EPA/635/R-18/292
IRIS Assessment Plan
www.epa.gov/iris

IRIS Assessment Plan for Methylmercury (Scoping and Problem Formulation Materials)

CASRN 22967-92-6

April 2019

Integrated Risk Information System
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

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ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
CAA	Clean Air Act
CDC	Centers for Disease Control and Prevention
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
CWA	Clean Water Act
DNT	developmental neurotoxicity
EICG	Effects Identification and Characterization Group
EPA	U.S. Environmental Protection Agency
HAP	hazardous air pollutant
HERO	Health and Environmental Research Online
IAP	IRIS Assessment Plan
IRIS	Integrated Risk Information System
NAS	National Academy of Sciences
NCEA	National Center for Environmental Assessment
NRC	National Research Council
OAR	Office of Air and Radiation
OLEM	Office of Land and Emergency Management
PBPK	physiologically based pharmacokinetic
PECO	Populations, Exposures, Comparators, and Outcomes
QRMG	Quantitative Risk Methods Group
RCRA	Resource Conservation and Recovery Act
RfD	reference dose
UNEP	United Nations Environment Programme

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1. INTRODUCTION

The Integrated Risk Information System (IRIS) Program is undertaking a reassessment of the health effects of methylmercury.[1] Methylmercury was included in the December 2015 IRIS Program multiyear agenda (https://www.epa.gov/iris/iris-agenda) as a chemical having high priority for assessment development. In December 2018, it was reconfirmed as a priority chemical.

IRIS assessments provide high-quality, publicly available information on the toxicity of chemicals to which the public might be exposed. These assessments are not regulations but can provide a critical part of the scientific foundation for decisions made in U.S. Environmental Protection Agency (EPA) program and regional offices to protect public health.

As part of the initial steps in assessment development, the IRIS Program undertakes scoping and initial problem formulation activities. During scoping activities, the IRIS Program consults with EPA program and regional offices to identify the nature of the hazard characterization needed, the most important exposure pathways, and the level of detail required to inform Agency decisions. A broad, preliminary literature survey also will be conducted to assist in identifying the extent of the evidence and health effects that have been studied for the chemical of interest. Based on the preliminary literature survey and the scope defined by EPA, the IRIS Program undertakes problem formulation activities to frame the scientific questions that will be the focus of the assessment. A summary of the IRIS Program's scoping and problem formulation conclusions is contained in the **IRIS Assessment Plan (IAP)**.

The IAP is followed by development of a **Systematic Review Protocol**, which presents detailed methods for conducting the full systematic review and dose-response analysis, including any adjustments made to the IAP in response to public input. The IAP describes *what* will be assessed, and the chemical-specific protocol describes *how* the assessment will be conducted. Figure 1 graphically displays the context of the IAP and Systematic Review Protocol in the systematic review process.

This document presents the draft IAP for methylmercury• a summary of the IRIS Program's scoping and initial problem formulation conclusions. It describes the Agency need for the assessment; objectives and specific aims of the assessment; draft Populations, Exposures, Comparators, and Outcomes (PECO) criteria that outline the evidence considered most pertinent to address the specific aims of the assessment; and identification of key areas of scientific complexity. Brief background information on uses and potential for human exposure is provided for context.

[1]This assessment evaluates methylmercury only. An IAP for inorganic mercury (i.e., mercury salts) is currently in development. Elemental mercury might be considered at a later date for an additional assessment.

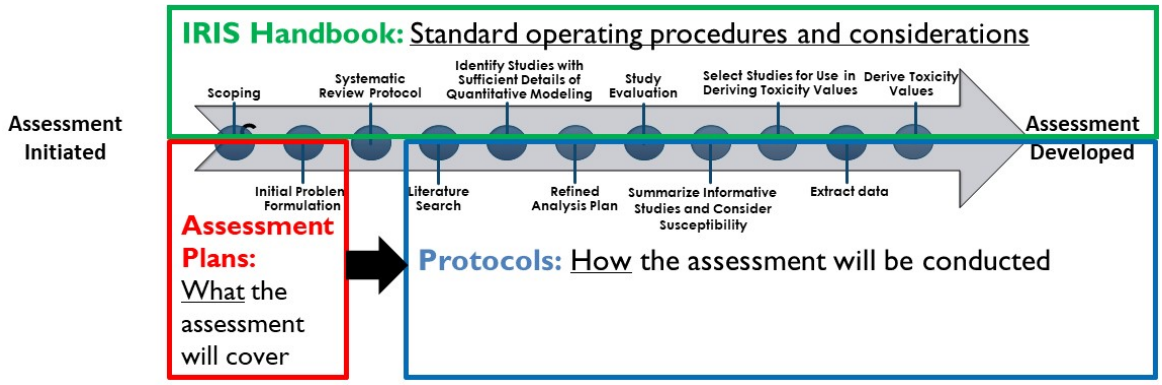

Figure 1. Methylmercury IRIS systematic review problem formulation and method documents.

2. SCOPING AND INITIAL PROBLEM FORMULATION

2.1. BACKGROUND

Multiple health agencies (Health Canada, 2007; UNEP, 2002; U.S. EPA, 2001; ATSDR, 1999; U.S. EPA, 1997) and the National Academy of Sciences' (NAS) National Research Council (NRC, 2000) have established that prenatal oral exposure to methylmercury in humans causes developmental neurotoxicity (DNT). An existing IRIS reference dose (RfD) for methylmercury was published in 2001 (U.S. EPA, 2001) and was based on an NAS assessment from 2000 (NRC, 2000). The outcomes described by the NAS included impaired cognitive function, motor function, visuospatial performance, and abnormal (increased or decreased) muscle tone following in utero methylmercury exposure (NRC, 2000). The RfD of 0.1 µg/kg-day[2] was derived from maternal daily intakes of methylmercury of 0.86–1.47 µg/kg-day, estimated to result in cord blood concentrations of 46–79 µg/L associated with multiple DNT measures (specifically, developmental neuropsychological[3] impairment) in a Faroe Island cohort described by Grandjean et al. (1997). This epidemiological study found impaired cognitive function in 7-year-old children from the Faroe Islands who were prenatally exposed to methylmercury (Budtz-Jørgensen et al., 1999; Grandjean et al., 1997). IRIS's previous 1995 RfD for methylmercury was the same as the 2001 RfD and was also based on DNT outcomes from in utero exposure using data from a 1971 Iraqi poisoning incident

[2]Expressed as a concentration in whole maternal blood, the RfD is approximately 3.5 µg/L (Mahaffey et al., 2009).

[3]In the 2001 IRIS Assessment of methylmercury, the term *developmental neuropsychological impairment* was used to describe the adverse effects on the nervous system that were identified in humans following exposures to methylmercury during developmental life stages. Developmental neuropsychological impairment is a type of DNT, the former terminology being used in many epidemiological studies.

[derivation described in U.S. EPA (1997)]. In both previous IRIS assessments, DNT outcomes were concluded to be the most sensitive.

Methylmercury is formed when inorganic mercury is methylated by biota in water and soil. Gaseous elemental mercury is released into the atmosphere from natural (e.g., volcanoes) and anthropogenic (e.g., fossil-fuel combustion) sources. Elemental mercury can be converted to inorganic mercury, which then can be transported to land or water through wet or dry deposition processes. Combustion processes can also release inorganic ionic mercury, which can adsorb to particulate matter (Srivastava et al., 2006). Inorganic divalent mercury adsorbed to particulates can deposit after relatively short distances, compared to elemental mercury vapor that can travel long distances. Once deposited, microorganisms convert inorganic mercury to methylmercury, which then bioaccumulates in fish tissue. Concentrations of methylmercury in fish tissue, particularly predatory fish higher on the food chain (e.g., swordfish), can be much greater than methylmercury concentrations found in ambient water (U.S. EPA, 2010).

Consumption of contaminated fish and other seafood is the major pathway for exposure to methylmercury in humans (NRC, 2000). Between 2011 and 2014, average blood methylmercury levels in the U.S. population ranged from 0.434 to 0.498 µg/L (CDC, 2017) and average total blood mercury levels, which often are used as a basis for determining methylmercury blood levels, ranged from 0.678 to 0.703 µg/L between 2011 and 2016 (CDC, 2018). Males had slightly higher methylmercury blood levels than females. For example, the average for males in 2013–2014 was 0.448 µg/L and, for females, it was 0.422 µg/L. Blood methylmercury levels were also found to increase with age. In 2011 and 2012, the most recent years that methylmercury blood levels were available for several age groups, the average for children 6 to 11 years of age was 0.209 µg/L; for 12 to 19 year-olds, it was 0.276 µg/L; and for adults over 19, it was 0.624 µg/L (CDC, 2018). The estimated mean daily intake of total mercury for women older than 20 years in the United States is approximately 1 µg/day[4] (CDC, 2016a; Birch et al., 2014).

Methylmercury readily crosses the placenta and concentrates in cord blood at approximately 1.7 times the levels in maternal blood (Straka et al., 2016; Stern and Smith, 2003; Yang et al., 1997). It is also transferred from mothers to children via breastmilk (CDC, 2009; ATSDR, 1999). As noted earlier, the developing nervous system is particularly sensitive to methylmercury, so these gestational, lactational, and other postnatal exposures are of great concern. Methylmercury exposures to women of childbearing age who could become pregnant might be harmful as well, as studies have reported an average half-life of methylmercury in the body of 50 days, which might then result in fetal exposure early in pregnancy (CDC, 2016b). A one-compartment toxicokinetic model estimated a longer half-life for methylmercury, 80 days, based on blood samples from an adult population (Jo et al., 2015). The half-life of methylmercury varies

[4]Based on the calculated average monthly mercury intake using 2009–2010 NHANES (National Health and Nutrition Examination Survey) data reported by Birch et al. and CDC's anthropometric reference values for 2011–2014 (CDC, 2016a; Birch et al., 2014).

among individuals, as some individuals have longer clearance times than others. For example, EPA's 2001 assessment reported half-lives for methylmercury ranging from 32 to 189 days after evaluating data from five studies (Smith et al., 1994; Sherlock et al., 1984; Kershaw et al., 1980; Al-Shahristani and Shihab, 1974; Miettinen et al., 1971).

Subsistence fishing communities and other populations with high dietary intakes of predatory fish species could be exposed to higher-than-average levels of methylmercury. Therefore, women of childbearing age and children in these communities could have high methylmercury exposures during susceptible life stages. People who consume fish from habitats with high methylmercury concentrations due to large microbial populations that convert inorganic mercury to methylmercury also might have particularly high exposures. This includes people eating fish from certain types of wetlands, rivers with a high proportion of wetlands in their watersheds, dilute and low-pH lakes in the Northeast and Northcentral United States, parts of the Florida Everglades, newly flooded reservoirs, and coastal wetlands particularly along the Gulf of Mexico, Atlantic Ocean, and San Francisco Bay (U.S. Department of the Interior, 2000). In some regions of the world, consumption of fish from waters polluted by mercury from small-scale and artisanal gold mining also might result in high methylmercury exposures. Contaminated rice and rice-based food products, such as infant cereals, also can be a source of methylmercury exposure (Cui et al., 2017; Rothenberg et al., 2017; Rothenberg et al., 2016).

2.2. SCOPING SUMMARY

During the scoping process, the IRIS Program met with EPA program and regional offices that had an interest in an IRIS reassessment of methylmercury to discuss specific needs. Table 1 provides a summary of input from this outreach.

Table 1. EPA program and regional office interest in a methylmercury assessment

EPA program or regional office	Oral	Inhalation	Statute/Regulation	Anticipated uses/interest
OLEM EPA Regions 1–10	✓	✓	Comprehensive Environmental Response, Compensation and Liability Act (CERCLA)	CERCLA authorizes EPA to conduct short- or long-term cleanups at Superfund sites and later recover cleanup costs from potentially responsible parties under section 107. Methylmercury toxicological information may be used to make risk determinations for such response actions (e.g., short-term removals, long-term remedial response actions).
			Resource Conservation and Recovery Act (RCRA)	Mercury is listed under RCRA as a characteristic (40 CFR 261.24) and hazardous waste (40 CFR 261.33). Methylmercury toxicological information may be used to evaluate mercury toxicity from releases of elemental mercury and mercury compounds as environmental sources of methylmercury.
			Clean Water Act (CWA)	CWA requires EPA to develop water quality criteria for states and tribes to use in developing water quality standards, requires states and tribes to adopt water quality criteria that protect designated uses such as fish consumption, and requires states and authorized tribes to review water quality standards every three years and modify them based on updated health effects studies derived by EPA.

2.3. PROBLEM FORMULATION

Based on a preliminary survey of the methylmercury literature, including review of assessments conducted by other agencies, potential health outcomes identified other than DNT include the following:

- Nervous system outcomes (non-developmental)
- Developmental outcomes (other than nervous system effects)
- Cardiovascular outcomes
- Immune system outcomes
- Reproductive outcomes

This assessment will only reassess and update the existing dose response for DNT outcomes. It will not reevaluate whether methylmercury causes DNT outcomes because DNT is a

well-established human hazard (as discussed in Section 2.1, Background). Also, it will not assess the potential for methylmercury exposure to cause the other possible health outcomes of interest described above, which might be the focus of subsequent analyses (see Section 2.4).

Because ingestion is the primary route of exposure for methylmercury (NRC, 2000), inhalation and dermal routes of exposure are not addressed in this assessment. OLEM expressed the need for an inhalation reference concentration (RfC) for methylmercury; however, at this time, sufficient data to derive an RfC are not available.

The reassessment of DNT dose response will focus on human studies because the availability of a large epidemiological database on methylmercury exposure and DNT outcomes [see review by Karagas et al. (2012)] eliminates uncertainties associated with interspecies extrapolation. During this reassessment, IRIS will evaluate epidemiological evidence for all types of DNT outcomes resulting from exposure to the fetus, infants, children, or adolescents. Mechanistic studies that address uncertainties in deriving reference values (e.g., by filling data gaps on susceptibility) will be considered.

A reassessment of DNT dose response is justified by recent epidemiological studies that analyzed effects at lower methylmercury exposure levels than those in studies used to derive the existing RfD (U.S. EPA, 2001; NRC, 2000). Many of these recent studies provide exposure-response information, which enables reevaluation of the 2001RfD. Several studies investigated cognitive function [e.g., Golding et al. (2016); Jacobson et al. (2015); Orenstein et al. (2014); Sagiv et al. (2012); Lederman et al. (2008); Oken et al. (2008); Oken et al. (2005)] and motor function [e.g., Prpić et al. (2017); Golding et al. (2016); Suzuki (2016); Lederman et al. (2008); Després et al. (2005); Daniels et al. (2004)] at various ages following prenatal or postnatal exposures to methylmercury. Other DNT outcomes (e.g., behavioral, structural, and electrophysiological) following methylmercury exposures also have been evaluated [e.g., Jin et al. (2016); Ng et al. (2015); Boucher et al. (2010)].

2.4. ASSESSMENT APPROACH

This assessment will use a modular approach. A "modular approach" means EPA will first evaluate the most important route(s) of exposure (based on scoping) and the associated selected health outcome(s). DNT resulting from oral exposure was selected as the focus of this first module because it is a well-established hazard and the two previous RfDs for methylmercury were derived for oral exposure DNT outcomes (see Section 2.1). Once completed, an assessment addressing the DNT dose-response relationship for oral exposure will be released, rather than waiting until all outcomes have been evaluated. This approach will expedite the release of important findings.

While completing this module, EPA also will survey the available hazard information for other adverse health outcomes (see Section 2.3 for list), primarily by reviewing methylmercury assessments by other agencies and organizations, and recent epidemiological studies. For health effects for which hazard has not been well-established, animal and mechanistic studies will also be

surveyed. Because there is insufficient data for all health effects following inhalation exposure to methylmercury, only oral exposure studies will be evaluated.

EPA will use this survey to determine whether there is sufficient evidence to develop new modules that assess hazard and/or derive reference values for these other adverse health outcomes and whether they are likely to occur at environmental exposure levels such that they would be important to consider for EPA decision making. If so, these new modules will have their own IAPs that will be released separately. Consequently, the remainder of this IAP focuses only on the first module, which is a methylmercury dose-response analysis of DNT outcomes in humans.

2.5. KEY SCIENCE ISSUES

Based on the preliminary literature survey, the following key scientific issues were identified that warrant evaluation in this assessment.

- Consider the accuracy of the different types of biomarkers (e.g., hair, maternal blood, cord blood) to measure methylmercury exposure. Consider the reliability and utility of these different measures, including whether different biomarkers provide useful information for developing a dose-response relationship for methylmercury exposure and neurodevelopmental effects.

- Some epidemiological studies will measure methylmercury directly in human blood, hair or nails. Other studies rely on measures of total mercury to estimate methylmercury exposure. Consider how best to use all of the different biomarkers that were used in PECO-relevant epidemiology studies to inform estimates of the relationship between methylmercury exposure and neurodevelopmental effects.

- Consider how potential confounding [e.g., Budtz-Jorgensen et al. (2007)] in studies is accounted for in the analysis. For example, many fish species that contain methylmercury also have beneficial nutrients, such as selenium and polyunsaturated fatty acids, which are important to brain development. In addition, fish could contain other contaminants that might be harmful to brain development, such as polychlorinated biphenyls.

- Consider the differences in DNT evaluation methods, and how their results may be utilized in this assessment. For example, developmental scores are consistently higher for both term and preterm infants when using the Bayley III test versus the Bayley II test, and some suggest using an adjustment factor to compare the two scores (Lowe et al., 2012).

3. OVERALL OBJECTIVE, SPECIFIC AIMS, AND DRAFT POPULATIONS, EXPOSURES, COMPARATORS, AND OUTCOMES (PECO) CRITERIA

The overall objective of this assessment is to characterize the dose-response relationship between methylmercury exposure and DNT outcomes and then use this information to update the existing RfD. Because the current RfD for methylmercury was posted by IRIS in 2001 and was based on an NAS (NRC, 2000) assessment, evaluation of studies since 1998 is expected to capture literature that was not considered in the earlier assessments. The relevant dose-response analyses included in these previous assessments will also be considered in this reassessment. Studies that evaluated the relationships between methylmercury exposures to women of childbearing age and the developing child and DNT outcomes that become apparent at any life stage (infancy through the elderly) will be considered. A conceptual model is presented below to illustrate the focus of the planned assessment (Figure 2).

Systematic review methods will be used to evaluate the epidemiological literature on DNT outcomes, and the analysis conducted will be consistent with all relevant EPA guidance.[5] As a part of this systematic review, potential susceptible populations and life stages will be considered. The Systematic Review Protocol will be disseminated after review of the draft assessment plan and will reflect changes made to the specific aims and PECO criteria in response to public input.

[5]EPA guidance documents: http://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance/.

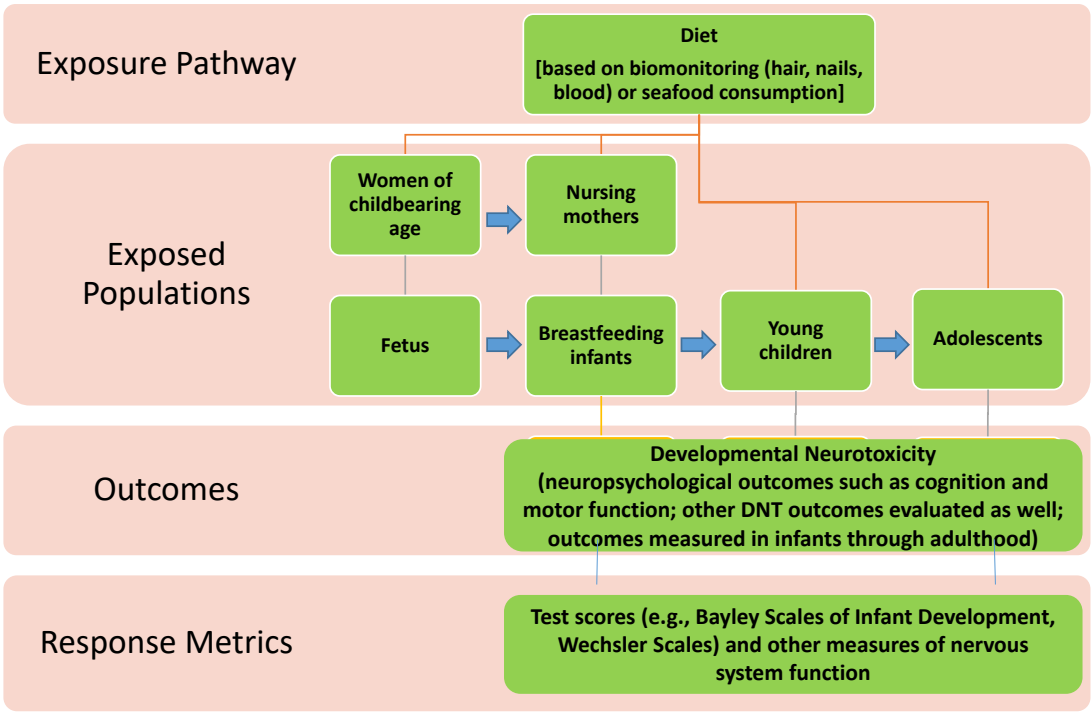

Figure 2. Simplified conceptual model of the reassessment of DNT resulting from exposure to methylmercury.

3.1. SPECIFIC AIMS

- Identify epidemiological literature examining effects of exposure to methylmercury as outlined in the PECO criteria (Section 3.2, Table 2). Develop and execute a literature search strategy to broadly capture data from methylmercury epidemiological studies published since 1998, and screen results for relevance.

- Use predefined criteria to identify epidemiological studies from the screened results that provide exposure-response information for DNT outcomes.

- Conduct study evaluations (risk of bias and sensitivity) for identified epidemiological studies. Studies with critical deficiencies generally will be considered uninformative and not considered further.

- Summarize study methods and results from epidemiological studies on DNT outcomes, including explicit identification and discussion of issues concerning potentially susceptible populations and life stages.

- Evaluate whether dose conversion [i.e., physiologically based pharmacokinetic (PBPK) modeling] is needed. Depending on the biomarker (e.g., cord blood), conduct a search and review of the relevant literature as needed to determine if calculations used in the previous assessment (to convert from cord blood to oral exposure) need to be updated. If necessary, individual PBPK models will be evaluated using predefined criteria, and their strengths and uncertainties will be summarized.

- Derive a toxicity value (e.g., RfD) for DNT outcomes as supported by the available data.
- Characterize uncertainties and identify key data gaps and research needs, such as limitations of the evidence base and the systematic review.
- Determine if the available data would also support the derivation of a dose-response relationship for DNT outcomes that would be useful for benefit analyses to quantify the health benefits of actions to reduce exposures to methylmercury.

3.2. DRAFT PECO CRITERIA

The PECO criteria are used to identify the evidence that addresses the specific aims of the assessment and to focus the search terms and inclusion/exclusion criteria in a systematic review. The draft PECO criteria for this methylmercury assessment (Table 2) were based on (1) basis for the chemical's prioritization for assessment, (2) discussions with scientists in EPA program and regional offices to determine the scope of the assessment that will best meet Agency needs, and (3) preliminary review of the DNT literature for methylmercury (primarily reviews and authoritative health assessment documents).

Table 2. Draft PECO criteria for the methylmercury assessment

PECO element	Evidence
Populations	Human populations exposed during life stages ranging from the fetus through adolescence.
Exposures	Any quantitative exposure to methylmercury based on biomonitoring data (e.g., hair, nails, blood), or, possibly, food consumption (e.g., fish and seafood, rice) expressed as a daily intake (e.g., mg/kg/d). Measurements must be either direct methylmercury measurements or measurements of total mercury (not other forms of mercury, e.g., mercury salts).
Comparators	Referent populations exposed to lower (within the study) levels of methylmercury will be used to examine specific effects. The results of the comparisons must be presented with sufficient detail of quantitative modeling (e.g., regression coefficients presented with statistical measure of variation).
Outcomes	DNT outcomes measured at any age including, but not limited to, tests or measures of cognition, motor function, behavior, vision, and hearing.

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