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By Electronic Submission to www.regulations.gov

Administrator Andrew Wheeler
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Docket ID No. EPA-HQ-ORD-2018-0655

Re: COMMENTS ON IRIS ASSESSMENT PLAN FOR METHYLMERCURY (SCOPING AND PROBLEM FORMULATION MATERIALS) [EPA/635/R-18/292] (Apr. 4, 2019)

On behalf of Philippe Grandjean, Elsie M. Sunderland, David C. Bellinger, Joel D. Blum, Esben Budtz-Jørgensen, Laurie H.M. Chan, Celia Y. Chen, Charles T. Driscoll Jr., David C. Evers, Kathy Fallon Lambert, Irva Hertz-Picciotto, Margaret Karagas, Sally Ann Lederman, Gina Muckle, Frederica Perera, and Ellen K. Silbergeld, the Emmett Environmental Law & Policy Clinic at Harvard Law School respectfully submits these comments on the IRIS Assessment Plan for Methylmercury (Scoping and Problem Formulation Materials) [EPA/635/R-18/292] (Apr. 4, 2019) (“the IAP”). The Emmett Environmental Law and Policy Clinic works on a variety of local, national, and international projects covering the spectrum of environmental law and policy issues under the direction of Professor Wendy B. Jacobs. The other signatories are scientists with considerable expertise in mercury exposure and health outcomes. One of Professor Grandjean’s epidemiological studies, for example, informed the calculation of the existing reference dose (“RfD”) for methylmercury.1

We commend the Environmental Protection Agency (“EPA”) for proposing to update the Integrated Risk Information System (“IRIS”) assessment of the health effects of methylmercury and for proposing to use systematic review methods for this reassessment. The current RfD is almost 20 years old and the development of a substantial body of research in the intervening years calls for its reassessment.

Methylmercury is a highly toxic and bioaccumulative contaminant. Human exposure to methylmercury occurs primarily through consuming seafood and freshwater fish.2 In addition,

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however, following the discovery that mercury-polluted rice fields result in methylmercury-contaminated rice, methylmercury-based foods were found to constitute a health risk.

Methylmercury targets the nervous system, and maternal dietary exposure to methylmercury can result in developmental neurotoxicity (“DNT”). As was shown in the Japanese city of Minamata in the 1950s, a pregnant mother could ingest contaminated fish without suffering any harm herself, yet give birth to a seriously poisoned child with mental retardation. Methylmercury exposure is also associated with a variety of other adverse health effects; for example, high concentrations of methylmercury in blood and tissue samples from adults have been strongly associated with adverse cardiovascular impacts. Cardiovascular abnormalities are also associated with prenatal exposures to methylmercury.

EPA has conducted two previous IRIS assessments for methylmercury. These assessments allowed EPA to establish a methylmercury RfD, a daily exposure “to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.” The current RfD of 0.1 μg/kg-day, published in 2001, was based on a 2000 assessment conducted by the National Academy of Science’s National Research Council (“NRC”), in which maternal daily intakes of methylmercury of 0.86-1.47 μg/kg-day were estimated to result in cord blood concentrations of 46–79 μg/L associated with multiple DNT measures. When calculating the RfD, EPA relied heavily on an epidemiological study of a Faroe Island cohort conducted by signatory Phillippe Grandjean.

As EPA acknowledges, that assessment is now outdated. We agree that 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.” Biologically, there does not appear to be a safe level of methylmercury exposure for humans. Recent studies have shown adverse effects on brain development in children with prenatal

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4 Hua Zhang et al., In Inland China, Rice, Rather than Fish, Is the Major Pathway for Methylmercury Exposure, 118 Envtl. Health Persp. 1183 (2010).
6 See Jyrki K. Virtanen et al., Mercury, Fish Oils, and Risk of Acute Coronary Events and Cardiovascular Disease, Coronary Heart Disease, and All-Cause Mortality in Men in Eastern Finland, 25 Arteriosclerosis, Thrombosis, & Vascular Biology 228, 232 (2005).
8 National Center for Environmental Assessment, EPA, CASRN 22967-92-6, Methylmercury Chemical Assessment Summary at 1 (2001) [hereinafter “2001 Assessment Summary”].
10 2001 Assessment Summary, supra note 8, at 3.
11 IAP, supra note 9, at 6.
methylmercury exposures similar to or below the RfD.\textsuperscript{12} Neonatal studies conducted in the United States,\textsuperscript{13} Canada,\textsuperscript{14} Europe,\textsuperscript{15} China,\textsuperscript{16} and Japan\textsuperscript{17} have consistently found such low-level exposure to be associated with adverse neurobehavioral development. A study conducted in New Bedford, Massachusetts, reached similar conclusions regarding memory and learning, especially visual memory, in children.\textsuperscript{18}

Although many studies of methylmercury toxicity focus on prenatal exposure because fetal brains are developing and thus more vulnerable,\textsuperscript{19} the effects of adult exposures have also been documented. A key concern with exposure in adults is that it may accelerate age-related declines.\textsuperscript{20} Neurocognitive functions, especially fine-motor function and verbal memory, are compromised among adults who are exposed to elevated amounts of methylmercury, which is consistent with the outcomes observed in children with prenatal exposures.\textsuperscript{21}

To ensure that the reassessment reflects the current scientific understanding of the public health harms associated with methylmercury exposure, we recommend that the IRIS assessment take into account the following considerations.

\textsuperscript{12} Margaret Karagas et al., \textit{Evidence on the Human Health Effects of Low-level Methylmercury Exposure}, 120 Envtl. Health Persp. 799, 806 (2012).


\textsuperscript{14} Joseph L. Jacobson et al., \textit{Relation of Prenatal Methylmercury Exposure from Environmental Sources to Childhood IQ}, 123 Envtl. Health Persp. 827 (2015); Olivier Boucher et al., \textit{Prenatal Methylmercury, Postnatal Lead Exposure, and Evidence of Attention Deficit/Hyperactivity Disorder among Inuit Children in Arctic Quebec}, 120 Envtl. Health Persp. 1456 (2012).

\textsuperscript{15} Kristine Vejrup et al., \textit{Prenatal Mercury Exposure, Maternal Seafood Consumption and Associations with Child Language at Five Years}, 110 Env’t Int’l 71 (2018); Wieslaw Jedrychowski et al., \textit{Effects of Prenatal Exposure to Mercury on Cognitive and Psychomotor Function in One-Year-Old Infants: Epidemiologic Cohort Study in Poland}, 16 Annals Epidemiology 439 (2006).


\textsuperscript{18} Sara T.C. Orenstein et al., \textit{Prenatal Organochlorine and Methylmercury Exposure and Memory and Learning in School-Age Children in Communities Near the New Bedford Harbor Superfund Site, Massachusetts}. 122 Envtl. Health Persp. 1253 (2014).


\textsuperscript{20} Id.

I. THE IMPRECISION OF METHYLMERCURY EXPOSURE BIOMARKERS HAS RESULTED IN THE RFD FROM PAST ASSESSMENTS BEING TOO LOW

In establishing a new RfD, EPA should take into account that the 2001 RfD was based on an inflated benchmark dose as a result of imprecision in exposure biomarkers. The total imprecision of a biomarker includes both the effects of laboratory uncertainty as well as preanalytical sources of variation, such as “specimen sampling, storage, transportation, toxicokinetic variability, and related factors.” The benchmark approach conducted to derive the current exposure limits was based on standard regression analysis and failed to correct for such systematic exposure errors that can severely underestimate the toxicity of mercury. Exposures are typically measured with a margin of error that should be corrected for in analysis to achieve appropriate validity. Ignoring the measurement errors results in underestimation of exposure effects and overestimation of residual variance in regression models.

Budtz-Jørgensen et al. have demonstrated that the benchmark dose established by the 2000 NRC assessment and applied by the EPA was too high: they studied regression models under the assumption that exposure markers had non-differential error and found that the calculated benchmark doses were biased toward a less protective standard. Methods to account for measurement error in cord blood and maternal hair mercury concentrations were developed, and these calculations showed that the NRC’s recommended exposure level was about 50% higher than the imprecision-corrected limit. The calculation of the Budtz-Jorgensen et al. study was confirmed by another assessment of cord-blood parameter imprecision.

In light of the expanded insight provided by the scientific studies mentioned above, EPA should acknowledge the imprecisions in exposure measurements that have deflated the RfD level, and account for such biomarker imprecisions in the reassessment.

II. THE ASSESSMENT SHOULD TAKE INTO ACCOUNT GENETIC DIFFERENCES IN SUSCEPTIBILITY TO METHYLMERCURY TOXICITY

Increasing evidence points to the possibility that there are genetic differences in susceptibility to methylmercury toxicity. For example, a Korean birth cohort study showed that the effect of methylmercury toxicity on infant birth weight could be modified by maternal glutathione S-transferase and glutathione S-transferase T1 polymorphisms. Another study indicated that individuals with a particular variant of Apolipoprotein E (APOE) were more susceptible to methylmercury toxicity, and this variant was associated with poorer neurodevelopment of

24 Grandjean & Budtz-Jørgensen, supra note 22.
children at 2 years of age. Further, in a study that initially found no association between mercury exposure and child behavior, such an association was revealed when genetic susceptibility was considered. Researchers have also identified several other gene polymorphisms, including Apolipoprotein A (APOA), that might modify the impact of methylmercury on intelligence quotient (IQ) in children.

We support the inclusion of “explicit identification . . . of potentially susceptible populations” as one of the specific aims in the IAP and urge that EPA consider genetic susceptibility during its reassessment. EPA and the scientific community have increasingly recognized the importance of incorporating genetic susceptibility into risk assessment and regulatory decision-making. Because the RfD is an estimate “of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime,” the RfD value should by definition be set at a level sufficiently protective of vulnerable subpopulations. Ignoring variations in genetic susceptibility by averaging the impacts across different genetically-disposed subgroups could lead to a RfD that underestimates the risk faced by the most vulnerable subgroups. Thus, we recommend that EPA account for genetic susceptibilities both in setting the RfD and in deriving the dose response relationship for DNT outcomes.

III. THE ASSESSMENT SHOULD CONSIDER A VARIETY OF DNT OUTCOMES

The IAP identifies several DNT outcomes to be evaluated. We support EPA’s effort to study a variety of DNT outcomes, including cognitive function and behavioral, structural, and electrophysiological effects, when setting the RfD. We also agree with EPA that “the differences in DNT evaluation methods” should be a “key scientific issue” in the reassessment. Specifically, IQ is not the optimal neurobehavioral outcome measurement for DNT effects of methylmercury. Recent epidemiological data have revealed a suite of more sensitive neurodevelopmental effects than full-scale IQ. Even in 2000, the NRC report conceded that full-IQ was not the most sensitive indicator of neurodevelopment.

28 Ng et al., supra note 25.
29 Jordi Julvez et al., Prenatal Methylmercury Exposure and Genetic Predisposition to Cognitive Deficit at Age 8 Years, 24 Epidemiology 643 (2013).
30 IAP, supra note 9, at 9.
32 2001 Assessment Summary, supra note 8.
33 IAP, supra note 9, at 7.
IV. EPA SHOULD CONSIDER DEVELOPING AN RfD BASED ON CARDIOVASCULAR IMPACTS

Although the IAP recognizes cardiovascular effects as one of the potential health outcomes of methylmercury exposure, at this time EPA does not plan to assess the potential of methylmercury exposure to cause any health outcomes other than DNT. Because the scientific literature has established the link between methylmercury exposure and cardiovascular outcomes, we urge EPA to include cardiovascular effects in the reassessment.

High concentrations of methylmercury in blood and tissue samples have been strongly associated with acute coronary events, coronary heart disease, and cardiovascular disease.35 A 2000 NRC report stated that it was reasonable to conclude that methylmercury accumulates in the heart and leads to blood pressure alterations and abnormal cardiac functions.36

Subsequent research has strengthened these findings. An expert panel convened in 2011 to study the health effects of methylmercury concluded that there was sufficient scientific evidence to incorporate cardiovascular health benefits in EPA’s regulatory assessments.37 According to the panel, methylmercury is both directly linked to acute myocardial infarction and intermediary to impacts that contribute to myocardial infarction risk.38 The intermediary impacts include oxidative stress, atherosclerosis, decreased heart rate variability, and to a certain degree, blood pressure and hypertension. A 2017 systematic review of the association between methylmercury exposure and heart diseases showed that methylmercury enhances production of free radicals resulting in a long-lasting range of effects on cardiac parasympathetic activity, such as myocardial infarction, hypertension, blood pressure, and death.39 A 2018 meta-analysis of 29 studies found significant positive associations between methylmercury and both elevated blood pressure and hypertension.40

Additionally, the effect of prenatal methylmercury exposure on blood pressure is more pronounced among children with lower birth weights. Comparing boys who had a mercury cord blood concentration of 10 ug/L to those who had 1 ug/L, heart rate variability was found to decrease significantly by 47%.41

This evidence of the cardiovascular effects of methylmercury exposure warrants the inclusion of cardiovascular impacts in the IRIS assessment. Even if the cardiovascular impacts at the

35 See Virtanen et al., supra note 6, at 232.
36 NRC, supra note 34, at 168-69.
38 Id.
41 Nicolina Sørensen et. al., Prenatal Methylmercury Exposure as a Cardiovascular Risk Factor at Seven Years of Age, 10 Epidemiology 370 (1999).
individual level occur at higher levels of exposure than the DNT impacts, the society-wide harm of the former should not be ignored. Unlike DNT effects that primarily involve exposure of pregnant women and affect embryonic developments, cardiovascular outcomes of methylmercury could also impact adults through diet.

V. THE ASSESSMENT SHOULD ENSURE THAT CONFOUNDING DOES NOT LEAD TO AN UNDERESTIMATION OF THE HARMs OF METHYLMERCURY TOXICITY

EPA identifies confounding related to fish consumption as a key issue to consider during the reassessment. While we fully recognize the importance of fish consumption for neurocognitive development, we emphasize that exposure to methylmercury from fish is significant and can in some cases offset the health benefits of fish consumption.42

Human exposure to methylmercury occurs primarily through consuming fish in which methylmercury has bioaccumulated. While fatty acids in fish oil are recommended for cardiovascular health and neurocognitive development,43 the consumption of methylmercury in fish counteracts the health benefits associated with consumption of seafood,44 a finding confirmed by studies conducted in Boston45 and New York City.46 Since 2005, more than a dozen epidemiologic studies have associated adverse effects as large as or larger than beneficial effects of fish nutrients with greater-than-average methylmercury exposure from fish consumption.47 In fact, it can be difficult to consume the amount of fish recommended by the American Heart Association while simultaneously remaining below EPA’s mercury reference dose because of the high levels of mercury present in most fish.48 The inverse is also true: past studies analyzing the effects of methylmercury in the human body have underestimated the dangers because nutrients in fish can at least partially mask the true adverse effects of methylmercury.49 Although the mercury-related damage may be masked, the result is that the benefits that consumers would otherwise obtain from a healthy diet are diminished, thus counteracting the purpose of including fish in the diet.

The IAS is correct to characterize the nutritional benefits and the methylmercury harms from fish as confounded variables, and we are sympathetic to the position that fish intake should be

43 Oken et al., supra note 13.
44 Choi et al., supra note 42.
45 Oken et al., supra note 13, at 1177–79.
46 Lederman et al., supra note 13, at 1090.
encouraged because of its neurodevelopmental and general health benefits. However, considering the possible harmful effects of methylmercury exposure at the recommended level of fish consumption, EPA should not discount methylmercury exposure from fish intake when calculating the RfD, and should be mindful of the possible complexities created by the confounding effects when interpreting studies of methylmercury exposure from fish consumption. Moreover, lowering methylmercury exposure and increasing fish intake need not be conflicting goals. As Grandjean et al. pointed out in a recent letter, both goals can be achieved “if advice stresses choosing low-mercury seafood varieties.” As an additional concern, methylmercury exposures may already be elevated from ingestion of contaminated rice or rice products, such as rice crackers.

We are attaching to this letter the scientific literature cited herein and other relevant studies. Thank you for your attention to these comments.

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