

ENVIRONMENTAL QUALITY AND HEALTH GOT MERC? REGULATING, MITIGATING AND LITIGATING MERCURY LEVELS FOR THE FISH WE EAT

Approaches of Public Health and Regulatory Agencies for Establishing Safe Levels of Exposure to Methylmercury

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I. BACKGROUND

Anthropogenic sources of mercury in the environment are primarily released from fossil-fuel power plants, especially coal-fired utility boilers. It is estimated that these plants release 40 tons of mercury annually in the United States.¹ Globally, coal-fired power plants and waste incinerators release about 1,500 tons of mercury annually.² Once introduced to the environment, the conversion of inorganic mercury to methylmercury occurs primarily in microorganisms especially in aquatic systems. Once in the methylated form, mercury bioaccumulates up the food chain; fish consume the microorganisms, and larger predatory fish consume the smaller fish (See Figure 1). But, mercury is not only found in fish but also other man-made materials, like dental amalgam. Thus, human exposure to mercury may be in the form of methylmercury *via* consumption of contaminated fish — particularly large predatory fish species such as tuna, swordfish, and shark³ - or as elemental mercury released from dental amalgam — which may contain approximately 50% mercury.⁴ In the absence of fish consumption, the mean concentration of mercury in whole blood is of the order of 5 – 10 mg/L (5 – 10 ppb);⁵ this concentration is likely due to dental amalgams, since inorganic mercury is not readily retained in the body compared to methylmercury and elemental mercury.⁶ Furthermore, human exposure to methylmercury from non-fish sources is very low.⁷

Once methylmercury is consumed, the estimated total body half-life is 70 – 80 days.⁸ Methylmercury is primarily eliminated from the body via feces (~90%) with the remainder excreted in the urine as mercuric mercury.⁹ Methylmercury that reaches the brain is slowly biotransformed to inorganic mercury, as is elemental mercury.^{10, 11} However, it is not clear whether the deleterious effects of methylmercury at the cellular level in the central nervous system are caused by methylmercury or its metabolite.¹² If the toxicity of

1. National Research Council (NRC), *Toxicological effects of methylmercury*, 1, 1 (2000), <http://www.nap.edu/books/0309071402/html/>.

2. M. Cone, *High levels of toxin seen at 9 chlorine plants*, LOS ANGELES TIMES A20, (January 26, 2005).

3. NRC, *supra* note 6, at 13.

4. *Id.* at 41.

5. *Id.*

6. *Id.*

7. *Id.*

8. *Id.* at 50.

9. *Id.* at 49.

10. *Id.* at 52.

11. *Id.* at 56.

12. *Id.* at 56-57.

methylmercury is in fact due to its inorganic metabolite, then the risks of toxicity from mercury from fish and dental amalgams may be cumulative.¹³

The deleterious effects of methylmercury on the central nervous system were tragically revealed with the mass poisonings that occurred in Minamata Bay, Japan in the 1950s and 1960s and Iraq in 1974.¹⁴ Both of these mass poisonings were attributed to the consumption of methylmercury either from fish that fed on microorganisms tainted with mercury-laden industrial effluent or grain dusted with methylmercury as a fungicide, respectively.¹⁵ These tragedies revealed the susceptibility of both the adult and fetal brain to methylmercury, although the developing nervous system was shown to be more sensitive.¹⁶ Differences in susceptibility have also been observed based on gender. For instance, in the Iraqi epidemic, neurological sequelae were observed with three times as many females as males.¹⁷ Opposite gender-specific effects have been noted among infants and children with males exhibiting greater effects than females.¹⁸ Moreover, the clinical manifestations of methylmercury-induced neurotoxicity varied with the degree of exposure and the age of the victims.¹⁹ In adults, the most prominent sites of injury were to areas of the brain controlling vision and voluntary muscle control.²⁰ In children, especially those exposed *in utero*, the damage to the central nervous system was widespread and resulted in mental retardation and paralysis.^{21 22}

13. *Id.* at 57.

14. D. C. Anthony et al., CASARETT & DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS, 544 (Curtis D. Klaassen ed., 6th ed., McGraw-Hill 2001).

15. *Id.*

16. NRC, *supra* note 6, at 53.

17. *Id.* at 74.

18. *Id.*

19. Anthony et al., *supra* note 19, at 544.

20. *Id.* (Massive degeneration to the neurons of the visual cortex and the small internal granular cell neurons of the cerebellar cortex lead to blindness and marked ataxia, respectively.)

21. *Id.*

22. L. G. Costa et al., *Developmental neuropathology of environmental agents*, 44 ANNU. REV. PHARMACOL. TOXICOL. 87, 88 & 90 (2004). (The susceptibility of the developing brain is based on the timing of neuronal development, the rapid growth that occurs in the third trimester and early infancy, and the lack of a protective barrier early in life. In the cerebellum, Purkinje cells develop early, weeks 5-7 in humans, whereas granule cells are generated much later, gestational weeks 24-40 in humans. The developing brain is distinguished by the absence of a blood-brain barrier. The development of this barrier is a gradual process, beginning *in utero* and complete at approximately six months of age. Because the blood-brain barrier limits the passage of substances from blood to brain, in its absence, toxic agents can freely enter the developing brain.)

Due to the public health concerns over levels of methylmercury and adverse health effects, several studies have been conducted to monitor the levels of methylmercury in readily obtainable samples. Typically, monitoring for methylmercury is performed using scalp hair, blood, or both.²³ Methylmercury incorporated into hair can serve as a historical record by comparing the segment of growth with an approximated time period of exposure.²⁴ About 90% of the mercury present in hair is in the form of methylmercury; however, external deposition of mercury compounds can pose one source of error, and requires adequate washing of the hair sample to minimize this source or error.²⁵ During late gestation, the level of mercury in umbilical cord blood is expected to most closely correlate with fetal-brain mercury concentrations, although umbilical cord blood is expected not to correlate as well with mercury intake compared to maternal hair mercury concentration.²⁶

Three large epidemiological studies have been conducted in populations that consume fish as a regular part of their diets. Two of these studies, one conducted in the Faroe Islands²⁷ and one in New Zealand²⁸, found an association between prenatal exposure to methylmercury and decrements in tests used to measure neurological development; however, a third major study conducted in the Seychelles Islands²⁹ did not find an adverse association.³⁰ These studies have formed the basis for establishing safe levels of exposure to methylmercury. However, controversy has shrouded this process because of the studies selected (*e.g.*, Faroe Islands versus Seychelles Islands) and the levels of uncertainty applied to deriving safe levels by different agencies. This article will provide an overview of the most frequently used studies for deriving safe levels of methylmercury and will address the process used by different agencies in study selection and addressing areas of uncertainty.

23. NRC, *supra* note 6, at 38.

24. *Id.*

25. *Id.*

26. *Id.* at 7.

27. Group of islands between the Norwegian Sea and the North Atlantic Ocean; geographic coordinates: 62° 00' N, 7° 00' W.

28. Island country located in the South Pacific Ocean, southeast of Australia; geographic coordinates: 36° 51' S, 174° 46' E.

29. Group of islands in the Indian Ocean, northeast of Madagascar; geographic coordinates: 4° 35' S, 55° 40' E.

30. NRC, *supra* note 6, at 4.

II. EPIDEMIOLOGY STUDIES USED BY DIFFERENT AGENCIES

In evaluating the adverse health effects due to prenatal (*in utero*) exposure to methylmercury for the establishment of a reference dose, three major study cohorts are often cited: the Faroe Islands birth cohort, Seychelles Child Development Study (SCDS), and a study focusing on a sample of children from New Zealand. These longitudinal studies³¹ all focus on prenatal exposure to methylmercury *via* fish and marine animal consumption by pregnant women. Methylmercury levels have also been measured in different populations worldwide including pregnant women in the Madeira Islands (Portugal),³² residents around the St. Lawrence River Basin (Quebec, Canada),³³ and mother-infant pairs along the Upper Madeira River (Brazil)³⁴ and Mancora (Peru).³⁵ Additionally, reports have been cited on high-level exposures to methylmercury in Iraqi children, residents of Minamata Bay (Japan), and in animal studies. However, the Faroe Islands, Seychelles, and New Zealand studies are preferred by regulatory agencies for determining safe levels of exposure because they are more reflective of low-level exposures to methylmercury that may occur in the general population.

Briefly, the Faroe Islands cohort study consisted of 1,022 births assembled between 1986 and 1987. Prenatal exposure was measured by cord blood³⁶ collected at birth with subsequent methylmercury exposure measured *via* hair samples collected from children at ages 7 and 14 years. In the most recent assessment,³⁷ at age 14 years, 878 of the children from the original cohort were evaluated for neurodevelopment effects.³⁸ Study findings were consistent with a previous evaluation³⁹ — of the same cohort at age

31. A study in which an individual or group of individuals is followed over a period of time to discover changes that may be attributable to exposure in the form of a treatment or environment, or influenced by maturation.

32. A. Renzoni et al., *Mercury levels along the food chain and risk for exposed populations*, 77 ENVIRON. RES. 68, 68-72 (1998).

33. K. R. Mahaffey & D. Mergler, *Blood levels of total and organic mercury in residents of the upper St. Lawrence River Basin, Quebec: association with age, gender, and fish consumption*, 77 ENVIRON. RES. 104, 104-14 (1998).

34. A. A. P. Boischio & E. Cernichiari, *Longitudinal hair mercury concentration in riverside mothers along the Upper Madeira River (Brazil)*, 77 ENVIRON. RES. 79, 79-83 (1998).

35. D. O. Marsh et al., *Fetal methylmercury study in a Peruvian fish-eating population*, 16 NEUROTOXICOLOGY 717, 717-26 (1995).

36. Also referred to as umbilical cord blood; blood collected from the umbilical cord of a fetus or newborn.

37. K. Murata et al., *Delayed brainstem auditory evoked potential latencies in 14-year-old children exposed to methylmercury*, 144 J. PEDIATR. 177, 177-83 (2004).

38. Details of the rationale for exclusion of the remainder of the original cohort were not provided.

39. P. Grandjean et al., *Cognitive performance of children prenatally exposed to "safe" levels*

7 years — that claim prenatal exposure to methylmercury may result in neurotoxic effects as indicated by prolonged III-IV interpeak latencies.⁴⁰

The SCDS originally enrolled 779 mother-infant pairs from 1989 to 1990 with maternal hair samples collected at time of birth to determine the level of prenatal methylmercury exposure.⁴¹ Children were enrolled into the study at six months of age with evaluations of neurodevelopmental effects performed at ages 0.5, 1.3, 2.4, 5.5, and 9 years. The most recent evaluation⁴² of this cohort of 643 children at age 9 years,⁴³ reported an association with decreased performance in the grooved pegboard test using the non-dominant hand in males, and improved scores on the hyperactivity index of the Conner's teacher rating scale - both tests are designed to detect neurodevelopmental deficits. These findings are consistent with previous studies⁴⁴ in this cohort in which the results do not provide evidence to support an association between prenatal exposure to methylmercury and neurodevelopmental effects.

The New Zealand study compared children of mothers with high hair mercury levels (> 6 ppm) during pregnancy with children whose mothers had lower hair mercury levels.⁴⁵ Hair samples were collected from 10,970 new mothers between 1977 and 1978. Sixty-one children with mothers that originally reported high fish consumption and had high hair mercury levels, were matched with three controls each, at 6-7 years, to evaluate the potential neurodevelopmental effects of methylmercury exposure from maternal fish consumption. A statistical association was found between high prenatal exposure and decreased neurodevelopment test performance.

of methylmercury, 77 ENVIRON. RES. 165, 165-72 (1998).

40. Brainstem auditory evoked potential (BAEP) is measured by a four-channel electromyograph with peaks used to reflect volume-conducted electric activity from the acoustic nerve (Peak I), pons (Peak III), and midbrain (Peak IV). Peak latencies correspond to the conduction time from the retina to the visual cortex.

41. Exposure was determined by assuming a hair growth rate of 1.1 cm/month and a delay of 20 days between current blood concentrations and appearance of mercury in the first cm of scalp hair.

42. G. J. Myers et al., *Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study*, 361 LANCET 1686, 1686-92 (2003).

43. Of the original 779 children, 717 (92%) were still eligible at age 9 years. Of the eligible children an additional 74 children were not tested with details of exclusion not provided. Final sample size: 643 children.

44. P. W. Davidson et al., *Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: outcomes at 66 months of age in the Seychelles Child Development Study*, 280 JAMA 701, 701-7 (1998).

45. K. S. Crump et al., *Influence of prenatal mercury exposure upon scholastic and psychological test performance: benchmark analysis of a New Zealand cohort*, 18 RISK ANAL. 701, 701-13 (1998).

Findings from these cohorts and subsequent extrapolations of reference doses for methylmercury, especially between the Faroe Islands studies and the Seychelles studies, have been controversial. The crux of controversy has been the discrepancy in findings between the two studies, *i.e.*, studies from the Faroe Islands cohort have found an association between prenatal methylmercury exposure and neurodevelopmental effects in children, while studies rooted in the Seychelles cohort do not support this hypothesis. A side-by-side comparison of findings from these cohorts is not a straightforward process, as the study logistics for each cohort differs in a marker for prenatal exposure and measurement of neurodevelopmental effects as well as a number of other confounding factors.⁴⁶ In the assessment of neurodevelopmental effects, a series of tests are performed to evaluate neurocognitive and behavioral function as well as language, memory, motor and perceptual motor skills (Table 1).

As the two main studies, *i.e.*, the Faroe Island and Seychelles studies, are longitudinal in design, they are both subject to the same general shortcomings such as the lack of a proper comparison group, as all persons in the studies had some level of exposure to methylmercury. To obtain a more accurate reflection of the true relationship between methylmercury exposure during pregnancy and neurological development, a proper comparison group is necessary. Ideally, the comparison group would be as similar as possible to the exposed mother-child pairs with the exception of being exposed to methylmercury. Such a comparison group would rule out cases with neurodevelopmental effects that were independent to methylmercury exposure and adjust for factors such as level of fish consumption, socioeconomic status, and demographics.

Some of the specific issues relating the Faroe Islands and Seychelles cohorts are outlined in Table 2. Among these is the use of cord blood and maternal hair samples as markers of prenatal exposure. In studies of methylmercury exposure in Minamata, Japan, where prenatal effects from ingestion of mercury-contaminated fish was first recognized, umbilical cord samples were used to estimate exposure. Such samples were attainable because of the Japanese tradition to keep part of the umbilical cord after birth.⁴⁷ It should be noted that data derived from the Japanese cohort is thus subject to bias, as only mothers that practiced the tradition and were willing to participate in the study were included.

46. An unknown or unaccounted factor in a study that may cause bias.

47. H. Akagi et al., *Methylmercury dose estimation from umbilical cord concentrations in patients with Minamata disease*, 77 ENVIRON. RES. 98, 98-103 (1998).

Cord blood samples, collected at birth, served as the prenatal biomarker for estimating methylmercury exposure in the Faroe Islands studies. Cord blood use is criticized because of its 50-day half-life and the inability to adequately measure methylmercury exposure that might result from binge eating during the first trimester of pregnancy.⁴⁸ Maternal hair samples, as used in the Seychelles studies, have been frowned upon due to the uncertainty of the dose that may be delivered to the fetus⁴⁹ and the lack of evidence to confirm that such samples are adequate biomarkers for *in utero* exposure. Maternal hair sample use is further scrutinized because the Seychelles studies have, thus far, failed to produce evidence to support the notion of neurodevelopmental risk from prenatal exposure to methylmercury.⁵⁰ Currently, there is no consensus on the most appropriate biomarker for assessing prenatal exposure to mercury.

Another major controversial issue between the Faroe Islands study and the SCDS is the form of methylmercury exposure. Methylmercury exposure among Seychellois is primarily *via* ingestion of contaminated fish. The most recent study of this population found a positive association between methylmercury exposure and better performance on one of the neurodevelopmental tests.⁵¹ This finding could be a confounder in which increased methylmercury exposure serves as a marker for increased fish consumption and better nutrition. Proponents of the Seychelles studies claim that the predominant exposure to methylmercury is *via* fish consumption, and thus the study findings are more reflective of potential health events in the general population. In addition to fish consumption, whale meat and blubber comprise a significant proportion of the Farose diet. Whale meat and blubber have been found to have higher levels of methylmercury (up to 3 ppm).⁵² A further confounder with consumption of whale meat is the exposure to other environmental contaminants such as PCBs and dioxins,⁵³ both of which have potential for adverse human health effects, including developmental neurotoxicity.^{54 55}

48. D. R. Palumbo et al., *Association between prenatal exposure to methylmercury and cognitive functioning in Seychellois children: a reanalysis of the McCarthy Scales of Children's Ability from the main cohort study*, 84 ENVIRON. RES. 81, 81-8 (2000).

49. Grandjean et al., *supra* note 44.

50. Myers et al., *supra* note 47.

51. Murata et al., *supra* note 42.

52. Palumbo et al., *supra* note 53, at 87.

53. *Id.*

54. G. Winneke et al., *PCB-induced neurodevelopmental toxicity in human infants and its potential mediation by endocrine dysfunction*, 181-182 TOXICOLOGY 161, 161-165 (2002).

55. M. Kakeyama & C. Tohyama, *Developmental neurotoxicity of dioxin and its related compounds*, 41 IND. HEALTH 215, 215-230 (2003).

The issues raised in discussing the most cited reports from the Faroe Islands and Seychelles studies, in conjunction with the discrepancies in comparative diets, possibly containing other contaminants, add to the uncertainty in determining a safe level of methylmercury in the diets of pregnant or lactating women and have been addressed with various approaches from different agencies for the establishment of safe levels of exposure.

III. HEALTH ASSESSMENTS FOR METHYLMERCURY

The recommended acceptable levels of methylmercury exposure by federal and state governments as well as by international organizations are summarized in Table 3. Two federal agencies are responsible for regulating mercury in the United States. The U.S. Environmental Protection Agency (U.S. EPA) monitors mercury levels in the environment and regulates industrial releases to the environment. The U.S. Food and Drug Administration (U.S. FDA) ensures levels of mercury in commercially sold seafood and fish do not exceed its action level. In addition, the U.S. FDA also regulates the use of mercury compounds in the cosmetics industry. The U.S. Agency of Toxic Substances and Disease Registry (U.S. ATSDR), although not a regulatory agency, also assesses the health effects of environmental pollutants.

The U.S. EPA derived the reference dose (RfD) for methylmercury using a series of benchmark dose analyses by the National Research Council (NRC) of the National Academy of Sciences.⁵⁶ Three longitudinal prospective studies were evaluated and adverse effects were identified in the Faroe Islands and the New Zealand studies but not in the Seychelles study. U.S. EPA evaluated all three studies for the purpose of deriving an RfD. That is, they were all considered as critical (principal) and supporting studies. U.S. EPA defines a critical (principal) study as the study that contributes most significantly to the qualitative and quantitative assessment of risk, and supporting studies as those studies that contain information that are useful for providing insight and supporting conclusions.⁵⁷

The RfD was derived based on developmental neurological abnormalities in human infants. A summary of this derivation is available in several public domains.⁵⁸ Briefly, five endpoints from

56. U.S. EPA, *Methylmercury (MeHg) (CASRN 22967-92-6)* (2001), <http://www.epa.gov/iris/subst/0073.htm#bib>.

57. U.S. EPA, <http://www.epa.gov/iris/gloss8.htm#c>. (Critical Study: The study that contributes most significantly to the qualitative and quantitative assessment of risk. Also called Principal Study.)

58. U.S. EPA, <http://www.epa.gov/IRIS/subst/0073.htm>; See also: Rice et al., *Methods and*

the Faroe Islands study were performed by benchmark dose analysis (BMD) to converge potential RfDs of 0.1 µg/kg-day, as did the integrative analysis of all three studies. The endpoint is defined by U.S. EPA as an observable or measurable biological event or chemical concentration (*e.g.*, metabolite concentration in a target tissue) used as an index of an effect of a chemical exposure.⁵⁹ A total uncertainty factor of 10 was applied for intrahuman toxicokinetic⁶⁰ and toxicodynamic⁶¹ variability and uncertainty. The uncertainty (or variability) factor is defined as “one of several, generally 10-fold, default factors used in operationally deriving the RfD and RfC from experimental data. The factors are intended to account for (1) variation in susceptibility among the members of the human population (*i.e.*, interindividual or intraspecies variability); (2) uncertainty in extrapolating animal data to humans (*i.e.*, interspecies uncertainty); (3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (*i.e.*, extrapolating from subchronic to chronic exposure); (4) uncertainty in extrapolating from a lowest observed adverse effect level (LOAEL) rather than from a no observed adverse effect level (NOAEL); and (5) uncertainty associated with extrapolation when the database is incomplete.⁶² In more details, benchmark doses (BMDs) were calculated for a number of endpoints for all three studies and the lower limit on the 95% confidence interval of the BMD (the BMDL) was calculated accordingly. In other words, a benchmark response (BMR) of 0.05 was chosen which could result in a doubling of the number of children with a response at or below the 5th percentile in an unexposed population. By U.S. EPA definition, BMR is an adverse effect, used to define a benchmark dose from which an RfD (or RfC) can be developed. The change in response rate over background of the BMR is usually in the range of 5-10%, which is the limit of responses typically observed in well-conducted animal experiments. These⁶³ BMDLs were considered as potential points of departure (PODs), as for a NOAEL for example,

rationale for derivation of a reference dose for methylmercury by the US EPA, 23 RISK ANAL. 107, 107-115 (2003).

59. U.S. EPA, <http://www.epa.gov/iris/gloss8.htm#e>. (Endpoint: An observable or measurable biological event or chemical concentration [*e.g.*, metabolite concentration in a target tissue] used as an index of an effect of a chemical exposure.)

60. U.S. EPA, <http://www.epa.gov/iris/gloss8.htm#t>. (Toxicokinetics: The determination and quantification of the time course of absorption, distribution, biotransformation, and excretion of chemicals [sometimes referred to as pharmacokinetics]).

61. *Id.* (Toxicodynamics: The determination and quantification of the sequence of events at the cellular and molecular levels leading to a toxic response to an environmental agent [sometimes referred to as pharmacodynamics]).

62. U.S. EPA, <http://www.epa.gov/iris/gloss8.htm#u>.

63. U.S. EPA, <http://www.epa.gov/iris/gloss8.htm#b>.

for the RfD derivation. POD is “the dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD), or a NOAEL or LOAEL for an observed incidence, or change in level of response.

The California Environmental Protection Agency (CalEPA) developed Proposition 65 (Safe Drinking Water and Toxic Enforcement Act of 1986) safe harbor levels no significant risk levels (NSRLs) for carcinogens and maximum allowable daily levels (MADLs) for chemicals that cause developmental and reproductive toxicity.⁶⁴ The MADL is the level at which the chemical would have no observable adverse reproductive effect assuming exposure at 1,000 times that level. The NSRLs and MADLs are promulgated in Title 22, California Code of Regulations, (CCR) Sections 12705 and 12805, respectively, to assist interested parties in determining whether discharges to sources of drinking water are prohibited. For the purpose of Proposition 65, a NOEL of 5 µg/kg-day was derived based on an animal study. The dose level was calculated by multiplying the selection NOEL by the assumed female human body weight of 58 kilogram per CCR 12803. (a)(7)(b). Using the NOEL, the MADL microgram per day dose level was calculated to be 290.⁶⁵ To derive the Proposition 65 MADL, the converted NOEL was derived by a scientifically undefined factor of 1,000. Using the 290 µg/day NOEL, the MADL for methylmercury was calculated to be 0.3 µg/day, for both oral and inhalation routes of exposure.

The U.S. FDA established the action level of 1 ppm for methylmercury in the edible portion of fish. The level was established to limit consumers' methylmercury exposure to levels 10 times lower than the lowest levels associated with adverse effects (paresthesia) observed in the poisoning incidents.

The U.S. ATSDR chronic oral minimal risk level (MRL) of 0.3 µg mercury/kg-day was based on the neurodevelopmental effects in a study where children were exposed *in utero* to methylmercury from maternal fish consumption. In more detail, the MRL is based on the results of the SCDS, which followed over 700 mother-infant pairs and tested from parturition through 66 months of age (however, more recent data on this cohort is now available).⁶⁶ The SCDS testing used maternal hair mercury as the index of fetal exposure. Developing fetuses were exposed *in utero* through maternal

64. *Id.*

65. M. Bornhausen et al., *Operant behavior performance changes in rats after prenatal methylmercury exposure*, 56 TOXICOL. APPL. PHARMACOL. 305, 305-310 (1980).

66. Davidson et al., *supra* note 49; U.S. Agency of Toxic Substances and Disease Registry (U.S. ATSDR), 509 (1999), <http://www.atsdr.cdc.gov/toxprofiles/tp46.html>.

consumption of fish before and during pregnancy. None of the tests in the study indicated an adverse effect of methylmercury. Hence, the highest exposure in the study (1.3 $\mu\text{g}/\text{kg}\text{-day}$) is considered a NOAEL by U.S. ATSDR and formed the basis for derivation of the chronic oral MRL for methylmercury. An aggregate uncertainty factor of 4.5 was based on three components with two being interrelated and the other being independent. The two interrelated values were added to give a composite uncertainty factor of three, *i.e.*, $1.5 + 1.5 = 3.0$, to account for the full range of variability (including human pharmacokinetic and pharmacodynamic variability) to be conservative. The independent factor of 1.5, which was used to address the domain-specific findings, as in the Faroe study but not in the SCDS study, was then multiplied by the aforementioned uncertainty factor of three (for uncertainty attributable solely to the SCDS) to yield an uncertainty factor of 4.5. Thus, the chronic oral MRL for methylmercury was set at $0.3 \mu\text{g}/\text{kg}\text{-day}$ ($1.3 \mu\text{g}/\text{kg}\text{-day} / 4.5 \text{ (UF)} = 0.3 \mu\text{g}/\text{kg}\text{-day}$).

A meeting of the Joint Food and Agriculture Organization of the United Nations/WHO Expert Committee on Food Additives (JECFA) was held in Rome, Italy, from 10 to 19 June 2003. The committee established a Provisional Tolerable Weekly Intake (pTWI) based on two epidemiological studies (Faroe Islands birth cohort and SCDS) that investigated the relationship between maternal exposure to mercury and impaired neurodevelopment in their children. The committee considered the update pTWI of $1.6 \mu\text{g}/\text{kg}\text{-week}$ (see below for previous pTWI information) sufficient to protect the developing fetus, the most sensitive subgroup of the population. For pTWI derivation, a steady-state intake of $1.5 \mu\text{g}/\text{kg}\text{-day}$ was estimated to represent the exposure that would be without appreciable adverse effects in children, and a total uncertainty factor of 6.4 (2×3.2) was applied. Detailed descriptions regarding how the steady-state intake and uncertainty factors were calculated and decided, respectively, are provided in Table 3. It should be noted that the JECFA previously derived a pTWI of $3.3 \mu\text{g}/\text{kg}$ body weight per week (JECFA June 1999 meeting), and the NRC established an intake limit of $0.7 \mu\text{g}/\text{kg}$ body weight per week.

The Canadian provisional tolerable daily intakes (pTDIs) are based on the previous JECFA pTWI in adults of $3.3 \mu\text{g}/\text{kg}$ body weight per week (June 1999 JECFA meeting). For adults, a pTDI of $0.5 \mu\text{g}/\text{kg}\text{-day}$ ($3.3 / 7.0$) was recommended. And for women of childbearing ages and children, a pTDI of $0.2 \mu\text{g}/\text{kg}\text{-day}$ was based on a qualitative assessment of available data.

IV. CONCLUSIONS

Public health-based risk guidance numbers are traditionally developed by selecting a critical study that is relevant with regards to exposure levels and sources of exposure to the population of concern. Epidemiological studies that are well-designed and executed, are preferable to animal studies. Additionally, studies that identify the most sensitive or conservative measure (*e.g.*, the NOAEL, LOAEL, or BMDL) provide public health and regulatory agencies with the greatest confidence in developing safe levels of exposure.⁶⁷

As discussed in Section III, different agencies have used different studies for calculating their respective safe level values for methylmercury. For example, CalEPA utilized an animal study, whereas the U.S. ATSDR chose a longitudinal epidemiology study. It is likely, however, that CalEPA will update their value given the body of information available on human subjects, *i.e.*, the Faroe Islands, Seychelles, and the New Zealand studies (personal communications). These studies contribute a substantial amount of knowledge to understanding the effects of chronic low-level methylmercury exposures.

The similarities and differences between the Faroe Islands and Seychelles studies have stirred much debate as to which is more appropriate as a critical study. For instance, maternal exposure levels to methylmercury are similar in both studies, yet the disparate findings may be reflective of differences in cohort characteristics or differences in study design. Further items of controversy include differences in the pattern of exposure and co-exposures to other neurodevelopmental toxicants in the Faroe Islands cohort (*i.e.*, PCBs). Though it has been deemed a shortcoming in the Faroe Islands cohort, it is interesting to note that one re-analysis of this data found an association between mercury exposures and language and verbal deficits, regardless of PCB level.⁶⁸

Despite the aforementioned differences, these studies, as compared to the high-level exposures observed in the Iraqi outbreak and the disaster in Japan, represent exposure scenarios that are more consistent with potential exposure in the United States.⁶⁹ However, the differences present a distressing choice when choosing a critical study, applying uncertainty factors, and establishing a safe level of exposure. Though the Seychelles study is well designed and

67. NRC, *supra* note 6.

68. Winneke et al., *supra* note 59.

69. NRC, *supra* note 6, at 312-313.

it is possible to derive a lower limit approximation of a NOAEL or BMD, the choice of a negative study to derive guidance numbers when well-designed positive studies are available would be contrary to the conservative nature of risk assessment guidelines. In addition, there is no consensus in the application of uncertainty factors within agencies in the United States or worldwide. Scientific policy judgment governs the selection and application of uncertainty factors, and ultimately the calculation of risk-management guidance numbers.

In summary, a conservative approach in establishing guidance numbers for methylmercury is warranted because the time at which neurological damage might manifest is uncertain, and thus may appear later in life in those children who display modest changes in neuropsychological performance tests. The issue of "silent" neurotoxicity is similar to that of carcinogenicity; whereby a chemical-exposure may seem to be innocuous over many decades, yet ultimately result in the development of cancer. Because of this, the basic tenet of risk assessment must be followed in that the values established by regulatory and public health agencies protect, rather than predict adverse neurodevelopmental outcomes.⁷⁰

70. Costa et al., *supra* note 27, at 99.

V. FIGURES

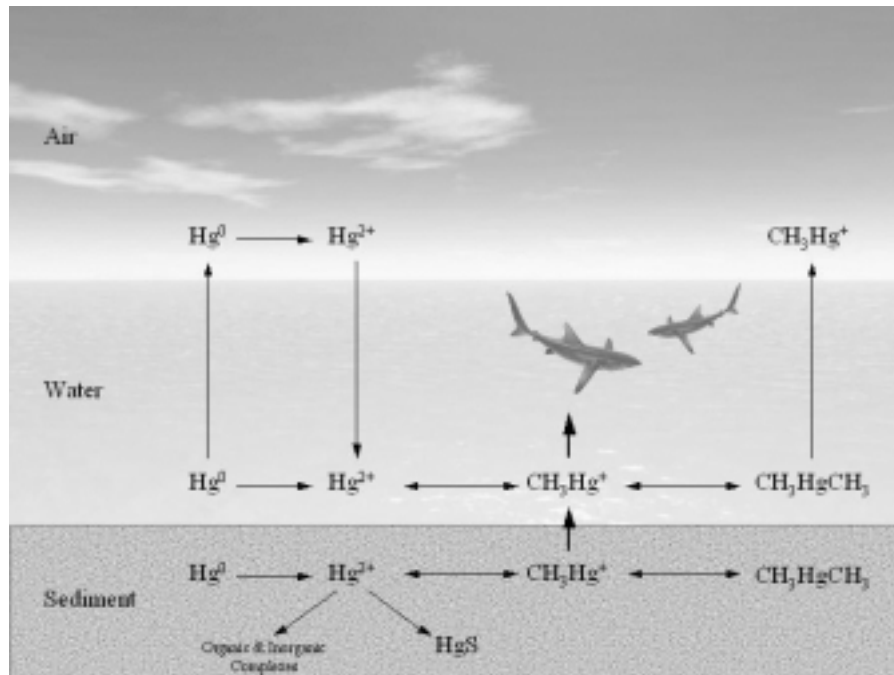


Figure 1. Fate and Transport of Mercury in the Environment. Mercury has three valence states (elemental mercury, Hg^0 ; mercurous mercury, Hg^{1+} ; and mercuric mercury, Hg^{2+}). Metallic mercury and various inorganic and organic complexes can be found in the environment. Degassing of elemental mercury occurs at the surface of soils and bodies of water. Once in the environment, the interconversion of different species of mercury can occur («). Mercuric mercury can be converted to insoluble complexes of mercury sulfide (HgS) or into methylmercury (CH_3Hg^+) and dimethylmercury (CH_3HgCH_3) by microorganisms in aquatic systems. The microorganisms may then be consumed by fish, which are consumed by larger fish, and eventually by large predatory fish, like shark. This results in an accumulation of methylmercury up the food chain.

71. NRC, *supra* note 6, at 17.

VI. TABLES

TABLE 1. OVERVIEW OF STUDY COHORTS IN SEYCHELLES, FAROE ISLANDS AND NEW ZEALAND

	Seychelles (SCDS) ⁷²	Faroe Islands ⁷³	New Zealand ⁷⁴
Size of original cohort	779 mother-infant pairs	1022 births	237 children ^a
Exposure	Fish and shellfish	Whole meat and blubber, fish and shellfish	Fish and shellfish
Measurement of prenatal exposure	Concentration of MeHg in maternal hair collected upon delivery	Concentration of MeHg in cord blood	Concentration of MeHg in maternal hair
Level of prenatal exposure	Mean (SD): 6.9 ppm (4.5 ppm)	Up to 174 µg/L	Range: 0 mg/kg - > 6 mg/kg
Measurement of neurodevelopmental effects	Series of tests including: <ul style="list-style-type: none"> • CBCL • CTBS hyperactivity index • Finger tapping • Grooved pegboard • VMI • W-J applied problems • WJ letter/word recognition 	Series of tests including: <ul style="list-style-type: none"> • Bender copying errors • Reinstem latency measurements • Boston naming test • CFT reaction time • CVLT: delayed recall • Finger tapping 	Series of tests including: <ul style="list-style-type: none"> • TOLD language development • McCarthy perceptual performance • McCarthy motor test • WISC-R: Performance IQ • WISC-R: Full-scale IQ
Children age at assessment	5.5 years, 9 years	7 years, 14 years	4 years, 6-7 years
Exclusion	Mothers and children with disorders highly associated with adverse neurodevelopment, e.g., epilepsy, traumatic brain injury etc.	Children with neurological disorders thought to be independent of MeHg exposure, e.g., epilepsy, Tourette syndrome etc.	Not listed

CBCL = children's behavior checklist; CFT = Neurobehavioral Evaluation System (NES); Conners Performance Test; CTBS = Conners Teachers Rating Scale; CVLT = California Verbal Learning Test; IQ = intelligence quotient; MeHg = methylmercury; ppm = parts per million; SD = standard deviation; TOLD = test of language development; VMI = visual motor integration; W-J = Woodcock-Johnson test of achievement; WISC-R = Wechsler Intelligence Scale for Children-Revised. ^aChildren of mothers with MeHg hair levels > 6 ppm and reported high fish consumption were matched with children of mothers with lower MeHg hair levels.

72. Myers et al., supra note 47.
73. Murata et al., supra note 42
74. Crump et al., supra note 50.

TABLE 2. SHORTCOMINGS AND ADDITIONAL ISSUES LEADING TO DISCREPANCIES IN THE SEYCHELLES AND FAROE ISLAND STUDIES

Study	Shortcomings and Additional Issues
Faroe Islands cohort ^{75, 76} ,	<p>Consumed whale meat and blubber, in addition to fish and shellfish. MeHg level in cord blood used as prenatal exposure measurement. Socioeconomic status might influence study findings. Advisory issued to pregnant women about fish consumption and pregnancy - fish consumption may be lower as a result. Unadjusted/ unmeasured confounders (details not mentioned). Exposure to other pollutants including PCBs and dioxins due to consumption of whale meat. 50-day half-life of cord blood may influence MeHg level detected. Binge eating during 1st trimester may not be reflected by cord blood.</p>
SCDS ^{77, 78} ,	<p>Primarily consumed fish and shellfish. MeHg level in maternal hair as prenatal exposure measurement. Socioeconomic status might influence study findings. Demographics of high and low consumers not provided. Length of breastfeeding not addressed. Nutritional practices, housing and lifestyle may influence study findings. Fish consumption might be a confounder - may serve as a marker for nutrition. Sequelae may not have manifested at the age children were evaluated (younger age than Faroe cohort). Cellular mechanisms that detoxify methylmercury may differ in mammals Recall bias about information relation to pregnancy, birth and feedings due to children enrollment at age 6 months.</p>

MeHg = Methylmercury.

75. Grandjean et al., supra note 44.

76. Murata et al., supra note 42

77. Myers et al., supra note 47.

78. Davidson et al., supra note 49.

TABLE 3. SUMMARY OF HEALTH ASSESSMENTS FOR METHYLMERCURY

Agency	Critical Effects	Point of Departure	Uncertainty/Safety Factor	Uncertainty parameters/factors	Chronic Acceptable Level	
U.S. EPA	Developmental neuropsychological impairment	BMD ⁷⁹ ; BMDL ₀₅ ⁸⁰ range of maternal daily intake: 0.857-1.472 µg/kg-day ⁸¹	10	intrahuman toxicokinetic; toxicodynamic variability; uncertainty (3 for each).	RfD ⁸² : 0.1 µg/kg-day	Grandjean et al. (1997) ⁸³
California EPA	Developmental effects	NOEL ⁸⁴ : 5 µg/kg-day	1000	Not an uncertainty factor but used for MADL per California Code of Regulation 12801. (b)(1) ⁸⁵	MADL: 0.3 µg/day ⁸⁶	Bornhausen et al. (1980) ⁸⁷
U.S. FDA	Overt neurological symptoms in adults ⁸⁸	LOAEL: 4.3 µg/kg-day ⁸⁹	10 ⁹⁰		Action level in fish, 1 ppm in edible portion (equivalent to 0.5 µg/kg-day) ⁹¹	
U.S. ATSDR JECFA ⁹⁶	Developmental neurotoxicity ⁹² Impaired neurodevelopment from <i>in utero</i> exposure ⁹⁷	NOAEL: 1.3 µg/kg-day ⁹³ Average of NOEL and BMD: 1.5 µg/kg-day ⁹⁸	4.5 ⁹⁴ 6.4 ⁹⁹		MRL: 0.3 µg/kg-day ⁹⁵ pTWI: 1.6 µg/kg-week (equivalent to 0.2 µg/kg-day) ¹⁰⁰	
Health Canada	Developmental neurotoxicity ¹⁰¹	BMD: 1 µg/kg-day ¹⁰²	5 ¹⁰³		pTDI: 0.5 µg/kg-day for adults and 0.2 µg/kg-day for women of childbearing ages and children ¹⁰⁴	

U.S. ATSDR = U.S. Agency for Toxic Substances and Disease Registry; BMD = Benchmark dose; BMDL₀₅ = A statistical lower confidence limit on the dose or concentration at the BMD or BMC, respectively; U.S. EPA = U.S. Environmental Protection Agency; U.S. FDA = U.S. Food and Drug Administration; JECFA = Joint FAO/WHO Expert Committee on Food Additives; LOAEL = Lowest observed adverse effect level; MADL = Maximum allowable daily level; MRL = Minimal risk level; NOEL = No observed effect level; pTDI = Canadian provisional tolerable daily intakes ; pTWI = Provisional tolerable weekly intake; RfD = Reference dose.

79. BMD: An exposure due to a dose of a substance associated with a specified low incidence of risk, generally in the range of 1% to 10%, of a health effect; or the dose associated with a specified measure or change of a biological effect, http://www.epa.gov/NCEA/bmds_training/appendices/glossary.htm.

80. BMDL: A statistical lower confidence limit on the dose or concentration at the BMD, <http://www.epa.gov/iris/gloss8.htm#b>.

81. Calculated from a range of 46-79 ppb in maternal blood for different neuropsychological effects in the offspring at 7 years of age.

82. RfD: a numerical estimate of a daily oral exposure to the human population, including sensitive subgroups such as children, that is not likely to cause harmful effects during a lifetime. RfDs are generally used for health effects that are thought to have a threshold or low dose limit for producing effects, <http://www.epa.gov/iris/gloss8.htm#r>.

83. P. Grandjean et al., *Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury*, 20 NEUROTOXICOL. TERATOL. 1, 1-12 (1997); E. Budtz-Jørgensen et al., *Methylmercury neurotoxicity independent of PCB exposure*, 107 ENVIRON. HEALTH PERSPECT. A236, A236-237 (1999).

84. NOEL: An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control, <http://www.epa.gov/iris/gloss8.htm#n>.

85. MADL: the level at which the chemical would have no observable adverse reproductive effect assuming exposure at 1,000 times that levels per the Safety Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65 of the Act) in California state, page 1 of http://www.oehha.org/prop65/policy_procedure/pdf_zip/Feb2001StatRpt.pdf.

86. California EPA, Proposition 65 status report. Safe harbor levels: no significant risk levels for carcinogens and maximum allowable dose levels for chemicals causing reproductive toxicity, 16 (2004), <http://www.oehha.ca.gov/prop65/pdf/June2004StatusRpt.pdf>.

87. Bornhausen et al, *supra* note 70.

88. Swedish Expert Group, *Methylmercury in fish: a toxicological-epidemiologic evaluation of risks*, Suppl. 4 NORD. HYG. TIDSKR. 19, 19-364 (1971).

89. LOAEL: lowest exposure level at which there are biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group, <http://www.epa.gov/iris/gloss8.htm#l>.

90. Safety Factor (SF): another term of UF, <http://www.greenfacts.org/glossary/tuv/uncertainty-factor-safety-factor.htm>; <http://www.atsdr.cdc.gov/glossary.html#Uncertainty%20Factor>.

91. U.S. FDA, Action levels for poisonous or deleterious substances in human food and animal feed, <http://www.cfsan.fda.gov/~lrd/fdaact.html>.

92. Measured by neurological evaluation, behavioral, psychological tests. Davidson et al., *supra* note 49.

93. NOAEL: The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects, <http://www.epa.gov/iris/gloss8.htm#n>.

94. The following uncertainty factors were applied: 1.5 for human pharmacokinetics variability, 1.5 for human pharmacodynamic variability, and 1.5 for domain-specific findings in the Faroe study (Grandjean et al., *supra* note 88). In more details, WHO defined the -kinetic and -dynamic components of intrahuman variability as being equal contributors to, and collectively constituting the total of, human variability. To ensure a conservative approach, these two interdependent components, the first two 1.5 in the previous sentence, were added to give a composite uncertainty of three (i.e., $1.5 + 1.5 = 3$) to account for the full range of variability attributable to mercury in the Seychelles Study (Davidson et al., *supra* note 49). The domain-specific effects were considered to be independent events; the modifying factor of 1.5 was then multiplied by the uncertainty factor of 3 to yield an aggregate uncertainty factor of 4.5 [U.S. ATSDR, Toxicological profile for mercury (update) (1999), U.S. Department of Health and Human Services, ATSDR, Atlanta, GA].

95. MRL: A U.S. ATSDR estimate of daily human exposure to a hazardous substance at or below which that substance is unlikely to pose a measurable risk of harmful (adverse), noncancerous effects. MRLs are calculated for a route of exposure (inhalation or oral) over a specified time period (acute, intermediate, or chronic). MRLs should not be used as predictors of harmful (adverse) health effects, <http://www.atsdr.cdc.gov/glossary.html>.

96. A meeting of the Joint Food and Agriculture Organization of the United Nations/WHO Expert Committee on Food Additives (JECFA) was held in Rome, Italy, from 10 to 19 June 2003. The provisional tolerable weekly intake (pTWI) for methylmercury of 3.3 $\mu\text{g}/\text{kg}$ body weight per week was revised to 1.6 $\mu\text{g}/\text{kg}$ body weight per week. The Committee considered that the updated pTWI was sufficient to protect the developing fetus, the most sensitive subgroup of the population, and reaffirmed its position that fish are an important part of a

balanced nutritious diet and that this has to be appropriately considered in public health decisions when setting limits for methylmercury concentrations in fish, <http://www.chem.unep.ch/mercury/Report/JECFA-PTWI.htm>.

97. Grandjean et al., *supra* note 88; G. J. Myers et al., A pilot neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from a maternal fish diet, 16 *NEUROTOXICOLOGY* 629, 629-638 (1995)

98. Estimates of maternal hair concentrations associated with the NOEL and BMDL for neurotoxicity associated with in utero exposure. A NOEL of 15.3 mg/kg maternal hair was identified for neurobehavioral effects for the Seychelles Islands study (U.S. ATSDR, *supra* note 99). A BMDL of 12 mg/kg maternal hair was determined for the Faroe Islands study (Budtz-Jørgensen et al., *supra* note 88; NRC, *supra* note 6 at 1-368; Rice et al., *supra* note 63). The committee (JECFA) subsequently averaged these two points of departure to get 14 mg/kg maternal hair-mercury as an estimate of the level in maternal hair reflecting exposures that would be without appreciable adverse effects in the offspring of these two populations. Finally, a steady-state ingestion of 1.5 $\mu\text{g}/\text{kg}\text{-day}$ was calculated by converting the concentration in maternal hair to that in maternal blood and then maternal blood concentration into maternal intake.

99. A factor of 2 was decided to allow for the likely inter-individual variability, which is indicated by the differences in study means (more precisely, per hair:blood ratio data) and by the limited available individual data, and a combined factor of 3.2 was recommended to account for the total human inter-individual variability for dose reconstruction (converting maternal blood concentration to a steady-state dietary intake).

100. pTWI is an endpoint used for food contaminants such as heavy metals with cumulative properties. Its value represents permissible human weekly exposure to those contaminants unavoidably associated with the consumption of otherwise wholesome and nutritious foods, <http://jecfa.ilsa.org/section1.htm>. The committee (JECFA) considered this to be sufficient to protect the developing fetus, the most sensitive subgroup of the population.

101. Grandjean et al., *supra* note 88; Davidson et al., *supra* note 49; T. Kjellstrom et al., Physical and mental development of children with prenatal exposure to mercury from fish. Stage 1: Preliminary test at age 4, NATL .SWED. ENVIRON. PROTEC. BD. Rpt. 3080 (1986); T. Kjellstrom et al., Physical and mental development of children with prenatal exposure to mercury from fish. Stage 2: Interviews and psychological tests at age 6, NATL .SWED. ENVIRON. PROTEC. BD. Rpt. 3642 (1989)

102. An approximate benchmark dose was estimated qualitatively based on available data.

103. This is an arbitrary value.

104. The Canadian provisional tolerable daily intakes (pTDIs) are based on the previous provisional tolerable weekly intake (pTWI) in adults of 0.5 $\mu\text{g}/\text{kg}\text{-day}$ [JECFA 53rd meeting, Rome, 1-10 June 1999, <http://www.who.int/pes/jeta/jeta.htm>]. A TDI is an estimate of the amount of a substance in air, food, or drinking water that can be taken in daily over a lifetime without appreciable health risk. TDIs are calculated on the basis of laboratory toxicity data to which uncertainty factors are applied. TDIs are used for substances that do not have a reason to be found in food (as opposed to substances that do, such as additives, pesticide residues, or veterinary drugs in foods), <http://www.greenfacts.org/glossary/tuv/TDI-tolerable-daily-intake.htm>. Uncertainty factors are also used when deriving a TDI from the most sensitive endpoint in the most relevant study. In addition, Canada has a pTDI for women of childbearing ages and children.