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Water Quality Criterion for the Protection of Human Health: Methylmercury

Final

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NOTICE

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Potential areas for conflict of interest were investigated via direct inquiry with the peer reviewers and review of their current affiliations. No conflicts of interest were identified.

CONTENTS

EXECUTIVE SUMMARY

About This Document

This document is the basis for a human health Ambient Water Quality Criterion (AWQC) for methylmercury. This AWQC replaces the AWQC for total mercury in published in 1980 and partially updated in 1997. Under Section 304(a) of the Clean Water Act, EPA must periodically revise criteria for water quality to accurately reflect the latest scientific knowledge on the kind and extent of all identifiable effects of pollutants on human health.

This document uses new methods and information described in the Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) (2000 Human Health Methodology) (U.S. EPA, 2000a,b). These new methods include updated approaches to determine toxicity dose-response relationships for both carcinogenic and noncarcinogenic effects, updated information for determining exposure factors, and new procedures to determine bioaccumulation factors.

The Mercury Study Report to Congress (MSRC) (U.S. EPA, 1997), an eight-volume report prepared by the U.S. Environmental Protection Agency (EPA) and submitted to Congress in 1997, serves as a primary information source on methylmercury. However, as the state of the science for methylmercury is continuously and rapidly evolving, the information from the MSRC has been supplemented by inclusion of published information since 1997.

Exposure to Methylmercury

The major pathway for human exposure to methylmercury is consumption of contaminated fish. Dietary methylmercury is almost completely absorbed into the blood and is distributed to all tissues including the brain; it also readily passes through the placenta to the fetus and fetal brain.

Major Health Effects of Methylmercury

Methylmercury is a highly toxic substance with a number of adverse health effects associated with its exposure in humans and animals. Epidemics of mercury poisoning following high-dose exposures to methylmercury in Japan and Iraq demonstrated that neurotoxicity is the health effect of greatest concern. These epidemics led to observation of methylmercury effects on the fetal nervous system. High-dose

human exposure results in mental retardation, cerebral palsy, deafness, blindness, and dysarthria in utero and in sensory and motor impairment in adults. Although developmental neurotoxicity is currently considered the most sensitive health endpoint, data on cardiovascular and immunological effects are beginning to be reported and provide more evidence for toxicity from low-dose methylmercury exposure.

Three large prospective epidemiology studies in the Seychelles Islands, New Zealand, and the Faroe Islands were designed to evaluate childhood development and neurotoxicity in relation to fetal exposures to methylmercury in fish-consuming populations. Prenatal methylmercury exposures in these three populations were within the range of some U.S. population exposures. No adverse effects were reported from the Seychelles Islands study, but children in the Faroe Islands exhibited subtle developmental dose-related deficits at 7 years of age. These effects include abnormalities in memory, attention, and language. In the New Zealand prospective study, children at 4 and 6 years of age exhibited deficiencies in a number of neuropsychological tests.

In addition to the three large epidemiological studies, studies on both adults and children were conducted in the Amazon; Ecuador; French Guiana; Madeira; Mancora, Peru; northern Quebec; and Germany. Effects of methylmercury on the nervous system were reported in all but the Peruvian population.

Other Health Effects of Methylmercury

Methylmercury causes chromosomal effects but does not induce point mutations. The MSRC concluded that because there are data for mammalian germ-cell chromosome aberration and limited data from a heritable mutation study, methylmercury is placed in a group of high concern for potential human germ-cell mutagenicity. There is no two-generation study of reproductive effects, but shorter term studies in rodents, guinea pigs and monkeys have reported observations consistent with reproductive deficits. There are no data to indicate that methylmercury is carcinogenic in humans, and it induces tumors in animals only at highly toxic doses. Application of the proposed revisions to the Guidelines for Cancer Risk Assessment (EPA 1999)leads to a judgment that methylmercury is not likely to be carcinogenic for humans under conditions of exposure generally encountered in the environment.

Quantitative Risk Estimate for Methylmercury

The quantitative health risk assessment for a noncarcinogen relies on a reference dose (RfD). This is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime. To derive an RfD, one first establishes a no adverse effect level (NOAEL) for a particular endpoint. This can be done by inspection of the available data or by using a mathematical modeling procedure to estimate the NOAEL; the latter approach was used for methylmercury. Next the NOAEL is divided by a numerical uncertainty factor to account for areas of variability and uncertainty in the risk estimate.

There has been considerable discussion within the scientific community regarding the level of exposure to methylmercury that is likely to be without an appreciable risk of deleterious health effects during a lifetime. In 1999, the Congress directed EPA to contract with the National Research Council (NRC) of the National Academy of Sciences to evaluate the body of data on the health effects of methylmercury. NRC was to concentrate on new data since the 1997 MSRC, and to provide recommendations regarding issues relevant to the derivation of an appropriate RfD for methylmercury. NRC published their report, *Toxicological Effects of Methylmercury*, in 2000. EPA generally concurred with the NRC findings and recommendations. The NRC document was used as a resource in determining the EPA RfD for methylmercury documented here.

Choice of Study

The adverse effect of methylmercury observed at lowest dose is neurotoxicity, particularly in developing organisms. The brain is considered the most sensitive target organ for which there are data suitable for derivation of an RfD. There is an extensive array of peer-reviewed, well-analyzed data from human studies of low-dose exposure to methylmercury. NRC and EPA considered three epidemiologic longitudinal developmental studies suitable for quantitative risk assessment: the Seychelles Child Development Study (SCDS); the ongoing studies of children in the Faroe Islands; and the study of children in New Zealand. All cohorts consisted of children exposed in utero through maternal consumption of mercury-contaminated fish or marine mammals. In all studies there were biomarkers of maternal exposure (hair), and in the Faroes study cord blood was also used as an additional measure of fetal exposure. The SCDS yielded no evidence of impairment related to methylmercury exposure, but the two other studies have found dose-related adverse effects on a number of

neuropsychological endpoints. EPA chose to base the RfD on data from the Faroes study. The SCDS has no findings of effects associated with methylmercury exposure, and thus is not the best choice for a public health protective risk estimate. While the New Zealand study does show mercury-related effects it relatively small by comparison to the other two. Advantages of the Faroes study include these:

- Large sample size (n > 900 for some measures)
- Good statistical power as calculated by conventional means
- Use of two different biomarkers of exposure
- Comprehensive and focused neuropsychological assessment
- Assessment at an age and state of development when effects on complex neuropsychological functions are most likely to be detectable
- Statistically significant observations which remain after adjusting for potential PCB effects
- Extensive scrutiny in the epidemiological literature

The Faroe Islands study was used for derivation of the RfD.

Estimation of the No Adverse Effect Level

A benchmark dose analysis was chosen as the most appropriate method of quantifying the dose-effect relationship. The level chosen was a Benchmark Dose Lower Limit (BMDL); this was the lower 95% limit on a 5% effect level obtained by applying a K power model ($K \geq 1$) to dose-response data based on mercury in cord blood. The BMDL was chosen as the functional equivalent of a no-adverse-effect level for calculation of the RfD.

Choice of Endpoint

Several endpoints are sensitive measures of methylmercury effects in the Faroese children. EPA considered the recommendations of the NRC and EPA's external scientific peer review panel in coming to a decision as to the appropriate endpoint. The NRC recommended the use of a BMDL of 58 ppb mercury in cord blood from the Boston Naming Test (BNT). The external peer panel felt that the BNT scores showed an effect of concomitant PCB exposure in some analyses. They preferred a PCB-adjusted BMDL of 71 ppb mercury in cord blood for the BNT. A difficulty with this choice is that this BMDL is based on scores from only about one-half of the total cohort. The peer panel further suggested using a composite index across several measures in the Faroes data set. EPA prepared a comparison of the

endpoints recommended by NRC and peer reviewers; this also included the BMDLs from the NRC integrative analysis and geometric means of four scores from the Faroes. These BMDLs and corresponding estimates of ingested methylmercury are within a very small range. Rather than choosing a single measure for the RfD critical endpoint, EPA considers that this RfD is based on several scores. These test scores are all indications of neuropsychological processes related to the ability of a child to learn and process information.

Calculation of Ingested Methylmercury Dose

In the risk assessment discussion EPA uses the NRC-recommended BMDL of 58 ppb mercury in cord blood as an example in the dose conversion and RfD calculation. The BMDL in terms of mercury in cord blood was converted to an estimate of ingested methylmercury. This was done by use of a one-compartment model similar to that used in the MSRC. Single-parameter estimates were used rather than a distributional approach. It was assumed that the cord blood methylmercury level was equal to maternal blood level. The ingested dose of methylmercury that corresponds to a cord blood level of 58 ppb is 1.081 μg/kg bw/day.

Uncertainty Factor

Several sources of variability and uncertainty were considered in the application of a composite uncertainty factor of 10. This included a factor of 3 for pharmacokinetic variability and uncertainty; one area of pharmacokinetic uncertainty was introduced with the assumption of equivalent cord blood and maternal blood mercury levels. An additional factor of 3 addressed pharmacokinetic variability and uncertainty. Other areas of concern include inability to quantify possible long-term sequelae for neurotoxic effects, questions as to the possibility of observing adverse impacts (such as cardiovascular effects) below the BMDL, and lack of a two-generation reproductive effects assay.

Methylmercury Reference Dose

The RfD derived in this assessment is 0.1 μg/kg bw/day or $1x10^{-4}$ mg/kg bw/day. The RfD for methylmercury was not calculated to be a developmental RfD only. It is intended to serve as a level of exposure without expectation of adverse effects when that exposure is encountered on a daily basis for a lifetime. In the studies so far published on subtle neuropsychological effects in children, there has been no definitive separation of prenatal and postnatal exposure that would permit dose-response modeling.

That is, there are currently no data that would support the derivation of a child (vs. general population) RfD.

Relative Source Contribution

The assessment of methylmercury exposure from common media sources (e.g., diet, air) and relative source contribution (RSC) estimates follows the 2000 Human Health Methodology. The RSC is used to adjust the RfD to ensure that the water quality criterion is protective, given other anticipated sources of exposure. The exposure assessment characterizes the sources of methylmercury exposure in environmental media, providing estimates of intake from the relevant sources for children, women of childbearing age, and adults in the general population. Based on available data, human exposures to methylmercury from all media sources except freshwater/estuarine and marine fish are negligible, both in comparison with exposures from fish and compared with the RfD. Estimated exposure from ambient water, drinking water, nonfish dietary foods, air, and soil are all, on average, at least several orders of magnitude less than those from freshwater/estuarine fish intakes. Therefore, these exposures were not factored into the RSC. However, ingestion of marine fish is a significant contributor to total methylmercury exposure. For the methylmercury criterion, the RSC is the estimated exposure from marine fish intake. This is subtracted from the RfD when calculating the water quality criterion. One hundred percent of the mercury in marine fish was assumed to be present as methylmercury. The estimated average exposure to methylmercury from marine fish is 2.7 x 10-5 mg/kg-day. This exposure represents almost 30% of the RfD.

Methylmercury Bioaccumulation

Methylmercury is a chemical that bioaccumulates and biomagnifies in aquatic food webs. The fates of mercury and methylmercury in the environment are complex processes affected by numerous biotic and abiotic factors that are subjects of ongoing research. Methylation of mercury is a key step in the entrance of mercury into food chains. The biotransformation of inorganic mercury forms to methylated organic forms in water bodies can occur in the sediment and the water column. Inorganic mercury can be absorbed by aquatic organisms but is generally taken up at a slower rate and with lower efficiency than is methylmercury. Methylmercury continues to accumulate in fish as they age. Predatory organisms at the top of aquatic and terrestrial food webs generally have higher methylmercury concentrations because methylmercury is typically not completely eliminated by organisms and is

transferred up the food chain. Nearly 100% of the mercury that bioaccumulates in upper-trophic-level fish (predator) tissue is methylmercury.

Numerous factors can influence the bioaccumulation of mercury in aquatic biota. These include, but are not limited to, the acidity (pH) of the water, length of the aquatic food chain, temperature, and dissolved organic material. Physical and chemical characteristics of a watershed, such as soil type and erosion or proportion of area that is wetlands, can affect the amount of mercury that is transported from soils to water bodies. Interrelationships among these factors are poorly understood and are likely to be site-specific. No single factor (including pH) has been correlated with extent of mercury bioaccumulation in all cases examined. Two lakes that are similar biologically, physically, and chemically can have different methylmercury concentrations in water, fish, and other aquatic organisms.

The Methylmercury Criterion is a Fish Tissue Residue Criterion

EPA concluded that it is more appropriate at this time to derive a fish tissue (including shellfish) residue water quality criterion for methylmercury rather than a water column-based water quality criterion. This decision considered issues of mercury fate in the environment, the NRC report on the toxicological effects of mercury, and in particular the methylmercury peer review comments. EPA believes a fish tissue residue water quality criterion is appropriate for many reasons. Such a criterion integrates spatial and temporal complexity that occurs in aquatic systems and that affects methylmercury bioaccumulation. A fish tissue residue water quality criterion is more closely tied to the CWA goal of protecting the public health because it is based directly on the dominant human exposure route for methylmercury. The concentration of methylmercury is also generally easier to quantify in fish tissue than in water and is less variable over the time periods in which water quality standards are typically implemented in water quality-based. Thus, the data used in permitting activities can be based on a more consistent and measurable endpoint. A fish tissue residue criterion is also consistent with how fish advisories are issued. Fish advisories for mercury are based on the amount of methylmercury in fish tissue that is considered acceptable, although they are usually issued for a certain fish or shellfish species in terms of a meal size. A fish tissue residue water quality criterion should enhance harmonization between these two approaches for protecting the public health.

The methylmercury water quality criterion is, thus, a concentration in fish tissue. It was calculated using the criterion equation in the 2000 Human Health Methodology rearranged to solve for a protective concentration in fish tissue rather than in water.

$$TRC = \frac{BW \times (RfD - RSC)}{\sum_{i=2}^{4} FI_i}$$

Where:

TRC = Fish tissue residue criterion (mg methylmercury/kg fish) for freshwater and estuarine fish

RfD = Reference dose (based on noncancer human health effects) of 0.0001 mg methylmercury/kg body weight-day

RSC = Relative source contribution (subtracted from the RfD to account for marine fish consumption) estimated to be 2.7×10^{-5} mg methylmercury/kg body weight-day

BW = Human body weight default value of 70 kg (for adults)

FI = Fish intake at trophic level (TL) i (i = 2, 3, 4); total default intake is 0.0175 kg fish/day for general adult population. Trophic level breakouts for the general population are: TL2 = 0.0038 kg fish/day; TL3 = 0.0080 kg fish/day; and TL4 = 0.0057 kg fish/day.

The resulting Tissue Residue Criterion is 0.3 mg methylmercury/kg fish. This is the concentration in fish tissue that should not be exceeded based on a total fish and shellfish consumption-weighted rate of 0.0175 kg fish/day. EPA strongly encourages States and authorized Tribes to develop a water quality criterion for methylmercury using local or regional data rather than the default values if they believe that such a water quality criterion would be more appropriate for their target population.