  - Exposed: 112.5 (71.6)
  - Referent: 120.0 (90.7)

Mean (SD) of static steadiness (duration of hits, s)

- Dominant hand, NS
  - Exposed: 7.2 (5.5)
  - Referent: 6.8 (4.4)
- Non-dominant hand, NS
  - Exposed: 7.6 (5.0)
  - Referent: 7.9 (5.1)

Interpretation: Tremor was not significantly different between exposed and referent groups; therefore, the working mean UHg in the exposed group (16.0 µg/g Cr) is a NAEL for tremor. The equivalent air mercury concentration (4.43 µg Hg/m^3) was weighted by the number of subjects in the exposed group (47).

Reference: Fawer et al. 1983

Study type and population: Cross-sectional cohort of florescent lamp workers (n=7), chloralkali workers (n=12), acetaldehyde production workers (n=7), and 25 referents from Belgium. Average exposure time (±SE) for workers was 15.3±2.6 years

Biomarkers:
UHg at testing (mean µg Hg/g Cr, SE)[b]
Referent: 6.0 (1.2)
Exposed: 20.1 (2.1)

Estimated air concentration: 5.57 µg Hg/m^3

Analysis: Criteria for excluding participation in the study were not reported. Data were analyzed by t-test of means between exposed and referents or paired t-test for changes between rest and load.

Table A-5. Summary of the Principal Studies Examining Tremor in Workers Exposed to Elemental Mercury

Results:

Mean (SE) for highest peak frequency of hand tremor

- At rest, p<0.001
  - Referent: 6.40 (0.19) Hz
  - Exposed: 7.60 (0.22) Hz
- Changes between rest and load, p<0.001
  - Referent: 2.69 (0.19) Hz
  - Exposed: 3.62 (0.29) Hz

Mean (SE) for second moment

- At rest, p>0.002
  - Referent: 10.9 (1.1) Hz
  - Exposed: 13.3 (0.9) Hz
- Changes between rest and load, p<0.002
  - Referent: 0.9 (1.1) Hz
  - Exposed: 4.1 (1.2) Hz

Interpretation: Tremor was significantly higher in the exposed group; therefore, the mean UHg in the exposed group (20.1 µg/g Cr) is an AEL for tremor. The equivalent air mercury concentration (5.57 µg Hg/m^3) was weighted by the number of subjects in the exposed group (26).

Reference: Langworth et al. 1992a

Study type and population: Cross-sectional cohort of 89 chloralkali workers and 75 referents from Sweden. Average exposure time (±SD) for workers was 13.5±8.7 years.

Biomarkers:

UHg at testing and while working[b] (median µg Hg/g Cr, range)
Referent: 1.9 (0–7.6)
Exposed: 25.4 (0.5–83.3)

Estimated air concentration[a]: 7.03 µg Hg/m^3

Analysis: Subjects were excluded for alcohol abuse, exposure to other heavy metals or organic solvents; or chronic neurological or kidney disease. Data analyzed using the Student's t test.

Results:

Incidence of slight finger tremor, NS

- Referent: 13/75 (17%)
- Exposed: 17/89 (19%)

Forearm tremor (exposed vs referents), NS

- Tremor frequency spectrum
- Tremor acceleration amplitude

Interpretation: Tremor was not significantly different in the exposed and referent group; therefore, the median UHg in the exposed group (24.4 µg/g Cr) is a NAEL for tremor. The equivalent air concentration (7.03 µg Hg/m^3) was weighted by the number of subjects in the exposed group who were evaluated for tremor (85 of 89).

Table A-5. Summary of the Principal Studies Examining Tremor in Workers Exposed to Elemental Mercury

Reference: Wastensson et al. 2006, 2008

Study type and population: Retrospective cohort of 43 chloralkali workers and 22 referents from Sweden. The average exposure time for workers was 15 years.

Biomarkers:
UHg cumulative work index (mean µg year/g Cr, range)
266 (8–1,440)
UHg average (calculated as 266/15 mean years worked)
17.7 µg/g Cr
UHg at testing (median µg Hg/g Cr, range)
Exposed: 5.9 (1.3–25)
Referent: 0.7 (0.2–4.1)

Estimated air concentration: 4.90 µg Hg/m^3 (based on cumulative work mean/mean years worked)

Analysis: Subjects were excluded based on medications, diseases (e.g., diabetes), essential tremor, skull or whiplash injury, or other circumstances that could affect tremor or coordination (e.g., pain in upper limb, lack of sleep, nervousness, colds). Data were analyzed using Student's t-test (n >20), Wilcoxon's rank sum test, chi-squared test, or Fisher's exact test to compare means between exposed and referents. Associations between the tremor measures and UHg were evaluated using Spearman's correlation coefficients (exposed and referent subjects combined). Multivariate linear regression was conducted, adjusting for age, shift work, and smoking.

Results:
Incidence (%) of clinically diagnosed tremor, NS

- Any tremor
  - Referent: 3/22 (14)
  - Exposed: 7/43 (16)
- Rest tremor
  - Referent: 0/22 (0)
  - Exposed: 1/43 (2)
- Postural tremor
  - Referent: 3/22 (14)
  - Exposed: 5/43 (12)
- Intention tremor
  - Referent: 2/22 (9)
  - Exposed: 5/43 (12)

Spearman's correlation coefficients for:
Postural hand tremor in laser-based system

- Amplitude (RMS), NS
  - Dominant hand: -0.01
  - Non-dominant hand: -0.11
- Proportional power (4–6 Hz), p<0.05
  - Dominant hand: -0.07
  - Non-dominant hand: 0.26
    - Adjusted linear regression NS after exclusion of one outlier

Spearman's correlation coefficients for:
Postural hand tremor in CATSYS system

- Tremor intensity (RMS), NS
  - Dominant hand: 0.00
  - Non-dominant hand: 0.03
- Tremor index, NS
  - Dominant hand: -0.06
  - Non-dominant hand: 0.04

Static hand tremor in laser-based system (1st recording, 2nd recording)

- Amplitude (RMS), NS
  - Dominant hand: -0.05, -0.07
  - Non-dominant hand: -0.10, -0.17

Kinetic hand tremor in laser-based system

- Mean tracking error, NS
  - Dominant hand: 0.00
  - Non-dominant hand: 0.01

Hand tremor detected during rapid pointing movements

- Tremor, NS
  - Dominant hand: -0.03
  - Non-dominant hand: -0.09

Table A-5. Summary of the Principal Studies Examining Tremor in Workers Exposed to Elemental Mercury

Interpretation: The outcome was designated as a NAEL because the weight of evidence did not support a significant difference in tremor between exposed and referents. Tremor based on all laser measurements was not significant. The only metric that was significant based on the CATSYS measurement was tremor index, which was different when means were assessed by the t-test, but was not significant when medians were assessed by the Wilcoxon rank sum test. Therefore, the UHg average in the workers (17.7 µg/g Cr) is a NAEL for tremor. The equivalent air concentration (4.90 µg Hg/m^3) was weighted by the number of subjects in the exposed group (43).

[a]See the *Calculation of Estimated Air Concentration* section below for how air concentrations were calculated.
[b]Reported as µmol Hg/mol creatinine and converted to µg Hg/g creatinine as follows: (µmol Hg/mol Cr x µg Hg/µmol Hg)/g Cr/mol Cr.

AEL = adverse-effect level; ANOVA = analysis of variance; CI = confidence interval; Cr = creatinine; MANOVA = multivariate analysis of variance; NAEL = no-adverse-effect level; NS = not significant; RMS = root mean square; SD = standard deviation; SE = standard error; UHg = urine mercury

Selection of the Point of Departure: The MRL was based on a 95% lower confidence limit of the weighted median estimated air concentration of 2.84 µg Hg/m^3, based on the seven principal studies.

Typically, the point of departure (POD) would be highest NAEL or lowest AEL. The problem with this approach being applied to the occupational worker tremor studies is that there is substantial overlap in reported NAELs and AELs. The overlap between the lower end of the AEL range and the NAEL range does not support selection of any single NAEL or AEL as a POD. As an alternative approach, the following was assumed:

1. A NAEL/AEL boundary exists and is located somewhere within the range of overlapping NAELs and AELs.
2. Each NAEL and AEL in this range represents an independent estimate of the NAEL/AEL boundary.
3. The best estimate of the NAEL/AEL boundary is the weighted median of the set of overlapping NAELs and AELs (weighted for study size which assumes greater confidence in estimates from larger studies).
4. The lower 95% confidence limit on the median was selected as the POD, to account for uncertainty in the estimated weighted median.

This approach avoids having to make a highly uncertain selection of a single study as the basis for the POD and, instead, utilizes information from multiple studies to identify an exposure that is most likely to be the NAEL/AEL boundary.

Overlapping NAELs and AELs include all AELs that are less than or equal to the highest NAEL for the outcome, plus all NAELs that are greater than or equal to the lowest AEL. For tremor, the highest NAEL is 8.74 µg Hg/m^3 (Boogaard et al. 1996) and the lowest reliable AEL is 4.90 µg Hg/m^3 (Wastensson et al. 2006, 2008). For selection of the studies to include in the estimate of the POD, all AELs that were <9 µg/m^3 and all NAELs that were >4 µg/m^3 were included in the calculation of the weighted mean. The NAELs and AELs for the principal studies that met the selection criteria are presented in Table A-6. Note that the Anglen et al. (2015) study was omitted for the following reasons: (1) during the 32-year retrospective period, mean UHg levels declined from 20 to 2 µg Hg/L, making it difficult to assign a central estimate UHg level to the outcome; and (2) tremor outcome was self-reported. The Echeverria et

al. (2005) study was omitted because of the extremely low AEL and low confidence in the reported mean UHg levels being representative of the steady state, given the expected highly intermittent exposures of dentists to mercury vapor.

Table A-6. NAEL and AEL Values for Studies Defining the NAEL/AEL Boundary for Tremor

Study	Population	Number of subjects	POD	Estimated air concentration (μg Hg/m^3)
Bast-Pettersen et al. 2005	Chloralkali workers	49	NAEL	4.57
Boogaard et al. 1996	Gas production	40	NAEL	8.74
Ellingsen et al. 2001	Chloralkali workers	47	NAEL	4.43
Langworth et al. 1992a	Chloralkali workers	85	NAEL	7.03
Wastensson et al. 2006, 2008	Chloralkali workers	43	NAEL	4.90
Chapman et al. 1990	Chloralkali workers	18	AEL	4.92
Fawer et al. 1983	Lamp and chloralkali workers	26	AEL	5.57
Median: 4.92 μg/m^3 (95% CI 3.02, 6.82)				
Weighted median: 4.92 μg/m^3 (95% CI 2.84, 7.00)				

AEL = adverse-effect level; CI = confidence interval; NAEL = no-adverse-effect level; POD = point of departure

For the principal studies, the unweighted median estimated air concentration is 4.92 μg Hg/m^3 (95% CI 3.02, 6.82) and the weighted median estimated air concentration is 4.92 μg Hg/m^3 (95% CI 2.84, 7.00). The 95% lower confidence limit of the weighted median is 2.84 μg Hg/m^3, which was selected as the POD for the MRL to account for uncertainty in the estimate of the median. Sensitivity of the POD to individual studies was tested by recomputing the POD after removing one of the studies. The POD was not highly influenced by removal of any single study. The mean of PODs calculated from censored data sets was 3.30 (range: 2.51–3.86).

Calculation of Estimated Air Concentration: Total mercury levels in urine (μg Hg/L or μg Hg/g creatinine) were used as the exposure metric for estimating human exposures (μg Hg/m^3) to mercury vapor. The urine biomarker is considered to be a more accurate reflection of mercury body burden than reported measurements of room air or breathing zone mercury concentrations, which were likely to be highly intermittent and variable. Non-occupational sources, including diet and mercury amalgam dental restorations, are likely to have contributed to the urinary mercury observed in the occupational studies that provide the basis for the chronic inhalation MRL. However, occupational exposures are likely to have been the dominant source of urinary mercury in the principal studies and support the use of urinary mercury for estimating air exposure concentrations. For example, it is unlikely that diet could account for the urinary mercury levels observed in the principal studies. Based on the urinary levels, the estimated inhaled mercury doses in the principal studies ranged from 1 to 2 μg/kg/day (approximately 70–140 μg/day for a 70-kg adult). By contrast, dietary mercury intakes have been estimated to range from 1 to 10 μg/day (Section 5.6, General Population Exposure). Another possible contributor to urinary mercury in the occupational studies would have been mercury released from mercury amalgam restorations. However, total mercury absorption in a person having 13 restorations was estimated to be approximately 3 μg/day (range 0.6–9.3; Section 5.6, General Population Exposure). Based on these estimates, it is likely that the dominant source of urinary mercury in the principal studies was occupational exposure to mercury, predominantly inhalation of mercury vapor, given the working environments described in these studies.

Reported UHg levels (mean or median for the study population) were converted to equivalent exposure concentrations by applying a steady-state mass balance model which did the following: (1) converted the reported urine level (assumed to represent steady state) to an equivalent steady-state excretion rate (µg Hg/day/kg body weight), and (2) converted the steady-state excretion rate to an equivalent steady-state exposure (µg Hg/m^3). The assumption of steady state requires that the exposures were relatively constant for periods >272 days. This is the exposure duration that would achieve 95% of steady-state body burden, assuming a terminal elimination half-time of 62 days (Jonsson et al. 1999; Equation 1):

$$Time\ to\ steady\ state = \frac{\ln(1-0.95)}{k_e} \quad \text{Eq. (1)}$$

where 0.95 is the fraction of steady state and k_e is ln(2)/half-time.

An alternative to the steady-state mass balance model would be to implement the complete biokinetics model described by Jonsson et al. (1999). However, this is not needed for the epidemiology or clinical studies used in the derivation of the MRL because the steady-state assumption can be reasonably assured for the exposures in these study groups. However, it must be assumed that the mean or median urine levels in each study adequately represent the corresponding steady-state exposures. Although there is an unknown level of uncertainty in this assumption, the same assumption would also apply to the application of the complete biokinetic model.

The calculated exposure concentration represents the continuous exposure that would achieve a steady-state UHg level equal to the observed mean urinary mercury level. Calculated exposure concentrations based on urinary levels are likely to be less than measured air concentrations observed during the workday by at least a factor of 3, assuming an 8-hour workday, because continuous exposure is assumed to occur 7 days/week 24 hours/day.

Conversion of UHg levels to equivalent steady-state excretion rates. UHg levels reported as µg Hg/g creatinine were converted to equivalent excretion rates (µg Hg/day) assuming a standard steady-state excretion rate of creatinine per kg of lean body mass. A more detailed example of this approach is given in ATSDR (2012) where it was used in the derivation of MRLs for cadmium. The rate of excretion of mercury (Hg_{ur}, µg Hg/day) was calculated as the product of the urinary level (µg Hg/g creatinine) and the urinary excretion rate of creatinine (g creatinine/day; Equation 2).

$$Hg_{ur} = Hg\ conc_{ur} \cdot Cr_{ur} \quad \text{Eq. (2)}$$

where Hg_{ur} is the rate of excretion of mercury (µg/day), $Hg\ conc_{ur}$ is the mercury concentration (µg/g creatinine) and Cr_{ur} is the rate of excretion of creatinine (g creatinine/day).

The rate of creatinine excretion (Cr_{ur}; g creatinine/day) was calculated from the relationship between lean body mass (LBM) and Cr_{ur} (Equation 3):

$$LBM = 27.2 \cdot Cr_{ur} + 8.58 \quad \text{Eq. (3)}$$

where the constants 27.2 and 8.58 are the sample size-weighted arithmetic mean of estimates of these variables from eight studies reported in Forbes and Bruining (1976). LBM was estimated as follows (ICRP 1981; Equation 4 and 5):

$$LBM\ of\ adult\ females = BW \cdot 0.85 \quad \text{Eq. (4)}$$

$$LBM\ of\ adult\ males = BW\ \cdot 0.88 \quad \text{Eq. (5)}$$

where the central tendency for adult body weight for males and females were assumed to be 70 and 58 kg for adult European/American males and females, respectively (ICRP 1981). Equation 5 predicts a lean body mass of 61.6 kg for a 70-kg male, which is similar to a mean lean body mass of 58.3 kg estimated for adults in the NHANES 1999–2006 (Lee et al. 2017c). These equations are applicable to higher average U.S. adult body weights (EPA 2011) because increases in average body weight in the United States derive primarily from increased body fat rather than increased average lean body mass (Hales et al. 2020). UHg levels reported as µg Hg/L were converted to equivalent excretion rates (µg Hg/day) assuming a standard rate of urine output of 1.5 L/day (approximately 1 L/day/kg body weight; CDC 2002; Equation 6).

$$Hg_{ur} = Hg\ conc_{ur} \cdot V_{ur} \quad \text{Eq. (6)}$$

where $Hg\ conc_{ur}$ is the mercury concentration (µg/L) and V_{ur} is the urine output (L/day).

The validity of the above approach was evaluated based on data reported in Frumkin et al. (2001) that reported mean UHg levels in units of µg Hg/g creatinine and µg Hg/L for 147 exposed chloralkali workers and 132 referents. For workers, the mean urinary levels were 3.42 µg Hg/L and 2.76 µg Hg/creatinine. The model predicted 3.6 µg Hg/L for an assumed 2.76 µg Hg/g creatinine. For referents, the mean urinary levels were 3.12 µg Hg/L and 2.31 µg Hg/creatinine, and the model predicted 3.0 µg Hg/L for an assumed 2.31 µg Hg/g creatinine.

Conversion of mercury excretion rate (µg Hg/day/kg) to an equivalent steady-state exposure (µg Hg/m^3). Steady-state exposures corresponding to steady-state rates of urinary excretion of mercury were calculated based on a simplified steady-state mass balance implementation of the biokinetic models reported by Jonsson et al. (1999). The simplified model is given by Equation 7:

$$Hg_{air} = \frac{Hg_{ur}}{f_r \cdot f_u \cdot IR} \quad \text{Eq. (7)}$$

where Hg_{ur} is the mercury excretion rate (µg Hg/day) calculated from UHg levels reported as µg Hg/g creatinine or µg Hg/L as described above; f_r is the fraction of the inhaled dose initially retained in the body (0.80; Leggett et al. 2001); f_u is the fraction of the retained mercury excreted in urine (0.55; Jonsson et al. 1999); and IR is the inhalation rate (16 m^3/day; EPA 2011).

Results from the mass balance model were compared to the results obtained from the Jonsson et al. (1999) biokinetics model (implemented in MATLAB). Both models predicted 0.5 for the inhalation dose (µg Hg/day)/UHg excretion rate (µg Hg/day) ratio.

Predictions of dose conversion coefficients from the steady-state mass balance model. The model predicts the following steady-state relationships between exposure levels and UHg levels:

Steady-state air concentration (µg Hg/m^3) = steady-state UHg (µg Hg/g creatinine) × 0.258
Steady-state air concentration (µg Hg/m^3) = steady-state UHg (µg Hg/L) × 0.198

Example of conversion of steady-state UHg levels (20.1 μg Hg/g creatinine; Fawer et al. 1983) to equivalent steady-state air mercury levels (5.57 μg Hg/m^3):

Convert body weight (BW, kg) to lean body mass (LBM, kg; Equation 5):

$$LBM\ of\ adult\ males = BW\ \times 0.88$$

$$LBM = 70\ \times 0.88 = 61.6$$

where 0.88 is the proportionality coefficient for males at 70 kg body weight (ICRP 1981).

Convert lean body mass (LBM, kg) to rate of urinary excretion of creatinine (Cr_{ur}; g creatinine/day; Equation 3):

$$LBM = 27.2\ \times Cr_{ur} + 8.58$$

which rearranges to:

$$Cr_{ur} = \frac{LBM - 8.58}{27.2}$$

$$Cr_{ur} = \frac{61.6 - 8.58}{27.2} = 1.949$$

where the constants 27.2 and 8.58 are the sample size-weighted arithmetic mean of estimates of these variables from eight studies reported in (Forbes and Bruining 1976).

Convert urinary mercury (UHg_{cr}, 20.1 μg Hg/g creatinine, Fawer et al. 1983) to rate of urinary excretion of mercury (Hg_{ur}, μg/day; Equation 2):

$$Hg_{ur} = UHg_{cr} \times Cr_{ur}$$

$$Hg_{ur} = 20.1 \times 1.949 = 39.17$$

where f_r is the fraction of the inhaled dose initially retained in the body (0.80; Leggett et al. [2001]); f_u is the fraction of the retained mercury excreted in urine (0.55; Jonsson et al. 1999); and IR is the inhalation rate (16 m^3/day; EPA 2011).

Convert rate of urinary excretion of mercury (Hg_{ur}, μg Hg/day) to air concentration (Hg_{air}, μg Hg/m^3; Equation 7):

$$Hg_{air} = \frac{Hg_{ur}}{f_r\ \times\ f_u\ \times\ IR}$$

$$Hg_{air}\ = \frac{39.17}{0.80 \times 0.55 \times 16} = 5.57$$

Example of conversion of steady-state UHg levels (41.0 µg Hg/L; Boogaard et al. 1996) to equivalent steady-state air mercury levels (8.74 µg Hg/m^3):

Convert urinary mercury (UHg_L, 41.0 µg Hg/L, Boogaard et al. 1996) to rate of urinary excretion of mercury (Hg_{ur}, µg/day; Equation 6):

$$Hg_{ur} = UHg_L \times UFR$$

$$Hg_{ur} = 41.0 \times 1.5 = 61.50$$

where UFR is the urine flow rate (1.5 L/day; approximately 1 L/day/kg body weight; CDC 2002).

Convert rate of urinary excretion of mercury (Hg_{ur}, µg Hg/day) to air concentration (Hg_{air}, µg Hg/m^3; Equation 7):

$$Hg_{air} = \frac{Hg_{ur}}{f_r \times f_u \times IR}$$

$$Hg_{air} = \frac{61.50}{0.80 \times 0.55 \times 16} = 8.74$$

where f_r is the fraction of the inhaled dose initially retained in the body (0.80; Leggett et al. [2001]); f_u is the fraction of the retained mercury excreted in urine (0.55; Jonsson et al. 1999); and IR is the inhalation rate (16 m^3/day; EPA 2011).

Uncertainty Factor: The 95% lower confidence limit (LCL) of the weighted median of the seven principal studies (Table A-6) is divided by a total uncertainty factor (UF) of 10.

- 10 for human variability

  Weighted Median$_{95\%LCL}$ ÷ UFs = MRL
  2.84 µg Hg/m^3 ÷ 10 = 0.28 µg Hg/m^3 ≈ 0.3 µg Hg/m^3

Other Additional Studies or Pertinent Information: A large number of studies in workers exposed to mercury vapor in various industries provide consistent evidence of the neurotoxicity of elemental mercury (Section 2.16.2, Elemental Mercury—Epidemiological Studies, for citations). A few shorter-term studies in animals also demonstrate neurotoxicity in animals exposed as adults; observed effects include impaired motor function and damage to the central nervous system (Ashe et al. 1953; Fukuda 1971; Sørensen et al. 2000; Stankovic 2006). Additionally, several animal studies have reported neurodevelopmental effects including altered motor activity and altered learning (Danielsson et al. 1993; Fredriksson et al. 1992, 1996; Yoshida et al. 2018).

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Elemental mercury
CAS Number: 7439-97-6
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for elemental mercury.

Rationale for Not Deriving an MRL: No acute-duration oral studies in humans or animals were identified.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Elemental mercury
CAS Number: 7439-97-6
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for elemental mercury.

Rationale for Not Deriving an MRL: No intermediate-duration oral studies in humans or animals were identified.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Elemental mercury
CAS Number: 7439-97-6
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for elemental mercury.

Rationale for Not Deriving an MRL: No chronic-duration oral studies in humans or animals were identified.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mercury, inorganic salts (mercuric acetate, mercuric chloride, mercuric sulfide)
CAS Numbers: 1600-27-7, 7487-94-7, 1344-48-5
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for inorganic mercury salts.

Rationale for Not Deriving an MRL: No human or animal studies evaluating acute-duration inhalation exposure to inorganic mercury salts or other inorganic mercury compounds were identified. Therefore, an acute-duration inhalation MRL was not derived.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mercury, inorganic salts (mercuric acetate, mercuric chloride, mercuric sulfide)
CAS Numbers: 1600-27-7, 7487-94-7, 1344-48-5
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for inorganic mercury salts.

Rationale for Not Deriving an MRL: No human studies or animal studies evaluating intermediate-duration inhalation exposure to inorganic mercury salts were identified. Two studies in rats evaluated effects of inhalation exposure to mercuric oxide on neurological (Altunkaynak et al. 2019) and female reproductive systems (Altunkaynak et al. 2016). In rats exposed to 1 mg Hg/m^3 for 45 days (9 hours/day), cerebellar gliosis and perineuronal and perivascular vacuolization, reduced cerebellar volume, and decreased number and density of Purkinje cells were observed (Altunkaynak et al. 2019). Purkinje cells from treated animals showed irregular cellular boundaries, eosinophilic cytoplasm, and heterochromatic nuclei. In female rats exposed to 0.9 mg Hg/m^3 for 45 days (24 hours/day), significant ovarian damage was observed, including thickened tunica albuginea, increased fibrils within connective tissue, congested capillaries and blood vessels, thinned walls of large and dilated veins, fibrin deposits in veins, edema and maldeveloped follicles in the stroma, and irregular oocyte borders within follicles (Altunkaynak et al. 2016). Treated females also showed reduced ovary volume and decreased number of follicles. Both studies evaluated a single exposure level and other systems were not evaluated. Therefore, effects of inhalation exposure to inorganic mercury have not been sufficiently characterized to derive an intermediate-duration inhalation MRL for inorganic mercury salts or other inorganic compounds.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mercury, inorganic salts (mercuric acetate, mercuric chloride, mercuric sulfide)
CAS Numbers: 1600-27-7, 7487-94-7, 1344-48-5
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for inorganic mercury salts.

Rationale for Not Deriving an MRL: No human or animal studies evaluating chronic-duration inhalation exposure to inorganic mercury salts or other inorganic mercury compounds were identified. Therefore, a chronic-duration inhalation MRL was not derived.

Agency Contacts (Chemical Manager): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mercury, inorganic salts (mercuric acetate, mercuric chloride, mercuric sulfide)
CAS Numbers: 1600-27-7, 7487-94-7, 1344-48-5
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.002 mg Hg/kg/day ($2x10^{-3}$ mg Hg/kg/day; 2 µg Hg/kg/day)
Critical Effect: Renal effects
Reference: Dieter et al. 1992; NTP 1993
Point of Departure: $BMDL_{1SD}$ of 0.29 mg Hg/kg/day ($BMDL_{ADJ}$ of 0.21 mg Hg/kg/day)
Uncertainty Factor: 100
LSE Graph Key: 6
Species: Rat

MRL Summary: An acute-duration oral MRL of 0.002 mg Hg/kg/day ($2x10^{-3}$ mg Hg/kg/day; 2 µg Hg/kg/day) was derived based on renal effects (increased relative kidney weight) in male rats exposed to mercuric chloride by gavage for 5 days/week for 16 days (Dieter et al. 1992; NTP 1993). The MRL is based on a $BMDL_{1SD}$ of 0.29 mg Hg/kg/day adjusted to a $BMDL_{ADJ}$ of 0.21 mg Hg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from rats to humans, and 10 for human variability).

The acute-duration oral MRL based on mercuric chloride is expected to be protective for all inorganic mercury salts. Mercuric chloride is water soluble (Section 3.1, Toxicokinetics) and the bioavailability of mercury salts is directly related to their solubility. Other mercuric salts are less soluble than mercury chloride and are expected to have lower oral bioavailability and, therefore, lower toxicity. For example, acute-duration oral LOAELs for mercuric sulfide and mercuric acetate range from 5 to 86 mg/kg/day (Section 2.1, Table 2-3), compared to the LOAEL of 1.8 mg/kg/day observed in the critical study.

Selection of the Critical Effect: Effects associated with acute-duration exposure of humans to inorganic mercury is limited to accidental or intentional exposure to near-fatal or fatal doses. Therefore, human data are not suitable for derivation of an acute-duration oral MRL. Several acute-duration oral studies have been conducted in laboratory animals. To identify the critical effect, ATSDR focused on: (1) reported effects associated with clear biological significance, and (2) high-quality acute-duration studies including, at minimum, five animals. The most sensitive LOAELs meeting these criteria are summarized in Table A-7.

Table A-7. Select LOAELs for Acute-Duration Oral Exposure to Mercuric Chloride

		NOAEL/LOAEL (mg Hg/kg/day)			
Species (n)	Duration	NOAEL	LOAEL	System: Effect	Reference
Rat (n=5)	16 days (5 days/week)	0.923	1.8	***Renal:*** 17% increase in relative kidney weight	Dieter et al. 1992; NTP 1993[a]
Rat (n=6)	3 or 7 days	ND	3	***Reproductive:*** Decreased sperm number and motility; non-monotonic changes in serum testosterone	Boujbiha et al. 2009

Table A-7. Select LOAELs for Acute-Duration Oral Exposure to Mercuric Chloride

	Duration	NOAEL/LOAEL (mg Hg/kg/day)		System: Effect	Reference
Mouse (n=16)	2 weeks	ND	3.7	***Endocrine:*** ~17% increase in baseline plasma insulin and ~60% decrease in fasting plasma insulin; ~15% decrease in blood glucose and impaired glucose tolerance; apoptosis in pancreatic islet cells	Chen et al. 2012
Mouse (n=5)	16 days (5 days/week)	ND	4	***Renal:*** 19% increase in relative kidney weight	NTP 1993[a]
Hamster (n=3–10)	Once (GD 7)	2.5	5	***Developmental:*** Decreased crown-rump length	Gale 1974

[a]These 16-day studies were classified as acute-duration studies because exposure only occurred on 12 of 16 days.

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; n = number; ND = not determined; NOAEL = no-observed-adverse-effect level

Renal toxicity was selected as the critical effect following acute-duration oral exposure to inorganic mercury because it represents the lowest reliable LOAEL (Dieter et al. 1992; NTP 1993). There is a preponderance of evidence that the kidney is a sensitive target for inorganic mercury salts, with substantial mechanistic support. Observed effects in acute-duration studies include elevated kidney weight at doses >1 mg Hg/kg/day (Dieter et al. 1992; Kim et al. 2003; NTP 1993) that progressed to histopathological changes (protein casts, cellular casts, interstitial sclerosis, necrosis) at ≥7.4 mg Hg/kg/day (Dieter et al. 1992; Lecavalier et al. 1994; Nielsen et al. 1991; NTP 1993). Nephrotoxicity of inorganic mercury is characterized primarily by damage to the *pars recta* segment of the proximal tubule, with involvement of the proximal convoluted tubule and distal tubule in severe toxicity (Berlin et al. 2015; Zalups and Diamond 2005). Damage to the *pars recta* segment of the proximal tubule is consistent with localized uptake of mercury in the renal cortex and outer stripe of the outer medulla (Section 3.1.2). In the proximal tubule, early changes include loss of the brush border membrane, resulting in urinary excretion of brush border enzymes, such as ALP and GGT. As damage to the proximal tubule becomes more severe and progresses to necrosis, intracellular enzymes, such as AAP and NAG, are excreted in the urine, and renal function declines. Substantial evidence from animal studies shows dose- and duration-dependent related damage to the kidneys.

Selection of the Principal Study: The acute-duration oral study in male rats reported by Dieter et al. (1992) and NTP (1993) was selected as the principal study because it identified the lowest LOAEL for the critical effect (renal toxicity).

Summary of the Principal Study:

Dieter MP, Boorman GA, Jameson CW, et al. 1992. Development of renal toxicity in F344 rats gavaged with mercuric chloride for 2 weeks, or 2, 4, 6, 15, and 24 months. J Toxicol Environ Health 36(4):319-340. http://doi.org/10.1080/15287399209531642.

NTP. 1993. Toxicology and carcinogenesis studies of mercuric chloride (CAS no. 7487-94-7) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC: National Toxicology Program. NTP TR 408. NIH publication no. 91-3139.

Fischer 344 rats (5/sex/group) were administered mercuric chloride for 16 days (5 days/week) at doses of 0, 1.25, 2.5, 5, 10, or 20 mg $HgCl_2$/kg/day (equivalent to 0, 0.923, 1.8, 4, 7.4, or 15 mg Hg/kg/day) via gavage in deionized water. Body weights were measured and a complete necropsy was performed. Urinalysis was conducted in the control and 4 mg Hg/kg/day dose groups only. Organ weights were obtained for the brain, heart, kidney, liver, lung, and thymus. Histopathology was evaluated in all dose groups for kidney, stomach, preputial gland (males), and clitoral gland (females). Other organs were microscopically evaluated only in the high-dose group.

Two high-dose males died during the first week of exposure (exposure day 4 and 5). Body weight gains were significantly decreased by 17–18% at 7.4 mg Hg/kg/day and 30–41% at 15 mg Hg/kg/day. In females, final body weight was significantly decreased by 11% at 15 mg Hg/kg/day. Absolute and relative kidney weights were significantly increased by ≥17% in males at ≥1.8 mg Hg/kg/day and ≥28% in females at ≥4 mg Hg/kg/day. Decreases in other absolute organ weights in high-dose females is attributed to decreased body weight. Urinary ALP and AST were significantly elevated in males at 4 mg Hg/kg/day by approximately 80 and 83% (estimated from graphically presented data); these changes were not observed in females. No changes in urinary LDH or GGT were observed in males or females at 4 mg Hg/kg/day. Increased incidence and severity of acute renal necrosis was observed in males at ≥7.4 mg Hg/kg/day and in females at 15 mg Hg/kg/day. No histopathological findings in the stomach, preputial gland, or clitoral gland were reported.

Selection of the Point of Departure for the MRL: In order to identify the POD, BMD modeling was conducted for relative kidney weight data from the acute-duration oral study in the rat (Dieter et al. 1992; NTP 1993). Male rat relative kidney weight data (Table A-8) were fit to all available continuous models in EPA's BMDS (version 3.2) using a BMR of 1 SD. Adequate model fit was judged by four criteria: goodness-of-fit statistics (chi-square p-value >0.1); visual inspection of the dose-response curve; BMDL that is not 10 times lower than the lowest non-zero dose; and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest BMDL values were selected as potential PODs when the difference between the BMDL estimated from these models was >3-fold; otherwise, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) was chosen.

Table A-8. Relative Kidney Weights in Male Rats Exposed to Mercuric Chloride via Gavage 5 days/week for 16 Days

Dose level (mg Hg/kg/day)	Number of animals	Relative kidney weight (mg/g body weight)		
		Mean	Reported SE	Calculated SD
0	5	4.83	0.16	0.36
0.923	5	5.36	0.17	0.38
1.8	5	5.63[a]	0.10	0.22
4	5	5.74[a]	0.16	0.36
7.4	5	6.54[a]	0.46	1.03
15	5	6.89[a]	0.32	0.72

[a]Significantly different from control, p<0.05.

SD = standard deviation; SE = standard error

Source: Dieter et al. 1992; NTP 1993

For elevated relative kidney weight in male rats, the Exponential 4 and 5-degree and Hill models provided adequate fit to the data using non-constant variance. BMDLs were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Hill). The frequentist, restricted Hill model estimated a BMD_{1SD} and $BMDL_{1SD}$ of 0.64 and 0.29 mg Hg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-9 and the model fit for the selected model is shown in Figure A-1.

The $BMDL_{1SD}$ of 0.29 mg Hg/kg/day for increased relative kidney weight in male rats was selected as the POD for deriving an MRL for acute-duration oral exposure to inorganic mercury salts.

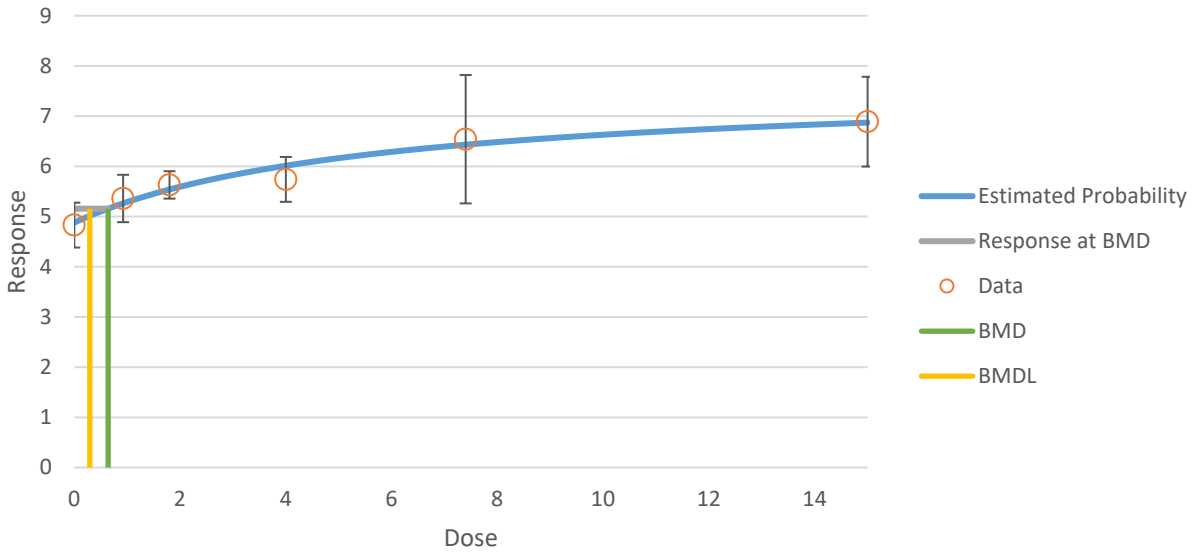
Table A-9. Results from BMD Analysis (Nonconstant Variance) of Relative Kidney Weight in Male Rats Exposed to Mercuric Chloride via Gavage 5 Days/Week for 16 Days (Dieter et al. 1992; NTP 1993)

Model	BMD_{1SD} (mg Hg/kg/day)	$BMDL_{1SD}$ (mg Hg/kg/day)	Test 4 p-value[a]	AIC	Scaled residuals[b]	
					Dose below BMD	Dose above BMD
Exponential 2[c]			0.02	56.24	1.23	0.18
Exponential 3[c]			0.02	56.24	1.23	0.18
Exponential 4[c,]	0.75	0.37	0.27	50.10	-0.57	0.75
Exponential 5[c]	0.75	0.37	0.27	50.10	-0.57	0.76
Hill[c,d]	**0.64**	**0.29**	**0.29**	**49.98**	**-0.40**	**0.62**
Polynomial Degree 5[c]			0.04	54.41	1.28	-0.01
Polynomial Degree 4[c]			0.04	54.41	1.28	-0.01
Polynomial Degree 3[c]			0.04	54.41	1.28	-0.01
Polynomial Degree 2[c]			0.04	54.41	1.28	-0.01
Power[c]			0.04	54.41	1.28	-0.01
Linear			0.04	54.41	1.28	-0.01

[a]Values <0.1 fail to meet adequate fit.
[b]Scaled residuals at doses immediately below and above the BMD.
[c]Restricted model.
[d]Recommended model. There was an adequate fit to the variance when assuming nonconstant variance. The Exponential 4- and 5-degree and Hill models provided adequate fit to the data. BMDLs were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Hill).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control); NA = not applicable, goodness-of-fit test could not be performed

Figure A-1. Fit of Hill Model to Data for Relative Kidney Weight in Male Rats Exposed to Mercuric Chloride via Gavage 5 days/week for 16 Days (Dieter et al. 1992; NTP 1993)



Adjustment for Intermittent Exposure: The $BMDL_{1SD}$ was adjusted from intermittent exposure to account for a continuous exposure scenario:

$BMDL_{ADJ}$ = 0.29 mg Hg/kg/day ppm x (5 days/7 days) = 0.21 mg Hg/kg/day

Uncertainty Factor: The $BMDL_{ADJ}$ of 0.21 mg Hg/kg/day was divided by a total uncertainty factor of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = $BMDL_{ADJ}$ ÷ UFs
MRL = 0.21 mg Hg/kg/day ÷ (10x10)
MRL = 0.0021 mg Hg/kg/day ≈ 0.002 mg Hg/kg/day = 2 µg Hg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: There is strong evidence for adverse renal effects in laboratory animals following oral exposure to mercuric chloride. Findings in acute-duration studies in rats and mice exposed to mercuric chloride include increased relative kidney weight, proximal tubular damage, and acute renal necrosis (Dieter et al. 1992; Kim et al. 2003; Lecavalier et al. 1994; Nielsen et al. 1991; NTP 1993). Numerous intermediate-duration studies in mice and rats also report elevated kidney weight, markers of altered renal function or renal damage, histopathological changes, and nephropathy and/or nephrosis (Table A-11, Renal Effects in Laboratory Animals Exposed to Oral Mercuric Chloride for Intermediate-Durations in the intermediate-duration inorganic mercury oral MRL worksheet for citations). Chronic-duration oral studies in rats and mice observed increased relative kidney weight and degeneration and atrophy of the proximal tubule, and increased incidence and/or severity of renal nephropathy (Dieter et al. 1992; NTP 1993). Kidney toxicity has been observed in human case studies of acute poisoning from ingestion of inorganic mercury compounds (Cappelletti et al. 2019).

Agency Contacts (Chemical Manager): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mercury, inorganic salts (mercuric acetate, mercuric chloride, mercuric sulfide)
CAS Numbers: 1600-27-7, 7487-94-7, 1344-48-5
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.00001 mg Hg/kg/day ($1x10^{-5}$ mg Hg/kg/day; 0.01 µg Hg/kg/day)
Critical Effect: Renal effects
Reference: Apaydin et al. 2016
Point of Departure: LOAEL of 0.015 mg Hg/kg/day
Uncertainty Factor: 1,000
LSE Graph Key: 37
Species: Rat

MRL Summary: An intermediate-duration oral MRL of 0.00001 mg Hg/kg/day ($1x10^{-5}$ mg Hg/kg/day; 0.01 µg Hg/kg/day) for inorganic mercury salts was derived based on renal effects (decreased renal function and histopathological changes) in rats exposed to mercuric chloride by gavage for 28 days (Apaydin et al. 2016). The MRL is based on a LOAEL of 0.015 mg Hg/kg/day and a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from rats to humans, and 10 for human variability).

The intermediate-duration oral MRL based on mercuric chloride is expected to be protective for all inorganic mercury salts. Mercuric chloride is water soluble (Section 3.1, Toxicokinetics) and the bioavailability of mercury salts is directly related to their solubility. Other mercuric salts are less soluble than mercury chloride and are expected to have lower oral bioavailability and, therefore, lower toxicity. For example, LOAELs for intermediate-duration oral exposure to mercuric sulfide, a poorly soluble salt, are approximately 3–380-fold greater than the corresponding LOAELs identified for mercuric chloride (Table A-10).

Selection of the Critical Effect: No epidemiological studies evaluating intermediate-duration oral exposure to mercuric salts were identified. Toxicity data for intermediate-duration oral exposure to mercuric chloride and mercuric sulfide are available from studies in animals; no intermediate-duration oral studies on other inorganic mercury salts were identified. The lowest NOAEL and LOAEL values reported for mercuric chloride and mercuric sulfide for each organ system are summarized in Table A-10.

Table A-10. Summary of Lowest LOAELs for Intermediate-Duration Oral Exposure to Mercuric Chloride and Mercuric Sulfide

		NOAEL/LOAEL (mg Hg/kg/day)			
Species	Duration	NOAEL	LOAEL	System: Effect	Reference
Mercuric chloride					
Rat	28 days	ND	0.015	***Renal:*** Decreased renal function and histopathological changes	Apaydin et al. 2016

Table A-10. Summary of Lowest LOAELs for Intermediate-Duration Oral Exposure to Mercuric Chloride and Mercuric Sulfide

		NOAEL/LOAEL (mg Hg/kg/day)			
Species	Duration	NOAEL	LOAEL	System: Effect	Reference
Rat	21 days	ND	0.033	***Hematological:*** Decreased clotting time, 13% decrease in erythrocyte count, 5% decrease in hemoglobin, and 17% increase in leukocyte count	Mahour and Saxena 2009
Rat	12 weeks	ND	0.07	***Cardiovascular:*** Increase in systolic blood pressure at 5 weeks but not 12 weeks	Takahashi et al. 2000b
Rat	21 weeks	ND	0.07	***Hepatic:*** Decreased plasma HDL cholesterol and triglycerides	Takahashi et al. 2000b
Mouse	10 weeks	0.07	0.118	***Immunological:*** Polyclonal B-cell activation	Hultman and Nielsen 2001; Nielsen and Hultman 2002
Mouse	61–79 days	ND	0.18	***Reproductive:*** Decreased fertility index	Khan et al. 2004
Rat	45 days	ND	0.277	***Neurological:*** Impaired motor coordination and balance; apoptosis and loss of neurons and astrocytes in motor cortex; decreased motor activity; impaired learning and memory	Teixeira et al. 2014, 2018
Rat	7 weeks	ND	0.4	***Developmental (neurodevelopmental):*** Decreased peripheral sensory nerve conduction velocity	Huang et al. 2011
Rat	3 months	ND	2.2	***Endocrine:*** Impaired thyroid function	Goldman and Blackburn 1979
Mercuric sulfide					
Mouse	4 weeks	ND	6	***Endocrine:*** Decreased plasma T4 (28–41%)	Sin and Teh 1992
Mouse	4 weeks	ND	17	***Immunological:*** Altered T-cell populations in spleen	Son et al. 2010
Guinea pig	21 days	ND	86	***Neurological:*** Abnormal vestibular ocular reflex	Chuu et al. 2001b

HDL = high-density lipoprotein; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; T4 = thyroxine

For mercuric chloride, the most sensitive effect for intermediate-duration oral exposure is renal toxicity in rats, with the lowest LOAEL value of 0.015 mg Hg/kg/day; a NOAEL was not identified as only one dose level was tested in this study (Apaydin et al. 2016). The next lowest LOAEL of 0.033 mg Hg/kg/day was for hematological effects in rats (Mahour and Saxena 2009), and is approximately 2-fold higher than the LOAEL for renal effects. For mercuric sulfide, the lowest LOAEL identified was 6 mg Hg/kg body

weight for endocrine effects in mice (Sin and Teh 1992). Available intermediate-duration oral studies on effects of mercuric sulfide did not evaluate renal effects. However, LOAEL values for mercuric sulfide for endocrine, immunological, and neurological effects are greater than corresponding LOAELs for mercuric chloride by approximately 3-, 144-, and 380-fold, respectively. Therefore, an MRL based on mercuric chloride is expected to be protective for exposure to mercuric sulfide.

Renal effects, long established as a sensitive target for inorganic mercury salts, were selected as basis for derivation of the intermediate-duration oral MRL. Nephrotoxicity of inorganic mercury is characterized primarily by damage to the *pars recta* segment of the proximal tubule, with involvement of proximal convoluted tubules and distal tubule in severe toxicity (Berlin et al. 2015; Zalups and Diamond 2005). Damage to the *pars recta* segment of the proximal tubule is consistent with localized uptake of mercury in the renal cortex and outer stripe of the outer medulla (Section 3.1.2). In the proximal tubule, early changes include loss of the brush border membrane, resulting in urinary excretion of brush border enzymes, such as ALP and GGT. As damage to the proximal tubule becomes more severe and progresses to necrosis, intracellular enzymes, such as AAP and NAG, are excreted in the urine, and renal function declines. Substantial evidence from animal studies shows dose- and duration-dependent related damage to the kidneys. Renal effects observed in intermediate-duration oral studies in laboratory animals are summarized in Table A-11.

Table A-11. Renal Effects in Laboratory Animals Exposed to Oral Mercuric Chloride for Intermediate-Durations

Effect	Species	References
Increased relative kidney weight	Rats and mice	Atkinson et al. 2001; Dieter et al. 1983, 1992; Jonker et al. 1993; Khan et al. 2004; NTP 1993; Takahashi et al. 2000a, 2000b; Wildemann et al. 2015a
Markers of altered renal function or renal damage (increased serum levels of urea, uric acid, and creatinine; elevated urine protein and/or ketones)	Rats	Apaydin et al. 2016; Carmignani et al. 1992; Jonker et al. 1993; Takahashi et al. 2000a
Histopathological changes (including tubular dilation and glomerular lobulation, tubular damage and degeneration, necrosis)	Rats and mice	Apaydin et al. 2016; Boscolo et al. 1989; Carmignani et al. 1989, 1992; Jonker et al. 1993; NTP 1993
Nephropathy and/or nephrosis	Rats and mice	Dieter et al. 1983, 1992; Jonker et al. 1993; NTP 1993

Selection of the Principal Study: The Apaydin et al. (2016) study provided the lowest LOAEL observed for renal effects in intermediate-duration animal studies and was selected as the principal study.

Summary of the Principal Study:

Apaydin FG, Bas H, Kalender S, et al. 2016. Subacute effects of low dose lead nitrate and mercury chloride on kidney of rats. Environ Toxicol Pharmacol 41:219-224.

Groups of six Wistar rats (90 days old; sex not specified) were administered distilled water or 0.02 mg/kg mercuric chloride in distilled water by gavage daily for 28 days (equivalent to 0.015 mg Hg/kg/day). At the end of the 28-day exposure period, blood samples were obtained and analyzed for serum urea, uric

acid, and creatinine levels. Kidneys were examined microscopically, and renal levels of the following were determined: malondialdehyde, glutathione peroxidase (GPX), glutathione S-transferase (GST), superoxide dismutase (SOD), and catalase.

In rats treated with mercuric chloride, serum levels of urea, uric acid, and creatinine were significantly increased by 28, 54, and 17%, respectively, compared to controls, indicating decreased renal function. Histopathological assessment of the kidneys showed tubular dilation and glomerular lobulation compared to normal appearance in controls. Kidney activity of antioxidant enzymes, GPX, GST, SOD, and catalase were significantly decreased by approximately 31, 25, 32, and 41%, respectively, compared to controls (data presented graphically). Kidney malondialdehyde levels were significantly increased by approximately 69%, compared to controls (data presented graphically). Findings are consistent with oxidative stress and peroxidation of lipid membranes.

Selection of the Point of Departure for the MRL: The LOAEL of 0.015 mg Hg/kg/day for decreased renal function and histopathological alterations in the kidneys was selected as the POD for deriving a MRL for intermediate-duration oral exposure to inorganic mercury salts. BMD modeling was not considered for this dataset, as only one dose level was tested in the study. Existing PBPK models were not suitable for extrapolation of inorganic mercuric mercury dosimetry between rats and humans.

Uncertainty Factor: The LOAEL of 0.015 mg Hg/kg/day was divided by a total uncertainty factor of 1,000:

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = LOAEL ÷ UFs
MRL = 0.015 mg Hg/kg/day ÷ (10x10x10)
MRL = 0.000015 mg Hg/kg/day ≈ 0.00001 mg Hg/kg/day = 0.01 µg Hg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: See *Selection of the Critical Effect* above for review of supporting evidence from intermediate-duration oral exposure studies in animals. In addition, acute- and chronic-duration oral studies in laboratory animals have observed renal toxicity. Findings in acute-duration studies in rats and mice exposed to mercuric chloride include increased relative kidney weight, proximal tubular damage, and acute renal necrosis (Kim et al. 2003; Lecavalier et al. 1994; Nielsen et al. 1991; NTP 1993). Chronic-duration oral studies in rats and mice observed increased relative kidney weight and degeneration and atrophy of the proximal tubule, and increased incidence and/or severity of renal nephropathy (Dieter et al. 1992; NTP 1993). Kidney toxicity has been observed in human case studies of acute poisoning from ingestion of inorganic mercury compounds (Cappelletti et al. 2019).

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Mercury, inorganic salts (mercuric acetate, mercuric chloride, mercuric sulfide)
CAS Numbers: 1600-27-7, 7487-94-7, 1344-48-5
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for inorganic mercury salts.

Rationale for Not Deriving an MRL: Epidemiological studies of chronic-duration oral exposure to inorganic mercury salts were not identified, and few studies have evaluated the effects of chronic-duration oral exposure to inorganic mercury salts in animals (Dieter et al. 1992; NTP 1993; Perry and Erlanger 1974). The lowest LOAELs identified for each study are summarized in Table A-12. The lowest LOAEL identified is 0.66 mg Hg/kg/day for increased systolic blood pressure in rats exposed to mercuric chloride in drinking water for 1 year, with a NOAEL of 0.33 mg Hg/kg/day (Perry and Erlanger 1974). The lowest chronic-duration LOAEL is 44-fold higher than the lowest intermediate-duration LOAEL of 0.015 mg Hg/kg/day that is the basis of the intermediate-duration oral MRL. Studies examining effects of chronic-duration oral exposure at lower levels were not identified. Therefore, a chronic-duration oral MRL was not derived for inorganic mercury.

Table A-12. Summary of LOAELs from Chronic-Duration Oral Studies in Laboratory Animals Exposed to Mercuric Chloride

		NOAEL/LOAEL[a] (mg Hg/kg/day)				
Species	Duration	NOAEL	LOAEL	SLOAEL	Effect	Reference
Rat	1 year	0.33 (F)	0.66 (F)	ND	Increased systolic blood pressure	Perry and Erlanger 1974
Rat	2 years	ND (M)	1.8 (M)	1.8 (M)	LOAEL: Decreased body weight, inflammatory lesions of the nasal mucosa, and epithelial hyperplasia of the forestomach SLOAEL: Decreased survival, degeneration and atrophy of the renal tubular epithelium	Dieter et al. 1992; NTP 1993
Mouse	2 years[b]	ND	4	ND	Nephropathy and increased kidney weight	NTP 1993

[a]Unless otherwise specified, NOAEL and LOAEL values are for both males and females.
[b]Continuous mating study.

F = female; LOAEL = lowest-observed-adverse-effect level; M = male; ND = not determined; NOAEL = no-observed-adverse-effect level; SLOAEL = serious lowest-observed-adverse-effect level

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methylmercury
CAS Number: 22967-92-6
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for methylmercury.

Rationale for Not Deriving an MRL: No human or animal studies evaluating acute-duration inhalation exposure to methylmercury were identified. Therefore, an acute-duration inhalation MRL was not derived.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methylmercury
CAS Number: 22967-92-6
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for methylmercury.

Rationale for Not Deriving an MRL: No human or animal studies evaluating intermediate-duration inhalation exposure to methylmercury were identified. Therefore, an intermediate-duration inhalation MRL was not derived.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methylmercury
CAS Number: 22967-92-6
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for methylmercury.

Rationale for Not Deriving an MRL: No human or animal studies evaluating chronic-duration inhalation exposure to methylmercury were identified. Therefore, a chronic-duration inhalation MRL was not derived.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methylmercury
CAS Number: 22967-92-6
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for methylmercury.

Rationale for Not Deriving an MRL: No studies examining effects of acute-duration oral exposure to methylmercury in humans were identified. Numerous studies in laboratory animals have investigated effects of acute-duration oral exposure to methylmercury. Table A-13 lists the lowest reported NOAELs and LOAELs for acute toxicity endpoints. The lowest LOAEL of 0.008 mg Hg/kg/day identified the developing nervous system as the most sensitive target for acute-duration oral exposure (Bornhausen et al. 1980). The associated NOAEL is 0.004 mg Hg/kg/day.

Table A-13. Summary of Lowest NOAELs and LOAELs for Acute-Duration Oral Exposure to Methylmercury

		NOAEL/LOAEL (mg Hg/kg/day)			
Species	Duration	NOAEL	LOAEL	System: Effect	Reference
Rat	4 days (GDs 6–9)	0.004	0.008	***Developmental (neurodevelopmental):*** Impaired operant conditioning at 4 months	Bornhausen et al. 1980
Rat	14 days	ND	0.5	***Reproductive:*** Nonmonotonic sperm effects (decreased count and motility, increased abnormal); inflammatory foci and thickening of epithelium in prostate	Fossato da Silva et al. 2011, 2012
Rat	1–2 weeks	ND	0.7	***Neurological:*** Ultrastructural changes in dorsal root ganglia and cerebellum	Chang and Hartmann 1972
Mouse	14 days	ND	1.6	***Endocrine:*** Altered glucose homeostasis; apoptosis in pancreatic islet cells	Chen et al. 2012
Rat	14 days	ND	1.9	***Body weight:*** Decreased body weight (~10%)	Chuu et al. 2007
Rat	14 days	0.93	2.8	***Renal:*** Increased relative kidney weight (18%)	Fossato da Silva et al. 2011
Rat	12 days	ND	4	***Musculoskeletal:*** Muscle weakness and wasting	Usuki et al. 1998
Mouse	14 days	ND	5.6	***Hepatic:*** Elevated total cholesterol	Moreira et al. 2012

Table A-13. Summary of Lowest NOAELs and LOAELs for Acute-Duration Oral Exposure to Methylmercury

	Duration	NOAEL/LOAEL (mg Hg/kg/day)		System: Effect	Reference
Rat	2 days	ND	12	***Cardiovascular:*** Decreased heart rate (10–18%)	Arito and Takahashi 1991

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

Several animal studies provide support for neurodevelopmental effects as the most sensitive target of acute-duration oral exposure to methylmercury. Studies observing neurodevelopmental effects at doses ≤0.5 mg Hg/kg/day (the lowest LOAEL for reproductive effects, the second most sensitive target of acute-duration oral exposure to methylmercury) are summarized in Table A-14. Two neurodevelop-mental studies reported similar LOAELs for neurodevelopmental effects: the Bornhausen et al. (1980) study in rats, with a LOAEL of 0.008 mg Hg/kg/day and the Montgomery et al. (2008) study in mice, with a LOAEL of 0.009 mg Hg/kg/day. The study in rats identified a NOAEL of 0.004 mg Hg/kg/day; however, the study in mice did not identify a NOAEL, as only one dose (0.009 mg Hg/kg/day) was tested.

Table A-14. Neurodevelopmental Effects in Laboratory Animals Exposed to Methylmercury Doses ≤0.5 mg Hg/kg/day for Acute Durations.

		NOAEL/LOAEL (mg Hg/kg/day)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Rat	4 days, GDs 6–9	0.004	0.008	Impaired operant conditioning at 4 months	Bornhausen et al. 1980
Mouse	11 days, GDs 8–18	ND	0.009	Impaired learning and memory, decreased motor activity and coordination in adult offspring	Montgomery et al. 2008
Mouse	5 days, PNDs 29–33	ND	0.2	Impaired balance and motor coordination on PND 38	Bellum et al. 2007
Mouse	Once, PND 10	ND	0.37	Decreased motor activity and impaired learning and memory at 2–6 months of age	Fischer et al. 2008
Rat	4 days, GDs 6–9	0.04	0.4	Increased startle response in adult offspring Effects at 4 mg Hg/kg/day: impaired swimming, impaired visual discrimination, decreased activity, and decreased habituation	Stoltenburg-Didinger and Markwort 1990

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level PND = postnatal day

The NOAEL of 0.004 mg Hg/kg/day in rats (Bornhausen et al. 1980) and the LOAEL of 0.009 mg Hg/kg/day in mice (Montgomery et al. 2008) were considered as possible PODs for an acute-duration oral MRL, as shown in Table A-15. Based on the NOAEL of 0.004 mg Hg/kg/day in rats and a total

uncertainty factor of 100, the MRL would be 0.00004 mg Hg/kg/day (0.04 µg Hg/kg/day). Based on the LOAEL of 0.009 mg Hg/kg/day and a total uncertainty factor of 1,000, the MRL would be 0.000009 mg Hg/kg/day (0.009 µg Hg/kg/day). These acute-duration MRLs are less than the chronic-duration oral MRL for methylmercury of 0.1 µg Hg/kg/day based on data in humans. Therefore, an acute-duration oral MRL for methylmercury was not derived.

Table A-15. Possible Acute-Duration Oral Minimal Risk Levels (MRLs) for Methylmercury Based on Neurodevelopmental Effects

Species	MRL (µg Hg/kg/day)	Critical effect	Point of departure (mg Hg/kg/day)	Uncertainty factors	Reference
Rat	0.04	Impaired operant conditioning at 4 months	NOAEL: 0.004	100[a]	Bornhausen et al. 1980
Mouse	0.009	Impaired learning and memory, and decreased motor activity and coordination in adult offspring	LOAEL: 0.009	1,000[b]	Montgomery et al. 2008

[a]Total uncertainty factor = 100 (10 for extrapolation from rats to humans; 10 for human variability).
[b]Total uncertainty factor = 1,000 (10 for use of LOAEL; 10 for extrapolation from mice to humans; 10 for human variability).

LOAEL = lowest-observed-adverse-effect level; NOAEL = No-observed-adverse-effect level

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methylmercury
CAS Number: 22967-92-6
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for methylmercury.

Rationale for Not Deriving an MRL: In humans, intermediate-duration oral exposure to methylmercury occurred in Iraq in 1972–1973 as a result of widespread consumption of bread made from wheat that had been treated with a methylmercuric fungicide (Al-Mufti et al. 1976; Bakir et al. 1973; Clarkson et al. 1976). BHg levels in poisoning cases measured approximately 65 days after exposure ranged from 10 to 3,000 µg Hg/L (Clarkson et al. 1976). Severe neurological and neurodevelopmental effects were observed in this population; therefore, findings in this population cannot be used to derive an intermediate-duration oral MRL for methylmercury.

Numerous studies in laboratory animals have investigated effects of intermediate-duration oral exposure to methylmercury. The lowest LOAELs for each system are summarized in Table A-16. The lowest dose of methylmercury tested in intermediate-duration oral studies was 0.0003 mg Hg/kg/day in rats exposed during pre-mating through PND 21 (Wild et al. 1997). At this dose, immunodevelopmental effects (enhanced lymphoproliferation in response to mitogens) were observed in offspring assessed on PND 84. This is the lowest LOAEL observed in intermediate-duration oral studies. The next lowest dose tested was 0.0004 mg Hg/kg/day in rats exposed for 8 weeks (Ortega et al. 1997a, 1997b); this dose is a LOAEL for immunological effects in adult rats (immune stimulation). The lowest LOAEL values for renal, neurological, and neurodevelopmental effects were 0.006, 0.0073, and 0.02 mg Hg/kg/day, respectively. Results of these studies indicate that the immune system is a sensitive target for methylmercury. Several animal studies provide support that the developing immunological system is the most sensitive target of methylmercury; studies are summarized in Table A-17. Immunodevelopmental effects have been observed at doses ranging from 0.0003 to 0.37 mg Hg/kg/day.

Table A-16. Summary of Lowest LOAELs for Intermediate-Duration Oral Exposure to Methylmercury

		NOAEL/LOAEL (mg Hg/kg/day)			
Species	Duration	NOAEL	LOAEL	System: Effect	Reference
Rat	14–16 weeks premating to PND 21	ND	0.0003	***Immunodevelopmental:*** Altered functional immune function (enhanced lymphoproliferation in response to mitogens) in PND 84 offspring	Wild et al. 1997
Rat	8 weeks	ND	0.0004	***Immunological:*** Immune stimulation followed by immune suppression at higher doses	Ortega et al. 1997a, 1997b
Rat	8 weeks	ND	0.0004	***Endocrine:*** Increase in adrenocorticotrophic hormone	Ortega et al. 1997b

Table A-16. Summary of Lowest LOAELs for Intermediate-Duration Oral Exposure to Methylmercury

	Duration	NOAEL/LOAEL (mg Hg/kg/day)		System: Effect	Reference
Rat	4 weeks	0.002	0.005	***Cardiovascular:*** Elevated systolic blood pressure and pulse pressure	Wildemann et al. 2015a
Rat	4 weeks	0.006	0.285	***Renal:*** Elevated urinary creatinine	Wildemann et al. 2016
Mouse	2 months	0.00046	0.0073	***Neurological:*** Impaired memory	Bourdineaud et al. 2011
Rat	19 weeks[a]	0.0008	0.008	***Reproductive:*** No viable litters produced	Friedmann et al. 1998
Mouse	10–17 weeks premating through PNDs 21–70	ND	0.02	***Neurodevelopmental:*** Decreased motor activity and impaired hearing and motor coordination in offspring	Huang et al. 2011
Rabbit	14 weeks	0.05	0.49	***Body weight:*** Decreased body weight gain	Koller et al. 1977
Mouse	21 days	ND	5.6	***Hepatic:*** Elevated plasma total cholesterol	Moreira et al. 2012

[a]Rats were dosed 2 times/week.

LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day

Table A-17. Summary of LOAELs for Immunodevelopmental Effects in Animals Exposed to Oral Methylmercury for Intermediate Durations

		NOAEL/LOAEL (mg Hg/kg/day)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Rat	14–16 weeks (premating through PND 21)	ND	0.0003	Altered functional immune endpoints (enhanced lymphoproliferation in response to mitogens) in PND 12 offspring	Wild et al. 1997
Rat	14–16 weeks (premating through PND 21)	ND	0.0006	Altered functional immune endpoints in PND 6–12 offspring (enhanced lymphoproliferation in response to mitogens; decreased NK cell activity)	Wild et al. 1997
Mouse[a]	5 weeks (GD 8 to PND 21)	ND	0.06	Cerebellar inflammation, attributed to autoimmune effects, at PNDs 21 and 70	Zhang et al. 2011

Table A-17. Summary of LOAELs for Immunodevelopmental Effects in Animals Exposed to Oral Methylmercury for Intermediate Durations

Species	Duration	NOAEL/LOAEL (mg Hg/kg/day)		Effect	Reference
Rat	26 days (GD 6 to PND 10)	ND	0.08	Altered functional immune endpoints in PND 21–70 offspring (decrease in the primary KLH-specific IgG antibody response on PND 35)	Tonk et al. 2010
Mouse	15–16 weeks (10 weeks premating through PND 15)	ND	0.098	Alterations in functional immune endpoints (increased primary antibody response to a viral antigen) and thymocyte cell populations in PNDs 10–22 offspring	Thuvander et al. 1996
Rat	15 days (PNDs 1–15, via dam)	ND	0.37	13% decrease in relative spleen weight; altered immune function in offspring (decreased splenic lymphoproliferative response to mitogen)	Ilback et al. 1991
Rat	~15 weeks (11 weeks premating through GD 21)	ND	0.37	45% increase in WBCs in offspring on PND 15	Ilback et al. 1991
Rat	~17 weeks (11 weeks premating through PND 15)	ND	0.37	Altered immune function in offspring (increased thymic lymphoproliferative response to mitogen, decreased cell-mediated cytotoxicity)	Ilback et al. 1991

[a]Immune susceptible mouse strain.

GD = gestational day; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NK = natural killer; NOAEL = no-observed-adverse-effect level; PND = postnatal day WBC = white blood cell

If an intermediate-duration oral MRL was derived based on the lowest LOAEL of 0.0003 mg Hg/kg/day (0.3 µg Hg/kg/day) for immunodevelopmental effects and a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), the intermediate-duration oral LOAEL for methylmercury would be 0.0003 µg Hg/kg/day. This value is lower that the chronic-duration oral MRL of 0.1 µg Hg/kg/day; therefore, an intermediate-duration oral MRL for methylmercury was not derived.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Methylmercury
CAS Number: 22967-92-6
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Chronic
MRL: 0.1 µg Hg/kg/day
Critical Effect: Neurodevelopmental effects (decreased IQ)
Reference: Axelrad et al. 2007a, 2007b
Point of Departure: NAEL of 0.41 µg Hg/kg/day
Uncertainty Factor: 3
LSE Graph Key: 173
Species: Human

MRL Summary: A chronic-duration oral MRL of 0.0001 mg Hg/kg/day (0.1 µg Hg/kg/day) was derived based on neurodevelopmental effects (decreased full-scale IQ) in humans chronically exposed to methylmercury from consumption of dietary fish (Axelrad et al. 2007a, 2007b). The MRL is based on a NAEL of 0.00041 mg Hg/kg/day (0.41 µg Hg/kg/day) and a total uncertainty factor of 3 for human variability.

Selection of the Critical Effect: Studies conducted in animals (nonhuman primates and rodents) and human epidemiological studies provide strong support for the developing nervous system being the most sensitive target of methylmercury. In humans, severe neurodevelopmental effects (congenital Minamata disease) occurred in association with maternal ingestion of methylmercury in seafood (Harada 1995) and from ingestion of wheat contaminated with a methylmercury fungicide (Iraq outbreak) (Amin-Zaki et al. 1974). In both incidents, exposure levels were sufficient to produce severe neurological effects in adults. Studies of lower levels of prenatal exposures have largely focused on populations that consume large amounts of marine fish. In these populations, the dominant source of the mercury body burden derives from consumption of methylmercury in fish, providing a strong basis for use of BHG or HHg as a biomarker of methylmercury exposure. Studies of general populations have also relied on biomarkers for assessing exposure; however, in these populations, BHg and HHg will be more greatly affected by exposures to other forms of mercury, including mercury released from mercury amalgam dental restorations. Therefore, general population studies that estimated oral intake of methylmercury are stronger designs for the purpose of dose-response assessments of methylmercury.

Cognitive and neurosensory effects have been observed in association with prenatal exposures to methylmercury via maternal fish consumption. Consistent findings have been observed at relatively high exposure levels (e.g., Iraq outbreak, Minamata outbreak). However, results of studies that have explored lower exposure levels have been inconsistent. Some studies found improved function or no associations with mercury, and some studies found non-monotonic responses (e.g., declines at lower levels of exposure and improvements at higher levels). Differences in effect estimates may be due to differences in confounders and how they were controlled in models. These variables include fish intake and related nutritional factors (e.g., 3-omega polyunsaturated long-chain fatty acids), co-exposure to other contaminants (e.g., lead, PCBs), and social variables affecting child development. In addition, presence of genetic susceptibility factors (of lack thereof) may act as effect measure modifiers, impacting the associations observed between mercury and a health outcome.

Several high fish consuming populations have been studied to evaluate possible associations between prenatal mercury exposure and neurodevelopment. These include populations in the Amazon River basin,

Arctic Canada, Faroe Islands, North Island New Zealand, and Seychelle Islands. Studies conducted in the Faroe Islands, North Island New Zealand, and Seychelle Islands are particularly important because of several features: (1) prospective design; (2) relatively large sample populations in main cohort (approximately 700–1,000); (3) high quality assurance procedures for biomarker measurements; (4) multiple follow-ups at different ages; (5) multiple tests of cognitive and neurosensory performance that assessed a wide range of cognitive domains; (6) extensive exploration and control of confounding; (7) assessments of biomarker measurement error (Faroe Islands and Seychelle Islands studies); and (8) multiple analyses of the data, which included linear and non-linear regression, cross-sectional and longitudinal analyses, individual and aggregated outcome metrics, and BMD analyses. For each study, observed biomarkers of exposure (e.g., BHg) were converted to estimates of oral mercury doses and categorized as either an AEL if an adverse effect was observed or a NAEL if no adverse effect was observed (Appendix E for definitions of AEL and NAEL).

Selection of the Principal Study: Neurodevelopmental outcomes from studies conducted on populations from the Faroe Islands, North Island New Zealand, and Seychelle Islands are summarized below. A summary of a meta-analysis that includes data from the Faroe Islands, North Island New Zealand, and Seychelle Islands is also described (Axelrad et al. 2007a, 2007b). In addition, detailed summaries of two studies evaluating neurodevelopmental outcomes in a large general population from Norway are included (Vejrup et al. 2016, 2018).

Faroe Islands study. The Faroe Islands study followed a prospective cohort of high fish and marine mammal consumers (n=1,022 mother-infant pairs, recruited 1986–1987) from age 2 weeks to 22 years. The primary methylmercury prenatal exposure metric was total mercury in cord blood, which was predominantly (>80%) methylmercury (Grandjean et al. 1992). The median cord blood mercury concentration was 24 µg Hg/L and the IQR (25^{th} to 75^{th} percentile range) was 13–40 µg Hg/L; approximately 25% of the cord mercury levels were >40 µg Hg/L (Grandjean et al. 1992). Cord blood mercury levels (µg Hg/L) were approximately 5 times maternal HHg levels measured at parturition with a median of 4.5 µg Hg/g, and an IQR of 2.5–7.7 (Grandjean et al. 1992). In most studies, depending on the outcome measured, outcome associations were adjusted for covariates: child age, sex, birth weight; breastfeeding; maternal age, alcohol, tobacco use, medical history; and caregiver general intelligence (Raven's Progressive Matrices). Other potential confounders were also explored (e.g., fish consumption, blood selenium, blood PCBs).

The study found associations between prenatal (cord) BHg and decreasing performance on tests of cognitive function assessed at age 7 years (Grandjean et al. 1997, 1998, 2003, 2014; Oulhote et al. 2019), 14 years (Debes et al. 2006; Julvez et al. 2010), and 22 years (Debes et al. 2016). The associations were not consistently observed in all tests of cognitive function. The associations tended to cluster into domains of fluid reasoning (e.g., identifying rules for visual similarities and differences), comprehension and knowledge (e.g., naming, word synonyms and antonyms), decision and reaction speed, and motor coordination (Debes et al. 2016). Latencies of brainstem auditory evoked potentials measured at age 7 or 14 years increased in association with increasing prenatal or child HHg levels (Grandjean et al. 1997; Murata et al. 2004a).

Exposure measurement error based on estimation of biomarker imprecision was estimated to exceed laboratory measurement error (Grandjean and Budtz-Jorgensen 2007; Grandjean et al. 2004b). The observed associations with cognitive test outcomes persisted after excluding subjects who had large variability in HHg levels during pregnancy (Grandjean et al. 2003). Findings from the Faroe Islands included:

- Postnatal HHg levels correlated with duration of breastfeeding, although breastfeeding was not a significant explanatory variable for cognitive test outcomes in the cohort (Grandjean et al. 1995; Jensen et al. 2005).

- Blood selenium levels correlated with BHg levels and whale consumption (Grandjean et al. 1992); however, prenatal selenium level (cord blood) was not a significant explanatory variable for cognitive test outcomes in the cohort (Choi et al. 2008b).
- Although cord blood PCB concentration correlated with BHg levels, associations between cord blood mercury levels and cognitive tests scores persisted after adjustment for cord blood PCB concentrations (Grandjean et al. 1997). Analysis of data from the 7-year follow-up found no evidence of interactions between mercury and exposure to PCBs and long-chain perfluoroalkyls (Oulhote et al. 2019).
- Adjustment for cord serum omega-3 long-chain polyunsaturated fatty acids (LCPUFA) strengthened associations between prenatal mercury exposure and cognitive test scores or brainstem evoked potential latencies (Choi et al. 2008b; Yorifuji et al. 2013).

Additional details for the Grandjean et al. (1997, 1999) studies are summarized in Table A-18. These studies were included in the Axelrad et al. (2007a, 2007b) meta-analysis.

Table A-18. Summary of the Grandjean et al. (1997) and Grandjean et al. (1999) Studies of the Faroe Islands Population

Study type and population: Prospective study of birth cohort, follow-up at age 7 years (n=917)

Biomarkers:
BHg (geometric mean µg Hg/L, IQR)
Cord: 22.9 (13.4–41.3)
Child (7 years): 8.82 (4.8–18.2)

HHg (geometric mean µg Hg/g, IQR)
Maternal: 4.27 (2.6–7.7)
Child (12 months): 1.12 (0.69–1.88)
Child (7 years): 2.99 (1.7–6.1)

Estimated oral dose[a]: 0.34 µg Hg/kg/day (based on cord BHg)

Analysis: Data were analyzed using multiple regression analysis. Outcome associations were adjusted for age and sex for all analyses. Additional covariates included strabismus (abnormal eye alignment) and eye glasses (VEP); current middle ear infection (BAEP); height (postural sway), maternal cognitive function, maternal smoking and alcohol use, social background, and major medical risk factors such as low birth weight, small-for-gestational date, history of head trauma and meningitis (neuropsychological tests); and child's acquaintance with computers and computer games (computer-assisted tests). Data from neuropsychological tests were also analyzed using the Peters-Belson approach. In this approach, any regression coefficients with p<0.1 in the lowest quartile of cord blood (<15 µg Hg/L) group were included in multiple regressing models for all children. By identifying potential confounders in the lowest quartile BHg group, rather than in the full cohort, this approach may provide a less biased estimate of the association between mercury exposure and outcomes in the presence of confounding.

Results[b]:

Adjusted regression coefficients between cord BHg and neurophysiological tests

- BAEPL at 40 Hz
  - I = 0.043, p=0.10
  - III = 0.053, p=0.06
  - V = 0.059, p=0.01
- VEPL at 15 minutes
  - N75 = 0.21, p=0.70

Peters-Belson regression coefficients between cord BHg and neuropsychological tests

- NES FTT
  - D hand =-1.18, p=0.03
  - ND hand = -0.37, p=0.47
  - Both hands = -1.86, p=0.08
- NES HECT = 0.033, p=0.20
- NES CPT

Table A-18. Summary of the Grandjean et al. (1997) and Grandjean et al. (1999) Studies of the Faroe Islands Population

- P100 = -0.75, p=0.33
- N145 = -0.99, p=0.37

- Postural sway
  - Eyes open = -0.04, p=0.90
  - Eyes closed = -1.54, p=0.09
  - Eyes open, on foam = -0.43, p=0.40
  - Eyes closed, on foam = -0.19, p=0.86
- HRV R-R interval: -0.39, p=0.29

Adjusted regression coefficients between cord BHg and neuropsychological tests

- WISC-R
  - Digit span[c] = -0.27, p=0.05
  - Similarities[c] = -0.05, p=0.90
  - Block design[c] = -0.17, p=0.11
- CVLT
  - Learning = -1.25, p=0.12
  - Short-term[c] = -0.57, p=0.02
  - Long-term = -0.55, p=0.05
  - Recognition = -0.29, p=0.15
- BNT
  - No cues[c] = -1.77, p=0.0003
  - Cues = -1.91, p=0.0001
- BVMGT
  - Copy error[c] = 0.67, p=0.15
  - Reproduction = -0.25, p=0.10
- NES FTT
  - D hand = -1.10, p=0.05
  - ND hand = -0.39, p=0.46
  - Both hands = -1.67, p=0.14
- NES HECT = 0.034, p=0.19
- NES CPT
  - Missed response = 0.12, p=0.02
  - Reaction time = 40.3, p=0.001
- TPT (D hand) = -14.3, p=0.63
- NVAPMS
  - Positive moods = 2.61, p=0.31
  - Negative moods = -0.04, p=0.99
  - Missed response = 0.14, p=0.007
  - Reaction time = 38.2, p=0.0002
- WISC-R
  - Digit span[c] = -0.27, p=0.05
  - Similarities[c] = 0.14, p=0.70
  - Block design[c] = -0.25, p=0.02
- CVLT
  - Learning = -1.30, p=0.11
  - Short-term[c] = -0.63, p=0.009
  - Long-term = -0.64, p=0.02
  - Recognition = -0.28, p=0.15
- BNT
  - No cues[c] = -1.66, p=0.0007
  - Cues = -1.82, p=0.0002
- BVMGT
  - Copy error[c] = 1.04, p=0.03
  - Reproduction = -0.16, p=0.31
- TPT (D hand) = -18.8, p=0.60
- NVAPMS
  - Positive moods = 2.39, p=0.34
  - Negative moods = 0.17, p=0.94

Adjusted regression coefficients between cord BHg and neuropsychological tests in low exposure children only (maternal HHg <10 µg Hg/g)

- WISC-R
  - Digit span[c] = -0.31, p=0.05
  - Similarities[c] = 0.65, p=0.15
  - Block design[c] = -0.13, p=0.27
- CVLT
  - Learning = -1.55, p=0.10
  - Short-term[c] = -0.74, p=0.009
  - Long-term = -0.56, p=0.08
  - Recognition = -0.22, p=0.34
- BNT
  - No cues[c] = -1.42, p=0.01
  - Cues = -1.57, p=0.005
- BVMGT
  - Copy error[c] = 0.71, p=0.19
  - Reproduction = -0.43, p=0.02
- CBCL
- NES FTT
  - D hand = -0.68, p=0.29
  - ND hand = -0.13, p=0.83
  - Both hands = -0.62, p=0.63
- NES HECT = 0.033, p=0.28
- NES CPT
  - Missed response = 0.21, p=0.0005
  - Reaction time = 46.9, p=0.0003

Table A-18. Summary of the Grandjean et al. (1997) and Grandjean et al. (1999) Studies of the Faroe Islands Population

		• TPT (D hand) = -11.3, p=0.76
		• NVAPMS
		  ○ Positive moods = 3.66, p=0.20
		  ○ Negative moods = 1.83, p=0.51

[a]See *Calculations* for how oral mercury doses were calculated.
[b]Interpretation of neurobehavioral test scores:
Age of crawling, sitting, or walking: increase = delay in development
BVMGT: higher score = lower performance
BNT: higher score = higher performance
CTRS: higher score = higher behavioral problems
CVLT: higher score = higher performance
Digit span: higher score = higher performance
NES CPT: longer response time = lower performance
NES FTT: higher score = higher performance
NES HECT: higher score = higher performance
Neurologic optimality score: higher score = higher performance
NVAPMS: higher score = more negative mood
Postural sway: higher score = lower performance
RSPM: higher score = lower performance
Spatial span: higher score = higher performance
ST-BI copying: higher score = higher performance
WFRT: higher score = higher performance
WISC-R: higher score = higher performance
WJTA: higher score = higher performance
WMS: higher score = higher performance
[c]Metric included in the meta-analysis by Axelrad et al. (2007a, 2007b).

BAEPL = brain steam auditory evoked potential latencies; BHg = blood mercury; BNT = Boston Naming Test; BVMGT = Bender Visual Motor Gestalt Test; CBCL = Child Behavior Checklist; CPT = Continuous Performance Task; CVLT = California Verbal Learning Test; FTT = Finger Tapping Test; HECT = Hand-Eye Coordination Test; HHg = hair mercury; HRV R-R = Heart Rate Variability of electrocardiogram RR interval; IQR = interquartile range; NES = Neurobehavioral Evaluation System; NVAPMS = Nonverbal Analogue Profile of Mood States; TPT = Tactual Performance Test; VEPL = visual evoked potential; VEPL = visual evoked potential latencies; WISC-R = Weschler Intelligence Scale for Children, Revised

New Zealand study. The New Zealand study followed a prospective cohort to age 6 years (Kjellstrom et al. 1989). The original cohort consisted of 10,930 children and mother pairs recruited in 1978. Consumption of marine fish was the major contributor to methylmercury exposure in this population. The prenatal exposure metric was the average total mercury in maternal hair during pregnancy. A subset of 935 high consumer subjects was selected based on consumption ≥4 fish meals per week. HHg levels in this group ranged from 6 to 86 μg Hg/g. From the ≥4 fish meals per week group, a subset of 73 high consumers was selected based on HHg level >6 μg Hg/g, from which 38 were tested at age 4 years, along with a set of 31 matched referents from mothers who consumed no more than one fish meal per week and matched for maternal ethnic group, age, residence time in New Zealand, tobacco smoking, and child birth date and sex. Assessment of neurodevelopmental outcomes occurred at age 4 and 6 years. At age 4 years, children were assessed for performance on the DDST (function, language, and personal-social behavior), Sheridan-Gardiner Letter Matching Test or Miniature Toy Test (vision), and tactile sensory function (touch, temperature), and parents were surveyed with a questionnaire on child health and neurological signs (Kjellstrom et al. 1986). The OR for abnormal or questionable scores on the DDST at age 4 years (n=31, relative matched referents) was 6.5 ($p<0.005$). Performance of high exposure children on vision and sensory function tests were not different from matched referents.

At age 6 years, 61 children in the high exposure group were re-evaluated, along with a set of three referent groups (n=58–60), each matched with the high exposure group for maternal ethnic group, age, residence time in New Zealand, tobacco smoking, and child birth date and sex (Kjellstrom et al. 1989). The geometric mean maternal HHg level was 8.3 µg Hg/g (range 6–86 µg Hg/g) in the high exposure group. Geometric mean HHg levels in the three referent groups ranged from 2.0 to 4.5 µg Hg/g. Children were assessed for cognitive performance, academic attainment, language development, motor coordination, intelligence, and behavior. Language development was assessed from performance on the TOLD (phonology, syntax, semantics) and Peabody picture vocabulary test (word knowledge). Intelligence was assessed using the McCarthy Scales for Children's Abilities (MSCA) and WISC. Increased maternal HHg was associated with lower scores on the TOLD spoken language quotient and WISC full-scale IQ and McCarthy perceptual scale. When the high exposure group (Group 1) was split into two maternal HHg categories, 6–<10 or ≥10 µg Hg/g, a larger fraction of variance in the TOLD and WISC tests was explained by that higher HHg category. Performance on the TOLD spoken language quotient was inversely associated with the HHg in lower category only (6–<10 µg Hg/g), whereas performance on both the TOLD spoken language quotient and WISC full scale were inversely associated with HHg in the higher category (≥10 µg Hg/g). Children scored as having an abnormal DDST at age 4 years had lower WISC full-scale IQ scores at age 6 years. Additional details of the Kjellstrom et al. (1989) study, which is included in the Axelrad et al. (2007a, 2007b) meta-analysis, are provided in Table A-19.

Table A-19. Summary of the Kjellstrom et al. (1989) Study of the North Island, New Zealand Population

Study type and population: Prospective study of birth cohort, follow-up at age 6 (n=238; 61 with high mercury exposure [maternal fish consumption ≥4 meals per week and HHg >6 µg Hg/L]) and matched referents from three referent populations (n=57 per group)

Biomarkers:
Maternal HHg (geometric mean µg Hg/g, range)
High mercury: 8.3 (6–86)
Referent 2 (≥4 fish meals/week): 4.5 (3–5.99)
Referent 3 (≥4 fish meals/week): 2.0 (0.1–2.99)
Referent 4 (≤3 fish meals/week): 2.0 (0.1–2.99)

Estimated oral dose[a]: 0.62 µg Hg/kg/day (based on high mercury group)

Analysis: Data were analyzed using robust weighted multiple regression analysis. This approach can decrease potential bias from outlier observations. Outcome associations were adjusted for significant covariates; variables explored included: maternal ethnic group, age, smoking and alcohol consumption, residence time in New Zealand, social class, language spoken at home, siblings, duration of breastfeeding, and child sex and birth weight, maturity at birth, and Apgar score.

Results[b]:
Adjusted regression coefficients between HHg (>6 µg Hg/g) and measures of intelligence

- WISC-R (FSIQ)[c] = -4.41, p=0.019
- WISC-R (PIQ)[c] = -3.79, p=0.072
- MSCA (perceptual scale)[c] = -4.23, p=0.0034

Adjusted regression coefficients between HHg (>6 µg Hg/g) and measures of language development

- TOLD[c] = -5.48, p=0.0064

Adjusted regression coefficients between HHg (>6 µg Hg/g) and measures of motor coordination

Table A-19. Summary of the Kjellstrom et al. (1989) Study of the North Island, New Zealand Population

- MSCA (motor scale) = -2.36, p=0.074

[a]See *Calculations* for how oral mercury doses were calculated.
[b]Inverse associations indicate declining performance.
[c]Metric included in the meta-analysis by Axelrad et al. 2007a, 2007b.

HHg = hair mercury; FSIQ = Full-Scale Intelligence Quotient; MCSA = McCarthy Scale of Children's Abilities; PIQ = Performance Intelligence Quotient; TOLD = Test of Language Development; WISC-R = Wechsler Intelligence Scales for Children, Revised

Seychelle Islands study. The Seychelle Islands study followed a prospective cohort of high fish consumers (n=779 mother-infant pairs, recruited 1989–1990) from age 6 months to 24 years. The primary methylmercury exposure metric was the average maternal gestational HHg level. Methylmercury accounted for >80% of total mercury in hair (Cernichiari et al. 1995). Annual median maternal HHg levels measured over the period 1986–1989 ranged from 5.9 to 8.2 µg Hg/g; the highest observed value was 36 µg Hg/g (Cernichiari et al. 1995). The main cohort, followed from age 6 months and later, had a median prenatal maternal level of 5.9 µg Hg/g (range 0.5–26.7 µg Hg/g) (Myers et al. 1995). Approximately half of the maternal HHg levels were ≤6 µg Hg/g, while the highest 15% (approximately 95 women) were >12 µg Hg/g; therefore, the power to discern significant associations was higher at HHg levels <12 µg Hg/g. Outcome associations were adjusted for covariates that included (in most studies): child sex, birth weight, birth order, gestational age, medical history and breastfeeding; maternal age, alcohol and tobacco use, and medical history; parental education, caregiver general intelligence (Raven's Progressive Matrices), family income, family language, home learning, and social stimulation (HOME score).

The Seychelle Islands has not found consistent evidence for associations between prenatal exposure (maternal HHg) and neurodevelopmental outcomes at any age studied thus far. This conclusion is supported by cross-sectional follow-ups of the cohort from ages 6.5 months to 24 years (Davidson et al. 1995, 1998, 1999, 2008a, 2010, 2011; Huang et al. 2005; Myers et al. 1995, 1997, 2000, 2003, 2009, 2020; Orlando et al. 2014; Thurston et al. 2022; van Wijngaarden et al. 2009, 2013, 2017; Young et al. 2020), longitudinal analyses of individual outcome metrics (Axtell et al. 1998; Davidson et al. 1998; Myers et al. 1997), and longitudinal analysis of metrics of global cognition based on aggregation of outcome metrics (Davidson et al. 2006a). Accounting for error in measuring HHg levels (and other covariates) had no appreciable effect on dose-response models assessed at 66 months (Huang et al. 2003). Although linear regression models consistently found no association between exposure (maternal or child HHg) and cognitive development, nonlinear models of cognitive test scores suggested that performance improved or declined in association with prenatal maternal HHg or child HHg, depending on the hair level (Axtell et al. 1998, 2000; Davidson et al. 1998, 2006a; Huang et al. 2005, 2007, 2018; Myers et al. 1997, 2003, 2020). For some outcomes, performance declined at lower HHg levels (e.g., ≤7 µg Hg/g), but improved at higher levels, and, for some outcomes, the opposite pattern was observed. At age 66 months, lower performance was not evident in a subgroup of the cohort that had a mean HHg level of 15.3 µg Hg/g (>85th percentile) (Davidson et al. 1998). It is uncertain if these nonlinear patterns reflect actual dose-level effects, differential statistical power across the HHg range, or, possibly, random outcomes from the numerous (>20) tests evaluated (Axtell et al. 2000; Davidson et al. 2006b; Huang et al. 2005, 2007). Age of walking increased with increasing prenatal maternal HHg over the range 1–7 µg Hg/g, however; the effect size was <1 day and the association was not evident at higher levels of HHg (Axtell et al. 1998). Aggregating scores of cognitive performance into metrics of global cognitive function (Davidson et al. 2006a) or dichotomizing test scores into a binomial metric (benchmark

response) also revealed no associations in cognitive development and prenatal maternal HHg <20 µg Hg/g (Crump et al. 2000; van Wijngaarden et al. 2006, 2009). After correction of statistical significance criteria for multiple comparisons, no association was found between mercury exposure and general cognition or fine motor speed assessed at ages 9, 10.5, 17, 19, 22, or 24 years (Thurston et al. 2022). Associations between exposure and cognitive function were modified by an interaction with maternal omega-3 fatty acid status, a source of negative confounding through fish consumption (Strain et al. 2008, 2012, 2021). Study details for the Myers et al. (2003) studies are summarized in Table A-20. These studies were included in the Axelrad et al. (2007a, 2007b) meta-analysis.

Table A-20. Summary of the Myers et al. (2003) Study of the Seychelle Islands Population

Study type and population: Prospective study of birth cohort, follow-up at age 9 years (n=643 of 779 in cohort)

Biomarkers:
Maternal HHg (mean µg Hg/g, SD)
6.9 (4.5)

Estimated oral dose[a]: 0.51 µg Hg/kg/day (based on mean maternal HHg)

Analysis: Data were analyzed using multiple regression analysis. Outcome associations were adjusted for sex, examiner, family resource scale, family status (number of biological parents in the home), Henderson early learning process scale, child's age at testing, child's medical history of IUGR or head circumference >2 SD from normal, maternal age, home observation for measurement of the environment (HOME) score, caregiver intelligence, socioeconomic status, and hearing.

Results[b]:

Adjusted regression coefficients (95% CI for a 10 µg Hg/g change in HHg) for measures of general intelligence, cognition and achievement

- WISC-III FSIQ[c] = -0.13 (-3.3, 0.7), p=0.20
- CVLT
  - Short[c] = 0.013 (-0.1, 0.3), p=0.19
  - Long = 0.011 (-0.1, 0.3), p=0.28
- BNT[c] = -0.012 (-1.0, 0.8), p=0.79
- WJTA
  - LWR = 0.19 (-5.8, 9.6), p=0.62
  - AP = -0.057 (-3.5, 2.4), p=0.71

Adjusted regression coefficients (95% CI for a 10 µg Hg/g change in HHg) for measures of motor, perceptual motor, and memory

- VMI[c] = -0.010 (-2.4, 2.2), p=0.93
- BOT = 0.093 (-0.2, 2.0), p=0.10
- HAPDT = -0.010 (-0.5, 0.3), p=0.60
- Grooved peg board
  - D hand = 3.3×10^{-5} (91.4, 98.1), p=0.08
  - ND hand, male = 6.5×10^{-5} (101.7, 112.9), p=0.01
  - ND hand, female = -2.5×10^{-5} (100.0, 111.3), p=0.34

Adjusted regression coefficients (95% CI for a 10 µg Hg/g change in HHg) for measures of attention and behavior

- CPT
  - Reaction time = -0.13 (-4.4, 1.8), p=0.41
  - Attention = -0.0063 (-2.1, 2.0), p=0.95
  - Risk taking = 0.11 (-3.1, 5.4), p=0.60
- CBCL = -0.031 (-2.3, 1.7), p=0.76
- CTRS = -0.0067 (49.4, 54.1), p=0.004

Adjusted regression coefficients (95% CI for a 10 µg Hg/g change in HHg) for measures of motor, perceptual motor, and memory

- Trail making
  - A = 0.0037 (32.5, 37.6), p = 0.33
  - B = 0.0067 (79.1, 96.0), p=0.17
- FTT
  - D hand = -0.050 (-1.5, 0.5), p=0.34
  - ND hand = 0.016 (-0.6, 1.0), p=0.69
- WRAML[c] = -0.021 (-0.8, 0.4), p=0.48

Table A-20. Summary of the Myers et al. (2003) Study of the Seychelle Islands Population

- FTT
  - D hand = -0.050 (-1.5, 0.5), p=0.34
  - ND hand = 0.016 (-0.6, 1.0), p=0.69
- WRAML[c] = -0.021 (-0.8, 0.4), p=0.48

[a]See *Calculations* for how oral mercury doses were calculated.
[b]Interpretation of neurobehavioral test scores:
Age of talking or walking: increase = delay in development
Barkley ADHD: higher score = lower performance
BNT: higher score = higher performance
BOT: higher score = higher performance
BVMGT: higher score = lower performance
CANTAB: higher score = higher performance
CVLT: higher score = higher performance
FTII: higher score = higher performance
BSID IBR: higher score = higher performance
BSID MDI: higher score = higher performance
BSID PDI: higher score = higher performance
BVMGT: higher score = lower performance
CBCL: higher score = lower performance
CDI: higher score = higher performance
CELF-5: higher score = higher performance
CTRS: higher score = lower performance
CVLT: higher score = higher performance
DDST: milestones evaluated against a standard; below standard = delayed development
DSA: higher score = higher performance
Finger tapping: higher score = higher performance
GPB: higher score = lower performance
HAPDT: higher score = higher performance
KBIT-2: higher score = higher performance
MSCA: higher score = higher performance
PLS: higher score = higher performance
SCQ: higher score = higher performance
SRS-2: higher score = higher performance
Stroop interference: higher score = higher performance
TSRSS: higher score = higher performance
VEXP: higher score = higher performance
WJTA: higher score = higher performance
WRAML: higher score = higher performance
[c]Metric included in the meta-analysis by Axelrad et al. (2007a, 2007b).

AP = applied problems; BNT = Boston Naming Test; BOT = Bruininks-Oseretsky Test of Motor Proficiency; CBCL = Child Behavior Checklist; CI = confidence interval; CPT = Continuous performance task; CTRS = Connors' Teacher Rating Scale (hyperactivity index); CVLT = California Verbal Learning Test; D = dominant; FSIQ = full-scale intelligence quotient; FTT = Finger Tapping Test; HAPDT = Haptic Discrimination Test; HHg = hair mercury; HOME = Home Observation Measurement of the Environment; IUGR = intrauterine growth retardation; LWR = letter word recognition; ND = non-dominant; SD = standard deviation; VMI = Visual Motor Integration; WJTA = Woodcock-Johnson Test of Achievement; WISC-III = Wechsler Intelligence Scales for Children, 3rd ed.; WRAML = Wide Range Assessment of Memory and Learning

Meta-analysis of Faroe Islands, North Island, New Zealand, and Seychelles Islands studies. Two meta-analyses of the populations from the Faroe Islands, North Island, New Zealand, and Seychelles Islands have been conducted; these are reported in publications by Axelrad et al. (2007a, 2007b) Cohen et al. (2005), and Ryan (2008). In the more recent analysis, Axelrad et al. (2007a, 2007b; Ryan 2008)

converted regression slopes for several cognitive test scores measured in each study into an IQ point scale (Axelrad et al. 2007a, 2007b). The meta estimate for the effect size was -0.18 IQ points per increase of 1 µg Hg/g hair (95% CI -0.378, -0.009). The meta-analysis is described in detail in the *Summary of the Principal Study* section. Ryan (2008) reported a sensitivity analysis of the meta-slope from Axelrad et al. (2007a, 2007b).

Cohen et al. (2005) used a similar analytical approach as Axelrad et al. (2007a, 2007b) in a meta-analysis of the Faroe Islands, North Island, New Zealand, and Seychelles Islands studies. However, Cohen et al. (2005) included results from a wider selection of cognitive tests. The meta estimate from Cohen et al. (2005) was an average decrease of 0.043 SDs in cognitive performance per increase of 1 µg Hg/g maternal hair. For a SD of 15 IQ points, the meta estimate corresponds to an equivalent change in IQ of 0.7 points per 1 µg Hg/g hair, with a plausible range of 0 to 1.5 points per 1 µg Hg/g hair (Cohen et al. 2005).

The Axelrad et al. (2007a, 2007b) meta-analysis was selected as the principal study over the Cohen et al. (2005) because bounds on the meta-estimate from the Cohen et al. (2005) meta-analysis were wider and included zero. A likely contributor to this difference was the inclusion of a wider selection of outcomes in the Cohen et al. (2005) metal-analysis.

Norwegian Mother and Child Cohort Study. In addition to the above studies of high fish consumers, a large prospective study of a general population found associations between dietary fish mercury intake and language proficiency (Vejrup et al. 2016, 2018, Table A-21). This study examined a birth cohort consisting of 46,750 mother-infant pairs recruited during the period 1999–2008 with outcomes measured at age 3 years (Vejrup et al. 2016) and 5 years (Vejrup et al. 2018). Dietary intake of mercury from fish consumption was estimated in each mother based on outcomes of a food frequency questionnaire completed during pregnancy and a survey of mercury levels in fish consumed by Norwegians (Jenssen et al. 2012). Median fish consumption was estimated to be 32 g/day. Median mercury intake from consumption of fish was estimated to be 0.14 µg Hg/kg/week. The 90th percentile was 0.29 µg Hg/kg/week (Vejrup et al. 2016). Estimation of dietary intakes of mercury in fish (which is dominated by methylmercury) precluded reliance on biomarkers as dose metrics for methylmercury exposure. The study evaluated language proficiency and communication skills using parent-reported questionnaires. This study found associations between increasing dietary intake of mercury in fish with decreasing performance on language proficiency tests administered at age 3 and 5 years. These associations persisted after adjustment for known important confounders related to fish consumption, including fish consumption rate (adjustment strengthened the association with mercury), 3-omega LCPUFA consumption, and exposure to PCBs (Vejrup et al. 2016). The language outcomes associated with mercury intake (>0.29 µg Hg/kg/week) were described as "unintelligible speech" on the Dale and Bishop Grammar Rating and "weak communication development" on the Ages and Stages Communication Scale.

In a follow-up at age 5 years, children were assessed with three outcome tests: Ages and Stages Communication Scale, Speech and Language Assessment Scale, and Twenty Statements about Language-Related Difficulties. At age 5 years, in the full cohort (n=38,297) among women who consumed <400 g fish/week, both fish consumption and mercury intake were associated with improvement of scores (negative error scores) in the Ages and Stages Communication Scale and Speech and Language Assessment Scale. When the analysis was confined to matched siblings (n=7,404), dietary fish mercury intake at the 90th percentile level (>3.18 µg Hg/day) was associated with decreasing performance on the Speech and Language Assessment Scale but not on the Ages and Stages Communication Scale or Language-Related Difficulties scale. No associations were observed with mid-pregnancy maternal BHg concentrations in a subcohort of the main cohort (2,239 subjects) in which BHg levels were measured (median 1.0 µg Hg/L; range 0, 14 µg Hg/L) (Vejrup et al. 2018). These results suggest that fish intake was a confounding variable in this study (correlation between dietary fish mercury intake and dietary

seafood intake was 0.88) and may have attenuated associations between dietary methylmercury intake and delays in attainment of language skills. The absence of an association with maternal BHg may represent variance in BHg levels that is unrelated to dietary methylmercury intake (e.g., mercury from amalgam restorations).

Table A-21. Summary of the Vejrup et al. (2016, 2018) Studies of the Norwegian Population

Study: Vejrup et al. 2016

Study type and population: Prospective cohort of mother-infant pairs, follow-up at age 3 years (n=46,750)

Estimated oral dose: 0.041 µg Hg/kg/day (based on 90th percentile weekly intake)

- Maternal dietary mercury intake from fish (median):
  - 1.3 µg Hg/day
  - 0.14 µg Hg/kg/week
- 90th percentile:
  - 2.6 µg Hg/day
  - 0.29 µg Hg/kg/week

Analysis: Maternal methylmercury was estimated based on fish intake reported in an FFQ administered mid-pregnancy. Outcomes evaluated were performance on the Dale Bishop Grammar Rating and Ages and Stages communication scale (ASQ). ORs were calculated to assess risk in children with high mercury exposure, defined as >90th percentile (>2.64 µg Hg/day, >0.29 µg Hg/kg/week), compared to children with mercury exposure <90th percentile. ORs were adjusted for parity, maternal education, paternal education, pre-pregnancy BMI, bilingual parents, and age of child when reporting language development. Additional models were further adjusted for intake of lean and oily fish, n-3 LCPUFA from diet, n-3 LCPUFA from supplements, and dioxin and PCB exposures.

Results:

Adjusted OR (95% CI) between high prenatal methylmercury exposure (>90th percentile) and language development for Dale and Bishop Grammar rating (n=46,750)

- Complete grammar (reference): 1
- Low grammar: 1.01 (0.93, 1.10)
- Moderate delay: 1.06 (0.88, 1.26)
- Unintelligible speech: 2.22 (1.31, 3.72)
- Severe delay: 1.04 (0.69, 1.57)

Further adjusted for intake of lean and oily fish

- Unintelligible speech: 3.02 (1.47, 6.21)

Adjusted OR (95% CI) between high prenatal methylmercury exposure (>90th percentile) and communication development (ASQ, n=45,332)

- Normal skills (reference): 1
- Weak skills: 1.33 (1.03, 1.70)

Further adjusted for intake of lean and oily fish

- Weak skills: 1.46 (1.07, 2.00)

Table A-21. Summary of the Vejrup et al. (2016, 2018) Studies of the Norwegian Population

Study: Vejrup et al. 2018

Study type and population: Prospective cohort of mother-infant pairs, follow-up at age 5 years (n=38,581)

Biomarker: Maternal BHg 1.03 µg Hg/L (median; n=2,239)

Estimated oral dose[a]: 0.049 µg Hg/kg/day (based on 90th percentile adjusted for 65 kg body weight)

- Maternal dietary mercury intake from fish
  - Median: 0.15 µg Hg/kg/week
  - 90th percentile: 3.18 µg Hg/week

Analysis: Outcomes evaluated were performance on the Speech and Language Assessment Scale, Ages and Stages communication scale, and Twenty Statements about Language-Related Difficulties. Data were analyzed using multiple regression analysis. Outcome associations were adjusted for maternal age, education, parity, pre-pregnancy BMI, Hopkins Symptom Checklist-5 (SCL-5), total energy intake, eicosapentaenoic acid and docosahexaenoic acid (DHA) from total diet and/or supplement. A sibling fixed-effect analysis was also conducted.

Results:

Adjusted regression coefficients (95% CI) between maternal BHg and measures of language and communication (n=2,239), NS

- ASQ: -0.02 (-0.1, 0.03)
- Language 20: 0.01 (-0.03, 0.05)
- SLAS: -0.01 (-0.1, 0.03)

Adjusted regression coefficients (95% CI) between dietary seafood mercury intake >400 g/week and measures of language and communication (n=4,375), NS

- ASQ: 0.1 (-0.1, 0.4)
- Language 20: 0.31 (-0.01, 0.6)
- SLAS: -0.17 (-0.4, 0.1)

Adjusted regression coefficients (95% CI) between maternal seafood intake >400 g/week and measures of language and communication (n=38,297), p<0.05

- ASQ: -0.06 (-0.1, -0.01)
- Language 20: -0.05 (-0.1, -0.01)
- SLAS: -0.07 (-0.1, -0.03)

Adjusted regression coefficients (95% CI) between >90th percentile maternal dietary mercury intake and measures of language and communication in sibling fixed effect analysis (n=647)

- ASQ: 0.03 (-0.1, 0.1), NS
- Language 20: 0.02 (-0.1, 0.1), NS
- SLAS: 0.1 (0.01, 0.2), p<0.05

[a]See *Calculations* for how oral mercury doses were calculated.

ASQ = Ages and Stages Communication Scale; BHg = blood mercury; BMI = body mass index; CI = confidence interval; DHA = docosahexaenoic acid; FFQ = food frequency questionnaire; Language 20 = Twenty Statements about Language-Related Difficulties; NS = not specified; OR = odds ratio; SLAS = Speech and Language Assessment Scale

Given the variable outcomes within and across the Faroe, New Zealand, and Seychelles studies of high fish consumers, selection of a single population as the basis for the MRL was not considered an ideal approach. Instead, the Axelrad et al. (2007a, 2007b) meta-analysis was considered a better representation of the weight of evidence from the three high fish consumer studies. The meta-analysis was selected over the Norwegian Mother and Child Cohort Study (Vejrup et al. 2016, 2018) as the principal study after weighing strengths and weaknesses of both studies (Table A-22). The key strength of the Axelrad et al. (2007a, 2007b) meta-analysis is that it included outcomes from multiple tests of cognitive performance from three independent prospective studies (approximately 1,800 subjects) after transforming the data into a global metric of full-scale IQ, which can be more readily generalized than individual test scores. The analysis included a test of language proficiency (New Zealand study, Test of Language Development). Language development was also evaluated in the Norwegian Mother and Child Cohort Study, using a different set of tests (Ages and Stages Communication, Dale Bishop Grammar Rating, Speech and Language Assessment Scale) (Vejrup et al. 2016, 2018). The studies included in the meta-analysis also provided biomarkers of exposure in each individual subject, which is likely to have decreased exposure misclassification inherent to using data from dietary recall and national data on mercury concentrations in recalled fish meals, as was used in the Norwegian Mother and Child Cohort Study.

Table A-22. Strengths and Weaknesses of Axelrad et al. (2007a, 2007b) and Vejrup et al. (2016, 2018) for Establishing a Point of Departure for the Chronic-Duration Oral MRL for Methylmercury

Study	Strengths	Weaknesses
Axelrad et al. 2007a, 2007b meta-analysis of Faroes, New Zealand, and Seychelles studies of high fish consumers	• Utilized and weighted data from three independent prospective studies (total number ~1,800) • Direct measure of individual subject exposure from biomarker (hair mercury) • Subjects were high fish consumers, which strengthens association between biomarkers and exposure to methylmercury • Included multiple tests of cognitive performance scaled to equivalent IQ points • Language proficiency included as an outcome metric • Sensitivity analysis indicated a narrow range for the effect size estimate • Effect size reported as linear regression β that can be transformed into a *di minimis* change in the biomarker (or equivalent dose); e.g., change in dose above background dietary level associated with a 1-point change in IQ	• Pharmacokinetic model needed to transform biomarkers to equivalent mercury intakes • To derive MRL, must select magnitude of change in IQ that corresponds to an IQ POD • Effect size may have been depressed by negative confounding with nutritional benefits from high fish consumption

Table A-22. Strengths and Weaknesses of Axelrad et al. (2007a, 2007b) and Vejrup et al. (2016, 2018) for Establishing a Point of Departure for the Chronic-Duration Oral MRL for Methylmercury

Study	Strengths	Weaknesses
Vejrup et al. 2016, 2018 Norwegian Mother and Child Cohort Study of general population	• Large prospective study • Larger size of cohort (~47,000 subjects) of general population, with lower fish consumption than high consumption studies	• Associations with dietary methylmercury intake were based on a semi-quantitative food survey and national data on fish mercury concentrations, rather than biomarkers of mercury exposure in individual subjects • The association with dietary methylmercury intake predicted lower language proficiency at age 3 years, whereas the association predicted higher proficiency at age 5 years • In a subset of the cohort with measurements of individual subject BHg levels, there was no association between language proficiency and BHg • Outcome evaluation was limited language proficiency, which was assessed using a parental self-report survey of their children and not by unbiased experts

BHg = blood mercury; CI = confidence interval; FFQ = food frequency questionnaire; IQ = intelligence quotient; MRL = Minimal Risk Level; POD = point of departure

Summary of the Principal Study:

Axelrad DA, Bellinger DC, Ryan LM, et al. 2007a. Dose-response relationship of prenatal mercury exposure and IQ: An integrative analysis of epidemiologic data. Environ Health Perspect 115(4):609-615. http://doi.org/10.1289/ehp.9303.

Axelrad DA, Bellinger DC, Ryan LM, et al. 2007b. Supplemental material: Dose-response relationship of prenatal mercury exposure and IQ: An integrative analysis of epidemiologic data. Environmental health perspectives. https://ehp.niehs.nih.gov/action/downloadSupplement?doi=10.1289%2Fehp.9303&file=9303_suppl.pdf. March 18, 2021.

Ryan L. 2008. Combining data from multiple sources, with applications to environmental risk assessment. Statist Med 27:698-710. http://doi.org/10.1002/sim.3053.

The meta-analysis included outcomes from the Faroe Islands study at age 7 years, New Zealand study at age 6 years, and Seychelles Islands study at age 9 years (Axelrad et al. 2007a, 2007b). Outcomes included in the analysis are summarized in Table A-23. Additional study details are provided in Table A-24.

Table A-23. Cognitive Performance Tests[a] Included in Meta-analysis of Faroe Islands, New Zealand, and Seychelle Islands Studies

Cognitive domain	Faroe Islands	New Zealand	Seychelles Islands
General intelligence	WISC-R (full-scale IQ)	WISC-R (full-scale IQ) WISC-R (performance IQ)	WISC-III (full-scale IQ)
Verbal learning and memory	CVLT (short term)	NE	CVLT (short term)
Visual-motor integration	BGT	NE	VMI
Visual memory	NE	NE	WRAML (design memory)
Confrontational naming	BNT (no cues)	NE	BNT (total score)
General development	NE	MSCA (perceptual)	NE
General verbal skills	NE	TOLD (spoken language coefficient)	NE
Visual memory	NE	NE	WRAML (design memory)

[a]Regression slopes derived in these tests were rescaled to full-scale IQ.

BGT= Bender Gestalt Test; BNT = Boston Naming Test; CVLT = California Verbal Learning Test; IQ = intelligence quotient; MSCA = McCarthy Scales of Children's Abilities; NE = not evaluated; TOLD = Test of Language Development; VMI = Visual–Motor Integration; WISC-R = Wechsler Intelligence Scales for Children, Revised; WISC-III = Wechsler Intelligence Scales for Children, 3rd ed.; WRAML = Wide Range Assessment of Memory and Learning

Table A-24. Summary of the Axelrad et al. (2007a, 2007b) Meta-Analysis Study

Study type and population: Meta-analysis of prospective birth cohorts in Faroe Islands (n=917), Seychelles Islands (n=643), and New Zealand (n=237; Grandjean et al. 1997, 1999; Kjellstrom et al. 1989; Myers et al. 2003) with follow-up at age 7, 9, and 6 years, respectively

Estimated oral dose: 0.41 µg Hg/kg/day (based on 1 IQ point per 5.56 µg Hg/kg/day; -0.18 IQ points per µg Hg/g hair)

Analysis: Bayesian hierarchical modeling integrated data from the three study populations. A primary mercury-IQ dose-response analysis model was built using metrics with coefficients that were rescaled to be interpretable in the same scale as FSIQ estimates. FSIQ for the Faroe Islands data was estimated by combining three WISC subsets (Digit Span, Similarities, Block Design), which Axelrad et al. (2007a, 2007b) concluded would provide valid estimates of full-scale IQ.

Table A-24. Summary of the Axelrad et al. (2007a, 2007b) Meta-Analysis Study

Results:

Rescaled regression coefficients (SE) for cognitive endpoints from the Faroe Islands

- WISC-R (FSIQ) = -0.124 (0.057)
- BGT = -0.104 (0.083)
- BNT = -0.260 (0.086)
- CVLT = -0.169 (0.093)

Rescaled regression coefficients (SE) for cognitive endpoints from the Seychelle Islands

- WISC-III (FSIQ) = -0.17 (0.130)
- CVLT = 0.19 (0.144)
- BNT = -0.038 (0.144)
- WRAML = -0.109 (0.15)
- VMI = -0.013 (0.15)

Rescaled regression coefficients (SE) for cognitive endpoints from New Zealand

- WISC-R (FSIQ) = -0.50 (0.268)
- WISC-R (PIQ) = -0.51 (0.310)
- TOLD = -0.56 (0.282)
- MSCA = -0.80 (0.315)

Estimated IQ decrement per µg Hg/g maternal HHg (95% CI), at different *R* levels (ratio of study-to-study variability relative to endpoint-to-endpoint variability)

- 4.0 = -0.188 (-0.398, -0.010)
- 3.5 = -0.182 (-0.390, -0.007)
- 3.0 = -0.180 (-0.378, -0.009)
- 2.5 = -0.183 (-0.384, -0.017)
- 2.0 = -0.178 (-0.371, -0.012)
- 1.5 = -0.168 (-0.360, -0.003)
- 1.0 = -0.165 (-0.338, -0.015)
- 0.5 = -0.160 (-0.321, -0.026)
- 0.25 = -0.151 (-0.283, -0.033)

BGT = Bender Gestalt Test; BNT = Boston naming test; CVLT = California Verbal Learning Test; FSIQ = Full-Scale Intelligence Quotient; HHg = hair mercury; IQ = intelligence quotient; MSCA = McCarthy Scales of Children's Abilities; PIQ = performance intelligence quotient; SE = standard error; TOLD = Test of Language Development; VMI = Visual Motor Integration; WISC-R = Wechsler Intelligence Scales for Children, Revised; WISC-III = Wechsler Intelligence Scales for Children, 3rd ed.

Linear regression parameters, slope (β) and intercept (Int) for associations between mercury and scores on tests of cognitive performance were rescaled to IQ by adjusting the parameters by a scaling factor. The scaling factor was the ratio of the SDs for the full-scale IQ (SD_{IQ}) and the test (SD_{test}), $SD_{IQ}/SDtest$, where SD_{IQ} was assigned a value of 15. The adjusted parameters were calculated as follows:

$$\beta^* = \beta \times SD_{IQ}/SD_{test}$$
$$Int^* = Int \times SD_{IQ}/SD_{test}$$
$$SE^* = SE \times SD_{IQ}/SD_{test}$$

where β^* and Int^* are the rescaled values for the slope and intercept, respectively.

The Faroe Islands parameters required additional factors. A factor of 10 adjusted the Faroe Islands log-normal model to a normal model (Budtz-Jorgensen et al. 2004). A factor of 200 µg Hg/kg per µg Hg/L was used to convert Faroe Islands cord BHg levels to HHg (Budtz-Jorgensen et al. 2004).

Meta-β estimates were weighted by study-to-study variance (σ^2) in β and endpoint-to-endpoint variance endpoint outcomes, using a Bayesian approach with exploratory values for the variance ratio R ($\sigma^2_{study}/\sigma^2_{endpoint}$). The meta estimate for the effect size was -0.18 IQ points per µg Hg/g hair (95% CI -0.378, -0.009). Ryan (2008) conducted a sensitivity analysis of the Axelrad et al. (2007a, 2007b) meta-β to varying correlations between error (standard errors) of different outcomes measured in the same study. The analysis supports the estimate of the meta-β estimated by Axelrad et al. (2007a, 2007b). Increasing

error correlation was predicted to decrease the estimated β. The range in the estimated β was -0.18 to -0.20 IQ points per µg Hg/g hair. The low end of the range, -0.18, was predicted when correlation of within study outcome error was ignored.

To determine the change in HHg levels, one IQ point is divided by the meta estimate of 0.18 µg Hg/g hair (as seen in Equation 6, below). Because the meta-β is a parameter of a linear regression equation, the change in IQ points is predicted to be proportional to the change in HHg levels near the center of the distribution of the HHg scale. The central estimates of HHg levels for the three contributing studies ranged from approximately 4 to 9 µg Hg/g hair. Therefore, the proportional relationship can be expected for HHg levels within this range. The corresponding estimates of the change in HHg level corresponding to a specific change in IQ are shown in Table A-25 (see the Calculations section for equation used to convert change in IQ or change in HHg). As can be ascertained from Table A-25, a change in HHg of 5.56 µg Hg/g hair is predicted to result in a 1-point decrease in IQ.

Table A-25. Estimates of the Change in Hair Mercury Level Corresponding to a Specific Change in IQ

Change in IQ (points)	Change in hair mercury (µg Hg/g)
-1	5.56
-2	11.1
-3	16.7
-4	22.2
-5	27.8

Selection of the Point of Departure for the MRL: The POD selected for derivation of the chronic-duration oral MRL for methylmercury is 5.56 µg Hg/g hair. This value is the change in HHg level that corresponds to a decrease of 1 point in full-scale IQ, based on the meta-β of -0.18 IQ points per 1 µg Hg/g hair (see *Calculations*). A decrease in full-scale IQ of ≤1 point is considered a NAEL.

Loss of IQ has been used as a metric for assessing the health burden of neurotoxicants, including methylmercury (Bellanger et al. 2013; Bellinger 2012; Bellinger et al. 2019; Chen et al. 2023c). While IQ losses ranging from 1 to 5 points are not significant for most children (the SD associated with IQ tests is approximately 5 points), these small decrements may represent meaningful intellectual and economic achievement at a population level (Bellanger et al. 2013, Bellinger et al. 2019; EPA 1998; Griffiths et al. 2007; Trasande et al. 2005). Based on the meta-β of -0.18 IQ points per µg Hg/g hair (Axelrad et al. 2007a, 2007b) and regional data on maternal HHg levels, the global disability life years attributed to methylmercury exposure was estimated to range from 7 per 100,000 to 44 per 100,000 (Bellinger et al. 2019). Using the same meta (-0.18 IQ points per µg Hg/g hair), Chen et al. (2023c) estimated the disability life years in China attributed to methylmercury exposure to be 3.67 per 1,000 births. The neurological impact of IQ score decrements (≥1, ≥2, and ≥3 IQ points) was used for the risk assessment of lead in paint, dust, and soil (EPA 1998) and estimates of the economic impact per 1-point decrease in IQ was used to estimate benefits of revisions of the National Ambient Air Quality Standards for Lead (EPA 2008). Risk assessments of fluoride exposure have been conducted based on IQ point losses of both 1 and 5 points (Hirzy et al. 2016).

Calculations:

Conversion of meta-β to HHg POD. The linear regression model predicts a proportional relationship between the change in IQ points and change in HHg. Therefore, the conversion of the meta-β to a mercury POD in units of HHg (POD_{hair}) is as follows (Equation 8):

$$POD_{hair} = \frac{1\ IQ\ point}{0.18\ IQ\ points\ per\ \mu g\ Hg/g\ hair} \quad \text{Eq. (8)}$$

The *POD* in units of HHg from Equation 1 is 5.56 µg Hg/g hair.

Conversion of HHg level to oral mercury dose. HHg levels were converted to equivalent oral doses by applying a steady-state mass balance model, which did the following: (1) converted the hair level (µg Hg/g, assumed to represent steady state) to an equivalent steady-state BHg level (µg Hg/L) and (2) converted the steady-state BHg level to an equivalent steady-state oral dose (µg Hg/kg/day). Steady-state mass balance models have been used to reconstruct methylmercury intakes in human populations (Sirot et al. 2008). The assumption of steady state requires that the exposures were relatively constant (or intermittent with a constant frequency) for periods >300 days. This is the exposure duration that would achieve 95% of steady-state body burden, assuming a terminal elimination half-time of 65 days (Albert et al. 2010; Equation 9):

$$Time\ to\ steady\ state = \frac{\ln(1-0.95)}{k_e} \quad \text{Eq. (9)}$$

where 0.95 is the fraction of steady state and k_e is ln(2)/half-time.

The steady-state model is based on Albert et al. (2010) and is given in Equation 10:

$$Hg_{bl} = \frac{Hg_{dose} \cdot AF \cdot f_{bl} \cdot BW}{k_e \cdot V_{bl}} \quad \text{Eq. (10)}$$

where Hg_{bl} is the steady-state BHg level (µg Hg/L), Hg_{dose} is the steady-state dose (µg Hg/kg/day) AF is the gastrointestinal absorption fraction, f_{bl} is the blood fraction of the mercury body burden, BW is body weight (kg), k_e is the terminal elimination rate constant for mercury and V_{bl} is the blood volume (L).

The corresponding steady-state HHg level was calculated assuming a hair/blood ratio (Equation 11):

$$Hg_{hair} = Hg_{bl} \cdot HBR \quad \text{Eq (11)}$$

where Hg_{hair} is the HHg level (µg Hg/g hair) HBR is the hair/blood ratio (µg Hg/g per µg/L blood).

Parameter values for Equations 8 and 9 are presented in Table A-26. With these parameter values, the conversion factors for HHg and BHg are as follows (Equations 12 and 13):

$$Dose = \frac{Hg_{bl}}{66.51} \quad \text{Eq. (12)}$$

$$Dose = \frac{Hg_{hair}}{13.50} \quad \text{Eq. (13)}$$

where the dose is in units of µg Hg/kg/day, BHg in units of µg Hg/L and HHg in units of µg Hg/g.

Table A-26. Parameter Values for the Methylmercury Dose Equivalence Model[a]

Parameter	Unit	Value
Blood elimination half-time	Day	65.4
Blood elimination rate constant	Day^{-1}	0.0106
Steady-state external dose	µg Hg/kg/day	1.00
Gastrointestinal absorption fraction	Fraction	0.94
Blood fraction of body burden	Fraction	0.060
Body weight	kg	60
Blood fraction of body weight	L/kg	0.080
Hair/blood ratio	µg Hg/kg per µg Hg/L	203

[a]Parameter values from Albert et al. (2010).

Basis for parameter values. Albert et al. (2010) was used as the basis for parameter values in the dose equivalence model because it provided estimates for the full set model parameters in a sample of the critical population represented in the MRL, pregnant females. Albert et al. (2010) estimated values for parameters in Equations 8 and 9 based on HHg levels and dietary seafood mercury intakes in 125 pregnant women. Scalp and hair mercury levels were measured at weeks 12 and 32 of pregnancy. Dietary mercury intakes were estimated in each subject from a food frequency questionnaire with seafood items paired to a national (France) database on methylmercury content of foods (Verger et al. 2007). Values for parameters were assigned prior distributions based on various sources (Albert et al. 2010) and posterior distributions were estimated in Markov Chain Monte Carlo simulations. Studies similar to Albert et al. (2010) have also estimated the full set of parameters for the model in other adult populations (Jenssen et al. 2012; Jo et al. 2015).

Additional support for the individual parameter values in the dose equivalence model derive from a variety of sources summarized below.

*Gastrointestinal absorption fraction. T*he value for the gastrointestinal absorption fraction used in the dose equivalence model is 0.94 (Albert et al. 2010). Studies conducted in humans, monkeys, and rodents have shown that gastrointestinal absorption of mercury is close to 100% following ingestion of methylmercury as the chloride salt or when incorporated into fish or other ingested protein (Aberg et al. 1969; Berlin et al. 1975; Clarkson 1971; Clarkson and Shapiro 1971; Miettinen et al. 1971; Mori et al. 2012; Nielsen 1992; Nielsen and Andersen 1991, Nielsen et al. 1992; Sundberg et al. 1999; Yannai and Sachs 1993).

Blood fraction of mercury body burden. The value for the blood fraction of the body burden used in the dose equivalence model is 0.06 (Albert et al. 2010). In clinical studies of known doses of methylmercury, BHg accounted for approximately 5–7% of the absorbed dose (Kershaw et al. 1980; Miettinen et al. 1971; Sherlock et al. 1984; Smith et al. 1994).

BHg elimination half-time. The value for the terminal blood elimination half-time used in the dose equivalence model is 65.4 days (Albert et al. 2010). The corresponding elimination rate constant used in Equation 8 is 0.0106 day^{-1}. Population-based estimates of the blood half-time for methylmercury have relied on fitting biokinetics models to data on BHg or HHg levels to dietary methylmercury intakes (Albert et al. 2010; Jo et al. 2015). Albert et al. (2010) estimated half-times in 125 pregnant women from measurements of HHg and dietary methylmercury intake estimated from a dietary survey. When estimated assuming a point estimate for the population dietary intake, the mean half-time was 65.4 days

(SD 6.0; 95% CI 54, 78). When interindividual variability in dietary mercury intake was included in the estimation of the half-time, the population mean half-time was 103 days (SD 9.5; 95% CI 83, 121). Jo et al. (2015) estimated half-times in 304 adults who were randomly selected from BHg quartiles of the KRIEFS cohort. The estimated population mean half-time (with interindividual variability in dietary intake included in the estimation) was 80.2 days (2.5–97.5 percentile range 64.0–97.4 days). The estimated mean half-time for males (n=167) was 81.6 days (range 66.0–98.8 days) and, for females (n=137), the estimated mean half-time was 78.9 days (range 62.8–96.4 days).

Hair/blood ratio. The value for the hair/blood ratio used in the dose equivalence model is 203 µg Hg/kg hair per µg Hg/L blood (Albert et al. 2010). The Faroe Islands study collected individual subject data on cord blood and parental hair at parturition (Budtz-Jorgensen et al. 2004). The median ratio (µg Hg/kg hair per µg Hg/L blood) was 190 (5^{th}–95^{th} percentile: 74–442) for full-length hair and 201 (5^{th}–95^{th} percentile: 89–439) for proximal hair (2-cm scalp segment). The hair/blood concentration ratio has been measured in numerous other studies and shows high inter-individual variability, with population means ranging from 100 to 400 (Akagi et al. 1995; Albert et al. 2010; Birke et al. 1972; Clarkson et al. 1988; Kershaw et al. 1980; Liberda et al. 2014; Muckle et al. 2001; Phelps et al. 1980; Sherlock et al. 1982; Yaginuma-Sakurai et al. 2012).

Blood volume. The value for the blood volume used in the dose equivalence model is 0.08 L/kg body weight (Albert et al. 2010). Data on blood volume in humans have been extensively reviewed (e.g., Brown et al. 1962; ICRP 1981; Stern 1997). These sources provide estimates that range from 0.06 to 0.08 L/kg. The upper end of the range is appropriate for the expanded blood volume that occurs during pregnancy (Hytten 1985).

Body weight. The value for body weight used in the dose equivalence model is 60 kg, based on ICRP (1981) and EPA (2011).

Evaluation of the dose equivalence model. The dose equivalence model was evaluated by comparing predicted doses with observed BHg or HHg levels in populations of pregnant women in which individual dietary methylmercury intakes were known or estimated (Pouzaud et al. 2010; Vejrup et al. 2018). The results of these comparisons are summarized below. The close agreement between the observed methylmercury intakes and dose equivalents predicted from BHG or HHG levels supports use of the model in derivation of the chronic-duration oral MRL.

Pouzaud et al. (2010) measured dietary scalp hair mercury levels in 137 pregnant women during weeks 12 and 32 of pregnancy and paired these data with estimates of dietary methylmercury intake from a dietary survey. The group mean hair level was 0.82 µg Hg/g at week 12 and 0.79 µg Hg/g at week 32. The corresponding mean dietary intakes were 0.56 µg Hg/kg/week (0.080 µg Hg/kg/day) and 0.67 µg Hg/kg/week (0.096 µg Hg/kg/day). The observed and predicted mercury doses for this study are as follows:

Observed mean HHg: 0.82, 0.79 µg Hg/kg
Observed mean mercury intake: 0.080, 0.096 µg Hg/kg/day
Predicted mean dose equivalent: 0.061, 0.059 µg Hg/kg/day
Predicted minus observed: -0.019, -0.037 µg Hg/kg/day

The differences between the predicted and observed mercury intakes ranged from 0.02 to 0.04 µg Hg/kg/day. Good agreement between the predicted and observed dietary methylmercury intakes are expected for this dataset, since it included data from 123 subjects used to estimate parameters for the dose equivalence model.

Vejrup et al. (2018) estimated median dietary fish mercury intakes and measured BHg levels for a subset of the full cohort of the Norwegian Mother and Child Cohort Study (n=2,239). The median maternal BHg level was 1.0 µg Hg/L (SD 0.9) and the median estimated dietary fish mercury intake was 0.15 µg Hg/kg/week (0.021 µg Hg/g/day). The observed and predicted mercury doses for this study are as follows:

Observed median BHg: 1.0 µg Hg/L (SD 0.9)
Observed median mercury intake: 0.021 µg Hg/kg/day
Predicted median dose equivalent: 0.015 µg Hg/kg/day
Predicted minus observed: -0.006 µg Hg/kg/day

The difference between the predicted and observed mercury intake was 0.006 µg Hg/kg/day.

Conversion of meta-β (IQ points per µg Hg/g hair) to POD_{dose} (µg/kg/day per 1 IQ point).

Calculate POD_{hair} (µg Hg/g hair per 1 IQ point) from meta-β (IQ points per µg Hg/g hair; Equation 8):

$$POD_{hair} = (IQ\ points)/(meta\beta)$$

$$POD_{hair} = \frac{1}{0.18} = 5.56$$

Calculate ratio of BHg to dose (µg/L blood per µg Hg/kg/day; Equation 10):

$$Ratio\ blood{:}\,dose = (AF \times f_{blood} \times BW)/(k_e \times V_{blood})$$

$$Ratio\ blood{:}\,dose = \frac{0.94\ \times 0.060\ \times 60\ kg}{0.0106\ day^{-1}\ \times 4.80\ L} = 66.51$$

where AF is the absorption fraction, f_{blood} is the fraction of the dose transferred to blood, BW is body weight, k_e is the elimination rate constant ($\ln(2)/t_{1/2}$) and V_{blood} is the blood volume (0.080 × body weight).

Calculate ratio of HHg to dose (µg Hg/g hair per µg Hg/kg/day; Equations 11 and 13):

$$Ratio\ hair{:}\,dose = (Ratio\ blood{:}\,dose \times Ratio\ hair{:}\,blood)/1{,}000$$

$$Ratio\ hair{:}\,dose = 66.51\ \times \frac{203}{1{,}000} = 13.50$$

Calculate POD_{dose} (µg Hg/kg/day) from POD_{hair} (µg Hg/g hair):

$$POD_{dose} = POD_{hair}\ /\ Ratio\ hair{:}\,dose$$

$$POD_{dose} = \frac{5.56}{13.50} = 0.41$$

Uncertainty Factor: An uncertainty factor of 3 was applied to the POD of 0.41 µg Hg/kg/day to account for expected human variability in pharmacokinetics and dynamics. The uncertainty factor was reduced from the standard factor for 10 for the following reasons: (1) the principal study examined a highly sensitive target population, the fetus and (2) a well-supported biokinetic model was used to calculate the equivalent maternal dose from a well-supported biomarker of exposure to methylmercury in high fish consuming populations.

- 3 for human variability

MRL = POD ÷ UF
MRL = 0.41 µg Hg/kg/day ÷ 3
MRL = 0.1 µg Hg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The chronic-duration oral MRL based on the meta-analysis of the Faroe Islands, North Island New Zealand, and Seychelle Islands is 0.1 µg Hg/kg/day. The MRL is lower than the equivalent doses predicted in the individual contributing studies, which were 0.34 µg Hg/kg/day for the Faroe Islands cohort, 0.61 µg Hg/kg/day for the North Island New Zealand cohort, and 0.41 µg Hg/kg/day for the Seychelle Islands cohort. The equivalent doses from the Faroe Islands and North Island New Zealand cohorts are AELs, while the equivalent dose from the Seychelle Island cohort is a NAEL.

In addition to the epidemiological studies conducted in the Faroe Islands, North Island New Zealand, and Seychelle Islands, studies of other populations have found associations between exposures to methylmercury and neurodevelopmental outcomes (Section 2.16). These include studies of high fish consumers in the Amazon River basin (Chevrier et al. 2009; Cordier et al. 2002), Arctic Canada (Boucher et al. 2012a, 2012b, 2014, 2016; Despres et al. 2005; Ethier et al. 2012; Jacobson et al. 2015), fishing villages on the Mediterranean coast (Murata et al. 1999a, 2004b), and populations residing in the vicinity of artisanal gold mining operations (Counter 2003; Counter et al. 1998, 2002, 2006, 2012; Nyanza et al. 2021; Ramirez et al. 2000, 2003; Reuben et al. 2020).

The MRL is approximately 2 times higher than the dietary fish methylmercury intakes in the Norwegian Mother and Child Cohort Study that were associated with effects on language proficiency. However, a POD based on the dietary intakes estimated in this study would have lower confidence than the POD used in the derivation of the MRL for several reasons: (1) the associations with dietary methylmercury intake were based on a semi-quantitative food survey and national data on fish mercury concentrations, rather than biomarkers of mercury exposure in individual subjects; (2) the association with dietary methylmercury intake predicted lower language proficiency at age 3 years, whereas the association predicted higher proficiency at age 5 years (Vejrup et al. 2016, 2018); (3) in a subset of the cohort for which measurements of individual subject BHg levels were available, there was no association between language proficiency and BHg (Vejrup et al. 2018); and (4) language proficiency assessment was assessed from results of a parental self-report survey of their children rather than an assessment made by professional, non-biased observers. The outcomes of the Kobayashi et al. (2022) study also contribute to uncertainty in the interpretation of the language outcomes from the Norwegian Mother and Child Cohort Study. This large-scale prospective study conducted in Japan (n=48,731), found no evidence for an association between maternal BHg levels (median 3.64 µg/kg) and communication skills assessed from scores on of the Ages and Stages Questionnaire, a survey instrument that was used in the Norwegian Mother and Child Cohort Study (Kobayashi et al. 2022). The median maternal BHg level in the Kobayashi et al. (2022) study (3.64 µg/L) was higher than the median in the Norwegian Mother and Child Cohort Study (1.03 µg/L; Vejrup et al. 2018). The Kobayashi et al. (2022) study adjusted their regression models for maternal n-3 PUFA consumption and other potential confounders, as was done in the Norwegian Mother and Child Cohort Study.

Studies conducted in animals (nonhuman primates and rodents) provide strong support for the developing nervous system being most sensitive target of methylmercury (Section 2.16.1, Neurodevelopmental Effects for references and additional details). Studies conducted in monkeys have shown that gestational exposure to methylmercury resulted in sensorimotor dysfunction, and vision and hearing deficits. Gestational exposures in rodents produced sensorimotor dysfunction, vision and hearing deficits, impaired learning and memory, and neuropathological changes in the central and peripheral nervous systems.

Agency Contacts (Chemical Managers): Rae Benedict

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR MERCURY

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to mercury.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for mercury. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of mercury have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of mercury are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the Draft Toxicological Profile for Mercury released for public comment in 2022; thus, the literature search was restricted to studies published between December 2018 and October 2023. The following main databases were searched in October 2023:

- PubMed
- National Technical Reports Library
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for mercury. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to mercury were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
10/2023	((("mercury/toxicity"[mh] OR "mercury/adverse effects"[mh] OR "mercury/poisoning"[mh] OR "mercury/pharmacokinetics"[mh] OR ("mercury"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury/blood"[mh] OR "mercury/cerebrospinal fluid"[mh] OR "mercury/urine"[mh] OR "mercury/antagonists and inhibitors"[mh]) OR ("mercury/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]))) OR "mercury/pharmacology"[majr])) OR ("phenylmercuric acetate/toxicity"[mh] OR "phenylmercuric acetate/adverse effects"[mh] OR "phenylmercuric acetate/poisoning"[mh] OR "phenylmercuric acetate/pharmacokinetics"[mh] OR ("phenylmercuric acetate"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional

Table B-2. Database Query Strings

Database search date	Query string
	activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("phenylmercuric acetate"[mh] AND toxicokinetics[mh:noexp]) OR ("phenylmercuric acetate/blood"[mh] OR "phenylmercuric acetate/cerebrospinal fluid"[mh] OR "phenylmercuric acetate/urine"[mh] OR "phenylmercuric acetate/antagonists and inhibitors"[mh]) OR ("phenylmercuric acetate/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("phenylmercuric acetate"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]))) OR "phenylmercuric acetate/pharmacology"[majr])) OR ("mercuric chloride/toxicity"[mh] OR "mercuric chloride/adverse effects"[mh] OR "mercuric chloride/poisoning"[mh] OR "mercuric chloride/pharmacokinetics"[mh] OR ("mercuric chloride"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercuric chloride"[mh] AND toxicokinetics[mh:noexp]) OR ("mercuric chloride/blood"[mh] OR "mercuric chloride/cerebrospinal fluid"[mh] OR "mercuric chloride/urine"[mh] OR "mercuric chloride/antagonists and inhibitors"[mh]) OR ("mercuric chloride/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercuric chloride"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]))) OR "mercuric chloride/pharmacology"[majr])) OR "Mercury poisoning"[mh] OR 13966-62-6[rn] OR 72172-67-9[rn] OR (("mercury"[mh] OR "phenylmercuric acetate"[mh] OR "mercuric chloride"[mh]) AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh])))) AND (2022/09/26:3000[mhda])) OR (("cinnabar"[tw] OR "mercuric sulfide"[tw] OR "mercuric sulphide"[tw] OR "mercury (ii) sulfide"[tw] OR "mercury monosulfide"[tw] OR "mercury sulfide"[tw] OR "mercury sulphide"[tw] OR "mercury(2+) sulfide"[tw] OR "mercury(ii) sulfide"[tw] OR "monomercury sulfide"[tw]) AND (2022/09/26:3000[edat] OR 2022/09/26:3000[crdat])) (("mercury compounds/toxicity"[mh] OR "mercury compounds/adverse effects"[mh] OR "mercury compounds/poisoning"[mh] OR "mercury compounds/pharmacokinetics"[mh] OR ("mercury compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury compounds/blood"[mh] OR "mercury compounds/cerebrospinal fluid"[mh] OR "mercury compounds/urine"[mh] OR "mercury compounds/antagonists and inhibitors"[mh]) OR ("mercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury compounds"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])))) OR "mercury compounds/pharmacology"[majr])) OR ("methylmercury compounds/toxicity"[mh] OR "methylmercury compounds/adverse effects"[mh] OR "methylmercury compounds/poisoning"[mh] OR "methylmercury compounds/pharmacokinetics"[mh] OR ("methylmercury compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene

Table B-2. Database Query Strings

Database search date	Query string
	expression profiling"[mh])) OR ("methylmercury compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("methylmercury compounds/blood"[mh] OR "methylmercury compounds/cerebrospinal fluid"[mh] OR "methylmercury compounds/urine"[mh] OR "methylmercury compounds/antagonists and inhibitors"[mh]) OR ("methylmercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("methylmercury compounds"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])) OR "methylmercury compounds/pharmacology"[majr])) OR ("mercury isotopes/toxicity"[mh] OR "mercury isotopes/adverse effects"[mh] OR "mercury isotopes/poisoning"[mh] OR "mercury isotopes/pharmacokinetics"[mh] OR ("mercury isotopes"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury isotopes"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury isotopes/blood"[mh] OR "mercury isotopes/cerebrospinal fluid"[mh] OR "mercury isotopes/urine"[mh] OR "mercury isotopes/antagonists and inhibitors"[mh]) OR ("mercury isotopes/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury isotopes"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])) OR "mercury isotopes/pharmacology"[majr])) OR ("organomercury compounds/toxicity"[mh] OR "organomercury compounds/adverse effects"[mh] OR "organomercury compounds/poisoning"[mh] OR "organomercury compounds/pharmacokinetics"[mh] OR ("organomercury compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND

Table B-2. Database Query Strings

Database search date	Query string
	("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("organomercury compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("organomercury compounds/blood"[mh] OR "organomercury compounds/cerebrospinal fluid"[mh] OR "organomercury compounds/urine"[mh] OR "organomercury compounds/antagonists and inhibitors"[mh]) OR ("organomercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("organomercury compounds"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])) OR "organomercury compounds/pharmacology"[majr])) OR (("mercury compounds"[mh] OR "methylmercury compounds"[mh] OR "mercury isotopes"[mh] OR "organomercury compounds"[mh]) AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh]))))) AND (2022/09/26:3000[mhda]) ((((("(acetato)phenylmercury"[tw] OR "(acetato-kappao)phenylmercury"[tw] OR "(acetato-o)phenylmercury"[tw] OR "(acetoxymercuri)benzene"[tw] OR "(acetoxymercurio)benzene"[tw] OR "acetic acid, mercuridi-"[tw] OR "acetic acid, mercury(2+) salt"[tw] OR "acetic acid, phenylmercury deriv."[tw] OR "acetic acid, phenylmercury(ii) salt"[tw] OR "acetoxyphenylmercury"[tw] OR "benzene, (acetoxymercuri)-"[tw] OR "benzene, (acetoxymercurio)-"[tw] OR "bis(acetyloxy)mercury"[tw] OR "calochlor"[tw] OR "calomel"[tw] OR "chloromethylmercury"[tw] OR "cinnabar"[tw] OR "cinnabarite"[tw] OR "diacetoxymercury"[tw] OR "dichloromercury"[tw] OR "dimercury dichloride"[tw] OR "dimethylmercury"[tw] OR "fungche"[tw] OR "hydrargyrum"[tw] OR "mercuriacetate"[tw] OR "mercuric acetate"[tw] OR "mercuric bichloride"[tw] OR "mercuric chloride"[tw] OR "mercuric diacetate"[tw] OR "mercuric nitrate"[tw] OR "mercuric sulfide"[tw] OR "mercuric sulphide"[tw] OR "mercuridiacetic acid, "[tw] OR "mercuriphenyl acetate"[tw] OR "mercurius 6a"[tw] OR "mercurous chloride"[tw] OR "mercury"[tw] OR "mercury(1+), methyl-"[tw] OR "mercury(2+) acetate"[tw] OR "mercury(2+) chloride"[tw] OR "mercury(2+) nitrate"[tw] OR "mercury(2+) sulfide"[tw] OR "mercury(i) chloride"[tw] OR "mercury(ii) acetate"[tw] OR "mercury(ii) acetate, phenyl-"[tw] OR "mercury(ii) chloride"[tw] OR "mercury(ii) nitrate"[tw] OR "mercury(ii) sulfide"[tw] OR "mercury, (acetato)phenyl-"[tw] OR "mercury, (acetato-kappao)phenyl-"[tw] OR "mercury, (acetato-o)phenyl-"[tw] OR "mercury, acetoxyphenyl-"[tw] OR "mercury, chloromethyl-"[tw] OR "mercury, dimethyl-"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"mercuryl acetate"[tw] OR "mercurymethylchloride"[tw] OR "methyl mercuric chloride"[tw] OR "methyl mercuric(ii) chloride"[tw] OR "methyl meruric chloride"[tw] OR "methylmercuric chloride"[tw] OR "methylmercury"[tw] OR "methylmercury chloride"[tw] OR "methylmercury monochloride"[tw] OR "methylmercury(1+)"[tw] OR "methylmercury(ii) cation"[tw] OR "millon's reagent"[tw] OR "monomercury sulfide"[tw] OR "monomethylmercury cation"[tw] OR "nitric acid, mercury(2+) salt"[tw] OR "nitric acid, mercury(ii) salt"[tw] OR "phenomercuric acetate"[tw] OR "phenyl mercuric acetate"[tw] OR "phenylmercuriacetate"[tw] OR "phenylmercuric acetate"[tw] OR "phenylmercury acetate"[tw] OR "phenylmercury(ii) acetate"[tw] OR "Anticon"[tw] OR "Celmer"[tw] OR "Femma"[tw] OR "Hexasan"[tw] OR "Hostaquick"[tw] OR "Kwiksan"[tw] OR "Lorophyn"[tw] OR "Parasan"[tw] OR "Phix"[tw] OR "Samtol"[tw] OR "Sanitol"[tw] OR "Sc-110"[tw] OR "Verdasan"[tw] OR "Volpar"[tw] OR "Caspan"[tw] OR "Liquid silver"[tw] OR "Quick silver"[tw] OR "Quicksilver"[tw] OR "Sulem"[tw] OR "Agrosan D"[tw] OR "Agrosan GN 5"[tw] OR "Algimycin 200"[tw] OR "Antimucin WBR"[tw] OR "Antimucin WDR"[tw] OR "Bufen"[tw] OR "Bufen 30"[tw] OR "Cekusil"[tw] OR "Ceresol"[tw] OR "Contra Creme"[tw] OR "Dyanacide"[tw] OR "Fungicide R"[tw] OR "Fungitox OR"[tw] OR "Gallotox"[tw] OR "Hl-331"[tw] OR "Hong nien"[tw] OR "Hostaquik"[tw] OR "Intercide 60"[tw] OR "Intercide PMA 18"[tw] OR "Liquiphene"[tw] OR "Meracen"[tw] OR "Mercron"[tw] OR "Mercuron"[tw] OR "Mergal A 25"[tw] OR "Mersolite"[tw] OR "Metasol 30"[tw] OR "Neantina"[tw] OR "Norforms"[tw] OR "Nuodex PMA 18"[tw] OR "Nylmerate"[tw] OR "PMA (fungicide)"[tw] OR "Pamisan"[tw] OR "Panomatic"[tw] OR "Parasan (bactericide)"[tw] OR "Phenmad"[tw] OR "Programin"[tw] OR "Purasan-SC-10"[tw] OR "Puraturf 10"[tw] OR "Quicksan"[tw] OR "Quicksan 20"[tw] OR "Riogen"[tw] OR "Ruberon"[tw] OR "Sanitized SPG"[tw] OR "Sanmicron"[tw] OR "Scutl"[tw] OR "Seed Dressing R"[tw] OR "Seedtox"[tw] OR "Setrete"[tw] OR "Shimmerex"[tw] OR "Spor-Kil"[tw] OR "Spruce Seal"[tw] OR "Tag (VAN)"[tw] OR "Tag 331"[tw] OR "Tag HL 331"[tw] OR "Tag fungicide"[tw] OR "Trigosan"[tw] OR "Troysan 30"[tw] OR "Troysan PMA 30"[tw] OR "Zaprawa Nasienna R"[tw] OR "Ziarnik"[tw] OR "Hydraargyrum bichloratum"[tw] OR "Calo-Clor"[tw] OR "Calocure"[tw] OR "Calogreen"[tw] OR "Calotab"[tw] OR "Abavit B"[tw] OR "Citrine ointment"[tw] OR "Ethiops mineral"[tw] OR "Mercurius vivus"[tw] OR "beta-Mercuric sulfide"[tw] OR "Phenylquecksilberacetate"[tw] OR "Quecksilber(II)-sulfid, rotes"[tw] OR "Rotes Quecksilbersulfid"[tw] OR "Paragite"[tw] OR "TL 898"[tw]) NOT medline[sb])) AND (2022/09/26:3000[edat] OR 2022/09/26:3000[crdat])) AND (toxicity[ti] OR death OR lethal OR fatal OR fatality OR necrosis OR LC50* OR LD50* OR "body weight" OR "weight loss" OR "weight gain" OR weight-change* OR overweight OR obesity OR inhal* OR respiratory OR pulmonary OR airway OR trachea OR tracheobronchial OR lung OR lungs OR nose OR nasal OR nasopharyngeal OR larynx OR laryngeal OR pharynx OR bronchial OR bronchi OR bronchioles OR bronchitis OR hemothorax OR alveolar OR alveoli OR irritation OR irritant OR sensitization OR sensitizer OR cilia OR mucocilliary OR cvd OR cardio OR vascular OR cardiovascular OR circulatory OR cardiac OR heart OR myocardial OR "chest pain" OR artery OR arteries OR veins OR venules OR cardiotox* OR intestinal OR gastrointestinal OR gastric OR digestive OR intestinal OR "gi tract" OR "gi disorder" OR abdominal OR esophagus OR stomach OR intestine OR pancreas OR pancreatic OR diarrhea OR nausea OR vomit OR ulcer OR constipation OR emesis OR "gut microbes" OR "gut flora" OR "gut microflora" OR anorexia OR hematological OR hematology OR hemato OR haemato OR blood OR anemia OR cyanosis OR erythrocytopenia OR leukopenia OR thrombocytopenia OR hemoglobin OR erythrocyte OR hematocrit OR "bone marrow" OR reticulocyte OR methemoglobin OR red-blood-cell OR musculoskeletal OR skeletal OR muscle OR muscular OR arthritis OR "altered bone" OR "joint pain" OR "joint-ache" OR "limb pain" OR "limb ache" OR hepatic OR liver OR hepatocytes OR

Table B-2. Database Query Strings

Database search date	Query string
	gallbladder OR cirrhosis OR jaundice OR hepatocellular OR hepatomegaly OR hepatotox* OR renal OR kidney OR urinary OR bladder OR urine OR "blood urea nitrogen" OR bun OR nephropathy OR nephrotox* OR dermal OR skin OR acanthosis OR dermatitis OR psoriasis OR edema OR ulceration OR acne OR ocular OR "eye function" OR "eye effect" OR "eye irritation" OR "eye drainage" OR "eye tearing" OR blindness OR myopia OR cataracts OR endocrine OR hormone OR "sella turcica" OR thyroid OR adrenal OR pituitary OR immunological OR immunologic OR immune OR lymphoreticular OR lymph-node OR spleen OR thymus OR macrophage OR leukocyte* OR white-blood-cell OR immunotox* OR neurological OR neurologic OR neurotoxic OR neurotoxicity OR neurodegenerat* OR "nervous system" OR brain OR neurotoxicant OR neurochemistry OR neurophysiology OR neuropathology OR "motor activity" OR motor change* OR behavior-change* OR behavioral-change* OR sensory-change* OR cognitive OR vertigo OR drowsiness OR headache OR ataxia OR reproductive OR "reproduction system" OR "reproduction function" OR "reproduction effect" OR "reproduction toxicity" OR fertility OR "maternal toxicity" OR developmental OR "in utero" OR terata* OR terato* OR embryo* OR fetus* OR foetus* OR fetal* OR foetal* OR prenatal* OR "pre-natal" OR perinatal* OR "post-natal" OR postnatal* OR neonat* OR newborn* OR zygote* OR child OR children OR infant* OR offspring OR elderly OR "altered food consumption" OR "altered water consumption" OR "metabolic effect" OR "metabolic toxicity" OR fever OR cancer OR cancerous OR neoplas* OR tumor OR tumors OR tumour* OR malignan* OR carcinoma OR carcinogen OR carcinogen* OR angiosarcoma OR blastoma OR fibrosarcoma OR glioma OR leukemia OR leukaemia OR lymphoma OR melanoma OR meningioma OR mesothelioma OR myeloma OR neuroblastoma OR osteosarcoma OR sarcoma OR mutation OR mutations OR genotoxicity OR genotoxic OR mutagenicity OR mutagenic OR "mechanism of action"[tiab:~0] OR "mechanism of absorption"[tiab:~0] OR "mechanism of distribution"[tiab:~0] OR "mechanism of excretion"[tiab:~0] OR "mechanism of metabolism"[tiab:~0] OR "mechanism of toxic effect"[tiab:~0] OR "mechanism of toxicity" OR "adverse effect" OR "adverse effects" OR "health effects" OR noncancer OR poisoning OR morbidity OR inflammation OR antagonist OR inhibitor OR metabolism OR "environmental exposure" OR toxicokinetics OR pharmacokinetics OR "gene expression" OR "population health" OR epidemiology OR epidemiological OR case-control* OR case-referent OR case-report OR case-series OR cohort* OR correlation-stud* OR cross-sectional-stud* OR ecological-studies OR ecological-study OR follow-up-stud* OR longitudinal-stud* OR metaanalyses OR metaanalysis OR meta-analysis OR prospective-stud* OR record-link* OR retrospective-stud* OR seroepidemiologic-stud* OR occupation* OR worker* OR workmen* OR workplace* OR "human health" OR "oral intake" OR "oral feed" OR "oral ingestion" OR "oral exposure" OR "oral administration" OR ingest* OR gavage* OR "drinking-water" OR NHANES OR "National Health and Nutrition Examination Survey" OR (human AND (risk OR toxic* OR safety)) OR mammal* OR ape OR apes OR baboon* OR balb OR beagle* OR boar OR boars OR bonobo* OR bovine OR C57 OR C57bl OR callithrix OR canine OR canis OR capra OR capuchin* OR cats OR cattle OR cavia OR chicken OR chickens OR chimpanzee* OR chinchilla* OR cow OR cows OR cricetinae OR dog OR dogs OR equus OR feline OR felis OR ferret OR ferrets OR flying-fox OR Fruit-bat OR gerbil* OR gibbon* OR goat OR goats OR guinea-pig* OR guppy OR hamster OR hamsters OR horse OR horses OR jird OR jirds OR lagomorph* OR leontopithecus OR longevans OR macaque* OR marmoset* OR medaka OR merione OR meriones OR mice OR monkey OR monkeys OR mouse OR muridae OR murinae OR murine OR mustela-putorius OR nomascus OR non-human-primate* OR orangutan* OR pan-paniscus OR pan-troglodytes OR pig OR piglet* OR pigs OR polecat* OR pongopygmaeus OR quail OR rabbit OR rabbits OR rat OR rats OR rhesus OR rodent OR

Table B-2. Database Query Strings

Database search date	Query string
	rodentia OR rodents OR saguinus OR sheep OR sheeps OR siamang* OR sow OR sows OR Sprague-Dawley OR swine OR swines OR symphalangus OR tamarin* OR vervet* OR wistar OR wood-mouse OR zebra-fish OR zebrafish) ("Cyclosan"[tw] OR "Mercurous iodide"[tw] OR "Mercury telluride"[tw] OR "Mercury hydride"[tw] OR "Mercurane"[tw] OR "Mercury bromide"[tw] OR "Mercury iodide"[tw] OR "Mercury oxide"[tw] OR "Mercuric selenide"[tw] OR "Mercury cyanide"[tw] OR ("Mercury chloride"[tw] NOT "mercuric chloride"[mh])) OR (("Cyclosan"[tw] OR "Mercury chloride"[tw] OR "Mercury bromide"[tw] OR "Mercuric bromide"[tw] OR "Mercuric dibromide"[tw] OR "Mercury dibromide"[tw] OR "Mercury(II) bromide"[tw] OR "Mercury fulminate"[tw] OR "Mercurous iodide"[tw] OR "Mercuric iodide"[tw] OR "Mercury iodide"[tw] OR "Mercury(II) iodide"[tw] OR "Mercuric oxide"[tw] OR "Mercury oxide"[tw] OR "Red Precipitate"[tw] OR "Yellow precipitate"[tw] OR "Mercuric selenide"[tw] OR "Mercury selenide"[tw] OR "Mercury-selenium complex"[tw] OR "Mercurous sulfate"[tw] OR "Mercury(I) sulfate"[tw] OR "Mercuric sulfate"[tw] OR "Mercuric sulphate"[tw] OR "Mercury sulfate"[tw] OR "Mercury sulphate"[tw] OR "Mercury telluride"[tw] OR "Mercuric cyanide"[tw] OR "Mercurius cyanatus"[tw] OR "Mercury cyanide"[tw] OR "Mercury hydride"[tw] OR "Mercurane"[tw] OR "Mercuric cation"[tw] OR "Mercuric cations"[tw] OR "Mercuric ion"[tw] OR "Mercuric ions"[tw]) NOT medline[sb]) AND (2022/09/26:3000[edat] OR 2022/09/26:3000[crdat])
9/2022	(("mercury/toxicity"[mh] OR "mercury/adverse effects"[mh] OR "mercury/poisoning"[mh] OR "mercury/pharmacokinetics"[mh] OR ("mercury"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury/blood"[mh] OR "mercury/cerebrospinal fluid"[mh] OR "mercury/urine"[mh] OR "mercury/antagonists and inhibitors"[mh]) OR ("mercury/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]))) OR "mercury/pharmacology"[majr])) OR ("phenylmercuric acetate/toxicity"[mh] OR "phenylmercuric acetate/adverse effects"[mh] OR "phenylmercuric acetate/poisoning"[mh] OR "phenylmercuric acetate/pharmacokinetics"[mh] OR ("phenylmercuric acetate"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("phenylmercuric acetate"[mh] AND toxicokinetics[mh:noexp]) OR ("phenylmercuric acetate/blood"[mh] OR "phenylmercuric acetate/cerebrospinal fluid"[mh] OR "phenylmercuric acetate/urine"[mh] OR "phenylmercuric acetate/antagonists and inhibitors"[mh]) OR ("phenylmercuric acetate/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("phenylmercuric acetate"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])))) OR "phenylmercuric acetate/pharmacology"[majr])) OR ("mercuric chloride/toxicity"[mh] OR "mercuric chloride/adverse effects"[mh] OR "mercuric chloride/poisoning"[mh] OR "mercuric chloride/pharmacokinetics"[mh] OR ("mercuric chloride"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercuric chloride"[mh] AND toxicokinetics[mh:noexp]) OR ("mercuric chloride/blood"[mh] OR "mercuric chloride/cerebrospinal fluid"[mh] OR "mercuric chloride/urine"[mh] OR "mercuric chloride/antagonists and inhibitors"[mh]) OR ("mercuric chloride/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercuric chloride"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]))))

Table B-2. Database Query Strings

Database search date	Query string
	OR "mercuric chloride/pharmacology"[majr])) OR ("cinnabar"[tw] OR "mercuric sulfide"[tw] OR "mercuric sulphide"[tw] OR "mercury (ii) sulfide"[tw] OR "mercury monosulfide"[tw] OR "mercury sulfide"[tw] OR "mercury sulphide"[tw] OR "mercury(2+) sulfide"[tw] OR "mercury(ii) sulfide"[tw] OR "monomercury sulfide"[tw] OR "Mercury poisoning"[mh])) AND (2018/12/01:3000[edat] OR 2018/12/01:3000[crdat] OR 2018/12/01:3000[mhda] OR 2018/12/01:3000[dp]) (("mercury compounds/toxicity"[mh] OR "mercury compounds/adverse effects"[mh] OR "mercury compounds/poisoning"[mh] OR "mercury compounds/pharmacokinetics"[mh] OR ("mercury compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury compounds/blood"[mh] OR "mercury compounds/cerebrospinal fluid"[mh] OR "mercury compounds/urine"[mh] OR "mercury compounds/antagonists and inhibitors"[mh]) OR ("mercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury compounds"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]))) OR "mercury compounds/pharmacology"[majr])) OR ("methylmercury compounds/toxicity"[mh] OR "methylmercury compounds/adverse effects"[mh] OR "methylmercury compounds/poisoning"[mh] OR "methylmercury compounds/pharmacokinetics"[mh] OR ("methylmercury compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("methylmercury compounds"[mh] AND

Table B-2. Database Query Strings

Database search date	Query string
	toxicokinetics[mh:noexp]) OR ("methylmercury compounds/blood"[mh] OR "methylmercury compounds/cerebrospinal fluid"[mh] OR "methylmercury compounds/urine"[mh] OR "methylmercury compounds/antagonists and inhibitors"[mh]) OR ("methylmercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("methylmercury compounds"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])) OR "methylmercury compounds/pharmacology"[majr])) OR ("mercury isotopes/toxicity"[mh] OR "mercury isotopes/adverse effects"[mh] OR "mercury isotopes/poisoning"[mh] OR "mercury isotopes/pharmacokinetics"[mh] OR ("mercury isotopes"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury isotopes"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury isotopes/blood"[mh] OR "mercury isotopes/cerebrospinal fluid"[mh] OR "mercury isotopes/urine"[mh] OR "mercury isotopes/antagonists and inhibitors"[mh]) OR ("mercury isotopes/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury isotopes"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])) OR "mercury isotopes/pharmacology"[majr])) OR ("organomercury compounds/toxicity"[mh] OR "organomercury compounds/adverse effects"[mh] OR "organomercury compounds/poisoning"[mh] OR "organomercury compounds/pharmacokinetics"[mh] OR ("organomercury compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR

Table B-2. Database Query Strings

Database search date	Query string
	"transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("organomercury compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("organomercury compounds/blood"[mh] OR "organomercury compounds/cerebrospinal fluid"[mh] OR "organomercury compounds/urine"[mh] OR "organomercury compounds/antagonists and inhibitors"[mh]) OR ("organomercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("organomercury compounds"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])) OR "organomercury compounds/pharmacology"[majr])) AND (2018/12/01:3000[edat] OR 2018/12/01:3000[crdat] OR 2018/12/01:3000[mhda] OR 2018/12/01:3000[dp]) ((("(acetato)phenylmercury"[tw] OR "(acetato-kappao)phenylmercury"[tw] OR "(acetato-o)phenylmercury"[tw] OR "(acetoxymercuri)benzene"[tw] OR "(acetoxymercurio)benzene"[tw] OR "acetic acid, mercuridi-"[tw] OR "acetic acid, mercury(2+) salt"[tw] OR "acetic acid, phenylmercury deriv."[tw] OR "acetic acid, phenylmercury(ii) salt"[tw] OR "acetoxyphenylmercury"[tw] OR "benzene, (acetoxymercuri)-"[tw] OR "benzene, (acetoxymercurio)-"[tw] OR "bis(acetyloxy)mercury"[tw] OR "calochlor"[tw] OR "calomel"[tw] OR "chloromethylmercury"[tw] OR "cinnabar"[tw] OR "cinnabarite"[tw] OR "diacetoxymercury"[tw] OR "dichloromercury"[tw] OR "dimercury dichloride"[tw] OR "dimethylmercury"[tw] OR "fungche"[tw] OR "hydrargyrum"[tw] OR "mercuriacetate"[tw] OR "mercuric acetate"[tw] OR "mercuric bichloride"[tw] OR "mercuric chloride"[tw] OR "mercuric diacetate"[tw] OR "mercuric nitrate"[tw] OR "mercuric sulfide"[tw] OR "mercuric sulphide"[tw] OR "mercuridiacetic acid, "[tw] OR "mercuriphenyl acetate"[tw] OR "mercurius 6a"[tw] OR "mercurous chloride"[tw] OR "mercury"[tw] OR "mercury(1+), methyl-"[tw] OR "mercury(2+) acetate"[tw] OR "mercury(2+) chloride"[tw] OR "mercury(2+) nitrate"[tw] OR "mercury(2+) sulfide"[tw] OR "mercury(i) chloride"[tw] OR "mercury(ii) acetate"[tw] OR "mercury(ii) acetate, phenyl-"[tw] OR "mercury(ii) chloride"[tw] OR "mercury(ii) nitrate"[tw] OR "mercury(ii) sulfide"[tw] OR "mercury, (acetato)phenyl-"[tw] OR "mercury, (acetato-kappao)phenyl-"[tw] OR "mercury, (acetato-o)phenyl-"[tw] OR "mercury, acetoxyphenyl-"[tw] OR "mercury, chloromethyl-"[tw] OR "mercury, dimethyl-"[tw] OR "mercuryl acetate"[tw] OR "mercurymethylchloride"[tw] OR "methyl mercuric chloride"[tw] OR "methyl mercuric(ii) chloride"[tw] OR "methyl meruric chloride"[tw] OR "methylmercuric chloride"[tw] OR "methylmercury"[tw] OR "methylmercury chloride"[tw] OR "methylmercury monochloride"[tw] OR "methylmercury(1+)"[tw] OR "methylmercury(ii) cation"[tw] OR "millon's reagent"[tw] OR "monomercury sulfide"[tw] OR "monomethylmercury cation"[tw] OR "nitric acid, mercury(2+) salt"[tw] OR "nitric acid, mercury(ii) salt"[tw] OR "phenomercuric acetate"[tw] OR "phenyl mercuric acetate"[tw] OR "phenylmercuriacetate"[tw] OR "phenylmercuric acetate"[tw] OR "phenylmercury

Table B-2. Database Query Strings

Database search date	Query string
	acetate"[tw] OR "phenylmercury(ii) acetate"[tw] OR "Anticon"[tw] OR "Celmer"[tw] OR "Femma"[tw] OR "Hexasan"[tw] OR "Hostaquick"[tw] OR "Kwiksan"[tw] OR "Lorophyn"[tw] OR "Parasan"[tw] OR "Phix"[tw] OR "Samtol"[tw] OR "Sanitol"[tw] OR "Sc-110"[tw] OR "Verdasan"[tw] OR "Volpar"[tw] OR "Caspan"[tw] OR "Liquid silver"[tw] OR "Quick silver"[tw] OR "Quicksilver"[tw] OR "Sulem"[tw] OR "Agrosan D"[tw] OR "Agrosan GN 5"[tw] OR "Algimycin 200"[tw] OR "Antimucin WBR"[tw] OR "Antimucin WDR"[tw] OR "Bufen"[tw] OR "Bufen 30"[tw] OR "Cekusil"[tw] OR "Ceresol"[tw] OR "Contra Creme"[tw] OR "Dyanacide"[tw] OR "Fungicide R"[tw] OR "Fungitox OR"[tw] OR "Gallotox"[tw] OR "HI-331"[tw] OR "Hong nien"[tw] OR "Hostaquik"[tw] OR "Intercide 60"[tw] OR "Intercide PMA 18"[tw] OR "Liquiphene"[tw] OR "Meracen"[tw] OR "Mercron"[tw] OR "Mercuron"[tw] OR "Mergal A 25"[tw] OR "Mersolite"[tw] OR "Metasol 30"[tw] OR "Neantina"[tw] OR "Norforms"[tw] OR "Nuodex PMA 18"[tw] OR "Nylmerate"[tw] OR "PMA (fungicide)"[tw] OR "Pamisan"[tw] OR "Panomatic"[tw] OR "Parasan (bactericide)"[tw] OR "Phenmad"[tw] OR "Programin"[tw] OR "Purasan-SC-10"[tw] OR "Puraturf 10"[tw] OR "Quicksan"[tw] OR "Quicksan 20"[tw] OR "Riogen"[tw] OR "Ruberon"[tw] OR "Sanitized SPG"[tw] OR "Sanmicron"[tw] OR "Scutl"[tw] OR "Seed Dressing R"[tw] OR "Seedtox"[tw] OR "Setrete"[tw] OR "Shimmerex"[tw] OR "Spor-Kil"[tw] OR "Spruce Seal"[tw] OR "Tag (VAN)"[tw] OR "Tag 331"[tw] OR "Tag HL 331"[tw] OR "Tag fungicide"[tw] OR "Trigosan"[tw] OR "Troysan 30"[tw] OR "Troysan PMA 30"[tw] OR "Zaprawa Nasienna R"[tw] OR "Ziarnik"[tw] OR "Hydraargyrum bichloratum"[tw] OR "Calo-Clor"[tw] OR "Calocure"[tw] OR "Calogreen"[tw] OR "Calotab"[tw] OR "Abavit B"[tw] OR "Citrine ointment"[tw] OR "Ethiops mineral"[tw] OR "Mercurius vivus"[tw] OR "beta-Mercuric sulfide"[tw] OR "Phenylquecksilberacetate"[tw] OR "Quecksilber(II)-sulfid, rotes"[tw] OR "Rotes Quecksilbersulfid"[tw] OR "Paragite"[tw] OR "TL 898"[tw]) NOT medline[sb])) AND (2018/12/01:3000[edat] OR 2018/12/01:3000[crdat] OR 2018/12/01:3000[dp]) (((7546-30-7[rn] OR 10031-18-2[rn] OR 7789-47-1[rn] OR 15385-58-7[rn] OR 628-86-4[rn] OR 7783-30-4[rn] OR 15385-57-6[rn] OR 7774-29-0[rn] OR 10415-75-5[rn] OR 14836-60-3[rn] OR 15829-53-5[rn] OR 21908-53-2[rn] OR 20601-83-6[rn] OR 11138-42-4[rn] OR 7783-36-0[rn] OR 7783-35-9[rn] OR 12068-90-5[rn] OR 592-04-1[rn] OR 631-60-7[rn] OR 14302-87-5[rn] OR 22542-11-6[rn]) AND (("mercury/toxicity"[mh] OR "mercury/adverse effects"[mh] OR "mercury/poisoning"[mh] OR "mercury/pharmacokinetics"[mh] OR ("mercury"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury/blood"[mh] OR "mercury/cerebrospinal fluid"[mh] OR "mercury/urine"[mh] OR "mercury/antagonists and inhibitors"[mh]) OR ("mercury/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND

Table B-2. Database Query Strings

Database search date	Query string
	(risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])))) OR "mercury/pharmacology"[majr])) OR ("phenylmercuric acetate/toxicity"[mh] OR "phenylmercuric acetate/adverse effects"[mh] OR "phenylmercuric acetate/poisoning"[mh] OR "phenylmercuric acetate/pharmacokinetics"[mh] OR ("phenylmercuric acetate"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("phenylmercuric acetate"[mh] AND toxicokinetics[mh:noexp]) OR ("phenylmercuric acetate/blood"[mh] OR "phenylmercuric acetate/cerebrospinal fluid"[mh] OR "phenylmercuric acetate/urine"[mh] OR "phenylmercuric acetate/antagonists and inhibitors"[mh]) OR ("phenylmercuric acetate/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("phenylmercuric acetate"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])))) OR "phenylmercuric acetate/pharmacology"[majr])) OR ("mercuric chloride/toxicity"[mh] OR "mercuric chloride/adverse effects"[mh] OR "mercuric chloride/poisoning"[mh] OR "mercuric chloride/pharmacokinetics"[mh] OR ("mercuric chloride"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercuric chloride"[mh] AND toxicokinetics[mh:noexp]) OR ("mercuric chloride/blood"[mh]

Table B-2. Database Query Strings

Database search date	Query string
	OR "mercuric chloride/cerebrospinal fluid"[mh] OR "mercuric chloride/urine"[mh] OR "mercuric chloride/antagonists and inhibitors"[mh]) OR ("mercuric chloride/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercuric chloride"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])) OR "mercuric chloride/pharmacology"[majr])) OR ("cinnabar"[tw] OR "mercuric sulfide"[tw] OR "mercuric sulphide"[tw] OR "mercury (ii) sulfide"[tw] OR "mercury monosulfide"[tw] OR "mercury sulfide"[tw] OR "mercury sulphide"[tw] OR "mercury(2+) sulfide"[tw] OR "mercury(ii) sulfide"[tw] OR "monomercury sulfide"[tw] OR "Mercury poisoning"[mh])) OR ((7546-30-7[rn] OR 10031-18-2[rn] OR 7789-47-1[rn] OR 15385-58-7[rn] OR 628-86-4[rn] OR 7783-30-4[rn] OR 15385-57-6[rn] OR 7774-29-0[rn] OR 10415-75-5[rn] OR 14836-60-3[rn] OR 15829-53-5[rn] OR 21908-53-2[rn] OR 20601-83-6[rn] OR 11138-42-4[rn] OR 7783-36-0[rn] OR 7783-35-9[rn] OR 12068-90-5[rn] OR 592-04-1[rn] OR 631-60-7[rn] OR 14302-87-5[rn] OR 22542-11-6[rn]) AND (("mercury compounds/toxicity"[mh] OR "mercury compounds/adverse effects"[mh] OR "mercury compounds/poisoning"[mh] OR "mercury compounds/pharmacokinetics"[mh] OR ("mercury compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury compounds/blood"[mh] OR "mercury compounds/cerebrospinal fluid"[mh] OR "mercury compounds/urine"[mh] OR "mercury compounds/antagonists and inhibitors"[mh]) OR ("mercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury compounds"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])) OR "mercury compounds/pharmacology"[majr])) OR ("methylmercury compounds/toxicity"[mh] OR "methylmercury compounds/adverse effects"[mh] OR "methylmercury compounds/poisoning"[mh] OR "methylmercury compounds/pharmacokinetics"[mh] OR ("methylmercury compounds"[mh] AND

Table B-2. Database Query Strings

Database search date	Query string
	("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("methylmercury compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("methylmercury compounds/blood"[mh] OR "methylmercury compounds/cerebrospinal fluid"[mh] OR "methylmercury compounds/urine"[mh] OR "methylmercury compounds/antagonists and inhibitors"[mh]) OR ("methylmercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("methylmercury compounds"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])) OR "methylmercury compounds/pharmacology"[majr])) OR ("mercury isotopes/toxicity"[mh] OR "mercury isotopes/adverse effects"[mh] OR "mercury isotopes/poisoning"[mh] OR "mercury isotopes/pharmacokinetics"[mh] OR ("mercury isotopes"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("mercury isotopes"[mh] AND toxicokinetics[mh:noexp]) OR ("mercury isotopes/blood"[mh] OR "mercury isotopes/cerebrospinal fluid"[mh] OR "mercury isotopes/urine"[mh] OR "mercury isotopes/antagonists and inhibitors"[mh]) OR ("mercury isotopes/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("mercury isotopes"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	"Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])))) OR "mercury isotopes/pharmacology"[majr])) OR ("organomercury compounds/toxicity"[mh] OR "organomercury compounds/adverse effects"[mh] OR "organomercury compounds/poisoning"[mh] OR "organomercury compounds/pharmacokinetics"[mh] OR ("organomercury compounds"[mh] AND ("environmental exposure"[mh] OR ci[sh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("organomercury compounds"[mh] AND toxicokinetics[mh:noexp]) OR ("organomercury compounds/blood"[mh] OR "organomercury compounds/cerebrospinal fluid"[mh] OR "organomercury compounds/urine"[mh] OR "organomercury compounds/antagonists and inhibitors"[mh]) OR ("organomercury compounds/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("organomercury compounds"[majr] AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])))) OR "organomercury compounds/pharmacology"[majr])))))) AND (2018/12/01:3000[edat] OR 2018/12/01:3000[crdat] OR 2018/12/01:3000[mhda] OR 2018/12/01:3000[dp]) ("Cyclosan"[tw] OR "Mercurous iodide"[tw] OR "Mercury telluride"[tw] OR "Mercury hydride"[tw] OR "Mercurane"[tw] OR "Mercury bromide"[tw] OR "Mercury iodide"[tw] OR "Mercury oxide"[tw] OR "Mercuric selenide"[tw] OR "Mercury cyanide"[tw] OR ("Mercury chloride"[tw] NOT "mercuric chloride"[mh])) OR (("Cyclosan"[tw] OR "Mercury chloride"[tw] OR "Mercury bromide"[tw] OR "Mercuric bromide"[tw] OR "Mercuric dibromide"[tw] OR "Mercury dibromide"[tw] OR "Mercury(II) bromide"[tw] OR "Mercury fulminate"[tw] OR "Mercurous iodide"[tw] OR "Mercuric iodide"[tw] OR "Mercury iodide"[tw] OR "Mercury(II) iodide"[tw] OR "Mercuric oxide"[tw] OR "Mercury oxide"[tw] OR "Red Precipitate"[tw] OR "Yellow precipitate"[tw] OR "Mercuric selenide"[tw] OR "Mercury selenide"[tw] OR "Mercury-selenium complex"[tw] OR "Mercurous sulfate"[tw] OR "Mercury(I) sulfate"[tw] OR "Mercuric sulfate"[tw] OR "Mercuric sulphate"[tw] OR "Mercury sulfate"[tw] OR "Mercury sulphate"[tw] OR "Mercury telluride"[tw] OR "Mercuric cyanide"[tw] OR "Mercurius cyanatus"[tw] OR "Mercury cyanide"[tw] OR "Mercury hydride"[tw] OR "Mercurane"[tw] OR "Mercuric cation"[tw] OR "Mercuric cations"[tw] OR "Mercuric ion"[tw] OR "Mercuric ions"[tw]) NOT medline[sb]) AND (2018/12/01:3000[edat] OR

Table B-2. Database Query Strings

Database search date	Query string
	2018/12/01:3000[crdat] OR 2018/12/01:3000[mhda] OR 2018/12/01:3000[dp]) 13966-62-6[rn] OR 72172-67-9[rn]
NTRL	
10/2023	2018-present, Titles or Keywords "mercuric" OR "mercurous" OR "mercury" OR "methylmercury" OR "methylmercuric" OR "phenylmercury" OR "phenylmercuric" OR "ethylmercury" OR "ethylmercuric" OR "calomel" OR "cinnabar" OR "Hg" "(acetato)phenylmercury" OR "(acetato-kappao)phenylmercury" OR "(acetato-o)phenylmercury" OR "(acetoxymercuri)benzene" OR "(acetoxymercurio)benzene" OR "acetic acid, mercuridi-" OR "acetic acid, mercury(2+) salt" OR "acetic acid, phenylmercury deriv." OR "acetic acid, phenylmercury(ii) salt" OR "acetoxyphenylmercury" OR "benzene, (acetoxymercuri)-" OR "benzene, (acetoxymercurio)-" OR "bis(acetyloxy)mercury" OR "calochlor" OR "calomel" OR "chloromethylmercury" OR "cinnabar" OR "cinnabarite" OR "diacetoxymercury" OR "dichloromercury" OR "dimercury dichloride" OR "dimethylmercury" OR "fungche" OR "hydrargyrum" OR "mercuriacetate" OR "mercuric acetate" OR "mercuric bichloride" OR "mercuric chloride" OR "mercuric diacetate" OR "mercuric nitrate" OR "mercuric sulfide" OR "mercuric sulphide" OR "mercuridiacetic acid, " OR "mercuriphenyl acetate" OR "mercurius 6a" OR "mercurous chloride" OR "mercury(1+), methyl-" OR "mercury(2+) acetate" OR "mercury(2+) chloride" OR "mercury(2+) nitrate" OR "mercury(2+) sulfide" OR "mercury(i) chloride" OR "mercury(ii) acetate" OR "mercury(ii) acetate, phenyl-" OR "mercury(ii) chloride" OR "mercury(ii) nitrate" OR "mercury(ii) sulfide" OR "mercury, (acetato)phenyl-" "mercury, (acetato-kappao)phenyl-" OR "mercury, (acetato-o)phenyl-" OR "mercury, acetoxyphenyl-" OR "mercury, chloromethyl-" OR "mercury, dimethyl-" OR "mercuryl acetate" OR "mercurymethylchloride" OR "methyl mercuric chloride" OR "methyl mercuric(ii) chloride" OR "methyl meruric chloride" OR "methylmercuric chloride" OR "methylmercury" OR "methylmercury chloride" OR "methylmercury monochloride" OR "methylmercury(1+)" OR "methylmercury(ii) cation" OR "millon's reagent" OR "monomercury sulfide" OR "monomethylmercury cation" OR "nitric acid, mercury(2+) salt" OR "nitric acid, mercury(ii) salt" OR "phenomercuric acetate" OR "phenyl mercuric acetate" OR "phenylmercuriacetate" OR "phenylmercuric acetate" OR "phenylmercury acetate" OR "phenylmercury(ii) acetate" OR "Anticon" OR "Celmer" OR "Femma" OR "Hexasan" OR "Hostaquick" OR "Kwiksan" OR "Lorophyn" OR "Parasan" OR "Phix" OR "Samtol" OR "Sanitol" OR "Sc-110" OR "Verdasan" OR "Volpar" OR "Caspan" OR "Liquid silver" OR "Quick silver" OR "Quicksilver" OR "Sulem" OR "Agrosan D" OR "Agrosan GN 5" OR "Algimycin 200" OR "Antimucin WBR" OR "Antimucin WDR" OR "Bufen" "Bufen 30" OR "Cekusil" OR "Ceresol" OR "Contra Creme" OR "Dyanacide" OR "Fungicide R" OR "Fungitox OR" OR "Gallotox" OR "HI-331" OR "Hong nien" OR "Hostaquik" OR "Intercide 60" OR "Intercide PMA 18" OR "Liquiphene" OR "Meracen" OR "Mercron" OR "Mercuron" OR "Mergal A 25" OR "Mersolite" OR "Metasol 30" OR "Neantina" OR "Norforms" OR "Nuodex PMA 18" OR "Nylmerate" OR "PMA (fungicide)" OR "Pamisan" OR "Panomatic" OR "Parasan (bactericide)" OR "Phenmad" OR "Programin" OR "Purasan-SC-10" OR "Puraturf 10" OR "Quicksan" OR "Quicksan 20" OR "Riogen" OR "Ruberon" OR "Sanitized SPG" OR "Sanmicron" OR "Scutl" OR "Seed Dressing R" OR "Seedtox" OR "Setrete" OR "Shimmerex" OR "Spor-Kil" OR "Spruce Seal" OR "Tag (VAN)" OR "Tag 331" OR "Tag HL 331" OR "Tag fungicide" OR "Trigosan" OR "Troysan 30" OR

Table B-2. Database Query Strings

Database search date	Query string
	"Troysan PMA 30" OR "Zaprawa Nasienna R" OR "Ziarnik" OR "Hydraargyrum bichloratum" OR "Calo-Clor" OR "Calocure" OR "Calogreen" OR "Calotab" OR "Abavit B" OR "Citrine ointment" OR "Ethiops mineral" OR "Mercurius vivus" OR "beta-Mercuric sulfide" OR "Phenylquecksilberacetate" OR "Quecksilber(II)-sulfid, rotes" OR "Rotes Quecksilbersulfid" OR "Paragite" OR "TL 898"
Toxcenter	
10/2023	FILE 'TOXCENTER' ENTERED AT 15:45:28 ON 09 OCT 2023 CHARGED TO COST=EH038.10.02.LB.05 L1 149470 SEA 7439-97-6 L2 31298 SEA 7487-94-7 OR 1344-48-5 OR 10112-91-1 OR 1600-27-7 OR 115-09-3 OR 593-74-8 OR 62-38-4 OR 22967-92-6 OR 10045-94-0 OR 19122-79-3 OR 7546-30-7 OR 10031-18-2 OR 7789-47-1 OR 15385-58-7 OR 628-86-4 L3 9164 SEA 7783-30-4 OR 15385-57-6 OR 7774-29-0 OR 10415-75-5 OR 14836-60-3 OR 15829-53-5 OR 21908-53-2 OR 20601-83-6 OR 11138-42-4 OR 7783-36-0 OR 7783-35-9 OR 12068-90-5 OR 592-04-1 OR 631-60-7 OR 14302-87-5 OR 22542-11-6 L4 175436 SEA L1 OR L2 OR L3 L5 6694 SEA L4 AND ED>=20220926 L6 6201 SEA L5 NOT PATENT/DT L7 6201 SEA L6 AND PY>1997 L8 6 SEA 13966-62-6 OR 72172-67-9 L9 0 SEA L8 AND ED>=20220926 ACT TOXQUERY/Q --------- L10 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L11 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L12 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L13 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L14 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L15 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L16 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L17 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L18 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L19 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L20 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L21 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L22 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR

Table B-2. Database Query Strings

Database search date	Query string
	SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L23 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR
	SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L24 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L25 QUE (ENDOCRIN? AND DISRUPT?)
	L26 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L27 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L28 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L29 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR
	NEOPLAS?)
	L30 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L31 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L32 QUE (NEPHROTOX? OR HEPATOTOX?)
	L33 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L34 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L35 QUE L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR
	L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR
	L27 OR L28 OR L29 OR L30 OR L31 OR L32 OR L33 OR L34
	L36 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE
	OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE
	OR PORCINE OR MONKEY? OR MACAQUE?)
	L37 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L38 QUE L35 OR L36 OR L37
	L39 QUE (NONHUMAN MAMMALS)/ORGN
	L40 QUE L38 OR L39
	L41 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L42 QUE L40 OR L41

	L43 3744 SEA L7 AND L42
	L44 760 SEA L43 AND MEDLINE/FS
	L45 1704 SEA L43 NOT CAPLUS/FS
	L46 944 SEA L45 NOT L44
	L47 1456 DUP REM L44 L46 (248 DUPLICATES REMOVED)
	D SCAN L47
9/2022	FILE 'TOXCENTER' ENTERED AT 15:30:27 ON 26 SEP 2022
	CHARGED TO COST=EH038.10.02.LB.05
	L1 143154 SEA FILE=TOXCENTER 7439-97-6
	L2 30530 SEA FILE=TOXCENTER 7487-94-7 OR 1344-48-5 OR 10112-91-1 OR

Table B-2. Database Query Strings

Database search date	Query string
	1600-27-7 OR 115-09-3 OR 593-74-8 OR 62-38-4 OR 22967-92-6 OR 10045-94-0 OR 19122-79-3 OR 7546-30-7 OR 10031-18-2 OR 7789-47-1 OR 15385-58-7 OR 628-86-4
	L3 8428 SEA FILE=TOXCENTER 7783-30-4 OR 15385-57-6 OR 7774-29-0 OR 10415-75-5 OR 14836-60-3 OR 15829-53-5 OR 21908-53-2 OR 20601-83-6 OR 11138-42-4 OR 7783-36-0 OR 7783-35-9 OR 12068-90-5 OR 592-04-1 OR 631-60-7 OR 14302-87-5 OR 22542-11-6
	L4 168057 SEA FILE=TOXCENTER L1 OR L2 OR L3
	L5 151731 SEA FILE=TOXCENTER L4 NOT PATENT/DT
	L6 151635 SEA FILE=TOXCENTER L5 NOT TSCATS/FS
	L7 22428 SEA FILE=TOXCENTER L6 AND ED>=20181201
	L8 22411 SEA FILE=TOXCENTER L7 AND PY>1997
	L9 6 SEA FILE=TOXCENTER 13966-62-6 OR 72172-67-9
	L10 4 SEA FILE=TOXCENTER L9 AND PY>1997
	D SCAN L10
	L11 3 SEA FILE=TOXCENTER L10 NOT 7439-97-6
	ACT TOXQUERY/Q

	L12 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L13 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L14 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L15 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L16 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L17 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L18 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L19 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L20 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L21 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L22 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L23 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L24 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L25 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L26 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L27 QUE (ENDOCRIN? AND DISRUPT?)

Table B-2. Database Query Strings

Database search date	Query string
	L28 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L29 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L30 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L31 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L32 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L33 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L34 QUE (NEPHROTOX? OR HEPATOTOX?)
	L35 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L36 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L37 QUE L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 OR L33 OR L34 OR L35 OR L36
	L38 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L39 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L40 QUE L37 OR L38 OR L39
	L41 QUE (NONHUMAN MAMMALS)/ORGN
	L42 QUE L40 OR L41
	L43 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L44 QUE L42 OR L43

	L53 13117 SEA FILE=TOXCENTER L8 AND L44
	L54 6220 SEA FILE=TOXCENTER L53 NOT CAPLUS/FS
	L55 2389 SEA FILE=TOXCENTER L54 AND MEDLINE/FS
	L56 3831 SEA FILE=TOXCENTER L54 NOT L55
	L57 5347 DUP REM L55 L56 (873 DUPLICATES REMOVED)
	L*** DEL 2389 S L54 AND MEDLINE/FS
	L*** DEL 2389 S L54 AND MEDLINE/FS
	L58 2389 SEA FILE=TOXCENTER L57
	L*** DEL 3831 S L54 NOT L55
	L*** DEL 3831 S L54 NOT L55
	L59 2958 SEA FILE=TOXCENTER L57
	L60 2958 SEA FILE=TOXCENTER (L58 OR L59) NOT MEDLINE/FS
	L61 21 SEA FILE=TOXCENTER L52 NOT L60
	L62 577 SEA FILE=TOXCENTER L60 NOT L52
	D SCAN L60

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
10/2023	No date limit Compounds searched: 7439-97-6; 7487-94-7; 1344-48-5; 10112-91-1; 1600-27-7; 115-09-3; 593-74-8; 62-38-4; 22967-92-6; 10045-94-0; 19122-79-3; 7546-30-7; 10031-18-2; 7789-47-1; 15385-58-7; 628-86-4; 7783-30-4; 15385-57-6; 7774-29-0; 10415-75-5; 14836-60-3; 15829-53-5; 21908-53-2; 20601-83-6; 11138-42-4; 7783-36-0; 7783-35-9; 12068-90-5; 592-04-1; 631-60-7; 14302-87-5; 22542-11-6; 13966-62-6; 72172-67-9
NTP	
10/2023	Terms searched; exact word or phrase 2018-present: mercuric; mercurous; mercury; methylmercury; methylmercuric; phenylmercury; phenylmercuric; ethylmercury; ethylmercuric; calomel; cinnabar; 7439-97-6; 7487-94-7; 1344-48-5; 10112-91-1; 1600-27-7; 115-09-3; 593-74-8; 62-38-4; 22967-92-6; 10045-94-0; 19122-79-3; 7546-30-7; 10031-18-2; 7789-47-1; 15385-58-7; 628-86-4; 7783-30-4; 15385-57-6; 7774-29-0; 10415-75-5; 14836-60-3; 15829-53-5; 21908-53-2; 20601-83-6; 11138-42-4; 7783-36-0; 7783-35-9; 12068-90-5; 592-04-1; 631-60-7; 14302-87-5; 22542-11-6; 13966-62-6; 72172-67-9
Regulations.gov	
10/2023	Terms searched: "mercuric"; "mercurous"; "mercury"; "methylmercury"; "methylmercuric"; "phenylmercury"; "phenylmercuric"; "ethylmercury"; "ethylmercuric"; "calomel"; "cinnabar"; "7439-97-6"; "7487-94-7"; "1344-48-5"; "10112-91-1"; "1600-27-7"; "115-09-3"; "593-74-8"; "62-38-4"; "22967-92-6"; "10045-94-0"; "19122-79-3"; "7546-30-7"; "10031-18-2"; "7789-47-1"; "15385-58-7"; "628-86-4"; "7783-30-4"; "15385-57-6"; "7774-29-0"; "10415-75-5"; "14836-60-3"; "15829-53-5"; "21908-53-2"; "20601-83-6"; "11138-42-4"; "7783-36-0"; "7783-35-9"; "12068-90-5"; "592-04-1"; "631-60-7"; "14302-87-5"; "22542-11-6"; "13966-62-6"; "72172-67-9"
NIH RePORTER	
3/2024	Search Criteria Fiscal Year: Active Projects Text Search: "mercuric" OR "mercurous" OR "mercury" OR "methylmercury" OR "methylmercuric" OR "phenylmercury" OR "phenylmercuric" OR "ethylmercury" OR "ethylmercuric" OR "calomel" OR "cinnabar" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2023 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 9,880
- Number of records identified from other strategies: 113
- Total number of records to undergo literature screening: 9,993

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on mercury:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

- Number of titles and abstracts screened: 9,993
- Number of studies considered relevant and moved to the next step: 929

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 929
- Number of studies cited in the pre-public draft of the toxicological profile: 1,614
- Total number of studies cited in the profile: 1,895

Prioritization of Human Data. Due to the extent of the literature database, it is not practical or realistic to cite all, or even most, of the studies on health effects of mercury. This profile is not to provide a comprehensive review of all literature; instead, the purpose and scope of this profile is to summarize the major lines of evidence regarding health effects associated with environmental and occupational exposure to mercury compounds. Therefore, human data were prioritized for inclusion as follows:

- Epidemiological studies of environmental and occupational exposures were only considered for inclusion if they were well-conducted and reported and included the following: measurements of mercury intakes or biomarker data, measures of variance for outcome metrics, and reported methods for addressing confounding.
  - Exception: Studies of mercury poisoning outbreaks that lacked biomonitoring data but provided critical hazard identification information (e.g., Minamata disease)
- Human studies reporting health effects associated with consumer or medicinal products containing mercury (e.g., vaccines) were excluded, as these studies are not focused on sources of environmental or occupational exposure.
- Case reports were not included in the profile due to the extensive number of available epidemiological studies.
  - Exception 1: Case reports that included discussion of acute-duration accidental or intentional exposure to near-fatal or fatal levels of mercury
  - Exception 2: Case reports that described portal-of-entry effects following acute-duration exposures

Quality criteria were considered in selecting studies to include in the mercury profile and, in particular, for consideration as support for MRLs. In general, epidemiological studies that attempted dose-response assessments (e.g., regression models) were included in the profile if the following criteria were met: (1) reported estimates of variance in the dose-response metrics (e.g., SE, CL); (2) included adjustments for confounding; and (3) reported biomarker data. For studies used to derive MRLs, reporting of quality assurance of analytical methods was also required.

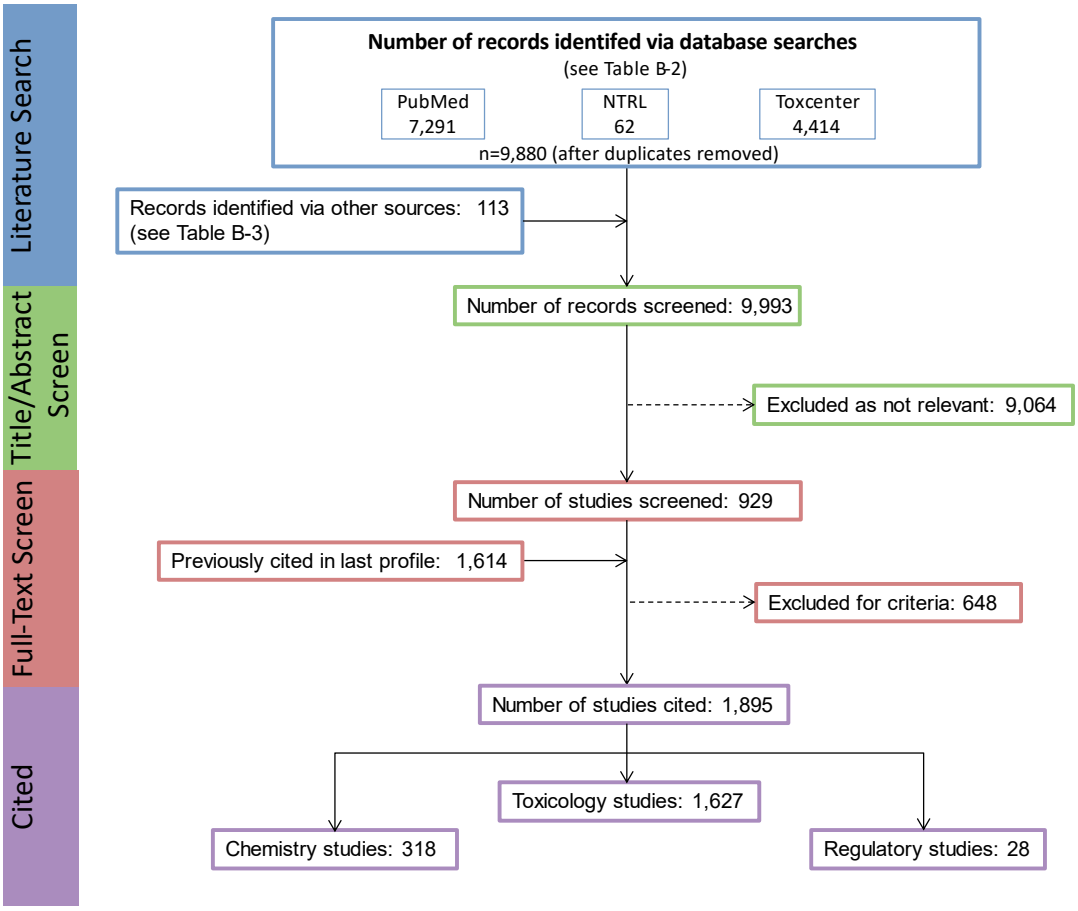
Prioritization of Animal Data

- All well-conducted and reported studies were considered for inclusion with a focus on routes of exposure most relevant to environmental exposure of humans (inhalation, oral, dermal).
- Parenteral studies were included only when needed to support understanding of mechanisms, but not for exposure-response relationships (since dose-response relationships observed following parenteral dosing may not accurately reflect exposure-response relationships).

- Animal studies focused on toxicity of traditional medicine or cultural uses of mercury-containing compounds (e.g., cinnabar) were excluded as not relevant to environmental exposures.

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. October 2023 Literature Search Results and Screen for Mercury



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

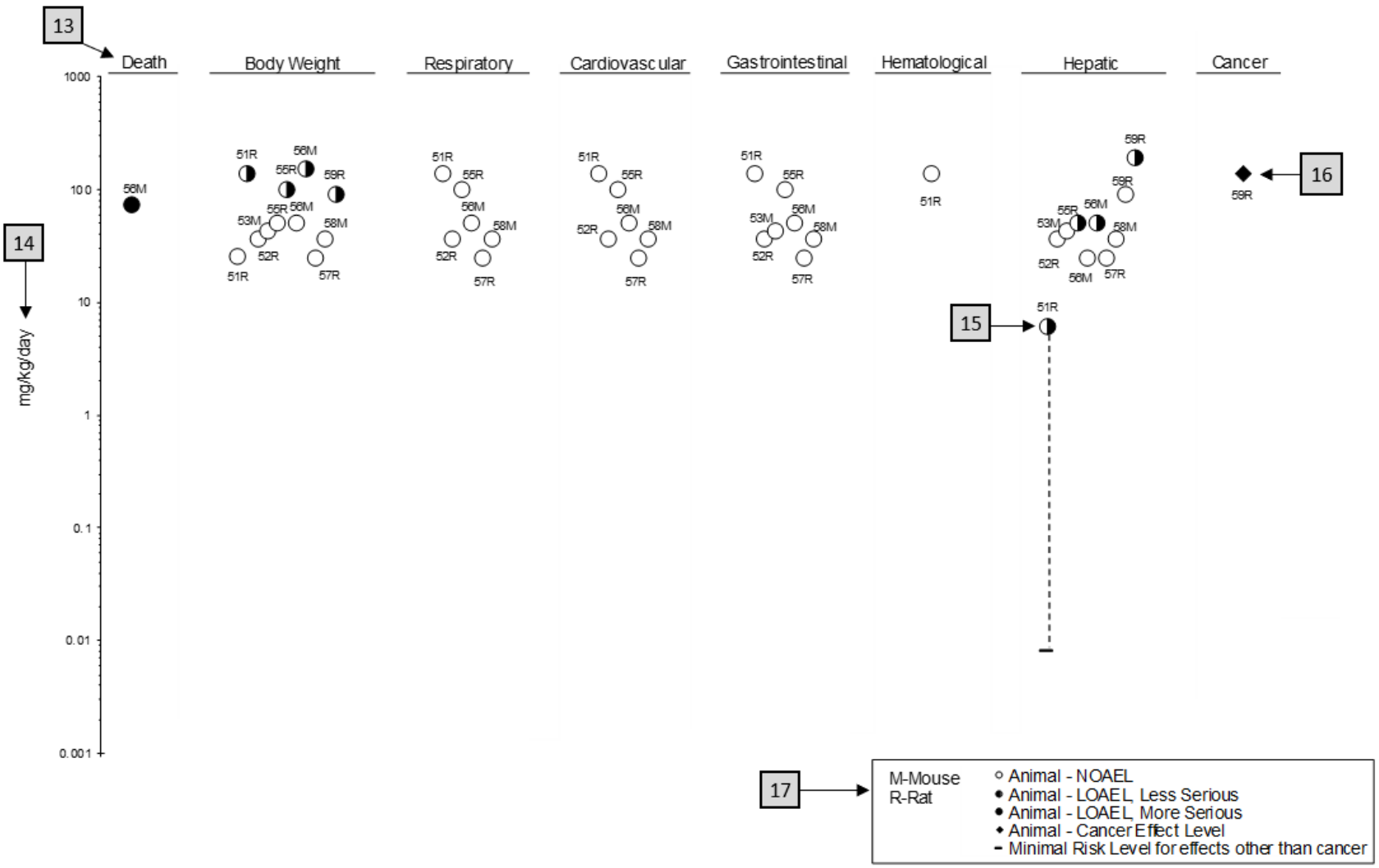
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

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

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/clinician-briefs-overviews.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Adverse-Effect Level (AEL)—An estimate of an exposure concentration or dose at which an adverse outcome was observed. For example, in the derivation of the chronic-duration inhalation MRL for elemental mercury, urine mercury levels were converted to equivalent exposure concentrations at which tremor was observed. Unlike a LOAEL, an AEL is not a point of departure from a dose-response relationship and may not represent the LOAEL.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or malignant tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Confounding—The confusion, or mixing, of effects; this definition implies that the effect of exposure, if mixed together with the effect of another variable, leads to bias. A confounder:

1. must be associated with the disease (as a cause or as a proxy for a cause but not as an effect of the disease);
2. must be associated with exposure, and
3. must not be an effect of the exposure.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Effect Measure Modification—In epidemiology, effect measure modification occurs when the measure of an effect or association (e.g., risk ratio) for an exposure of interest changes over the values of some other variable. This other variable results in a departure from the underlying statistical model.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Adverse-Effect Level (NAEL)—An estimate of an exposure concentration or dose at which an adverse outcome was not observed. For example, in the derivation of the chronic-duration inhalation MRL for elemental mercury, urine mercury levels were converted to equivalent exposure concentrations at which tremors were not observed. Unlike a NOAEL, a NAEL is not a point of departure from a dose-response relationship and may not represent the highest NOAEL.

No-Observed-Adverse-Effect Level (NOAEL)—The exposure level of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this exposure level, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AEL	adverse-effect level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANoA	antinucleolar antibody
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation

FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAEL	no-adverse-effect level
NAS	National Academy of Science
NCEH	National Center for Environmental Health

ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average

UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result