

June 3, 2003

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International Programme on Chemical Safety
World Health Organization
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Re: 61st JECFA meeting, 10 June 2003

Dear Dr. Page:

In early June, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) will consider revising the Provisional Tolerable Weekly Intake (PTWI) for methyl mercury. To support this discussion, Dr. Michael Bolger and colleagues drafted a review of the literature several years ago. This 2000 review, (included in *WHO Food Additives 44*), takes stock of a wide literature but concludes that inconsistencies between two key epidemiological studies -- the Faroe Islands and Seychelles studies -- are of such a magnitude as to preclude a revision or update of the W.H.O. permissible exposure level for methyl mercury.

We are writing to call attention to a number of important research findings and key policy developments over the past three years that merit attention. The research developments are detailed in an attachment to this letter but can be summarized as follows:

- Some scientific issues related to the Faroe Islands study, particularly the possibilities of PCB confounding and bolus exposures to methyl mercury in that work, have been resolved, leading to greater confidence in the results of these studies;
- Tests on the Faroe Islands children's cohort have continued as the children have matured, providing additional evidence of neurological and other impacts beyond seven years of age;
- Evidence is continuing to emerge linking increased risk of coronary heart disease to mercury exposure, with the publication of at least two additional studies; and
- Substantial evidence is accumulating that exposure to methyl mercury is widespread in the general public and occurring at higher than health-based levels of concern.

Since 2000, national and international food safety authorities have adopted lower limits on methyl mercury exposure and/or stronger warnings designed to help sensitive populations, particularly pregnant women and children, avoid or reduce exposure. In particular:

- The U.S. Environmental Protection Agency (EPA) has recommended a reference dose (RfD) of 0.1 µg/kg body weight per day for methyl mercury. EPA has also issued a general fish consumption advisory for methyl mercury advising women who are or may become pregnant, nursing mothers and young children to limit consumption of freshwater fish based on its RfD.
- The National Research Council of the US National Academy of Sciences (NRC) has reviewed the evidence as a whole and has concluded that the Faroe Islands study, rather than the Seychelles study, is the most appropriate study for deriving a Reference Dose and that the two studies should be seen in conjunction with an important New Zealand study. An NRC committee recommended the EPA reference dose of 0.1 ug/kg/d as appropriate.
- The European Commission has endorsed the US EPA's reference dose as the appropriate methyl mercury exposure standard.
- The Food Standards Agency of the United Kingdom (FSA) has advised pregnant and breastfeeding women, and women who intend to become pregnant, to limit their consumption of tuna to no more than two medium-size cans or one fresh tuna steak per week, and
- The United Nations Environmental Programme (UNEP) Governing Council has agreed that there is sufficient evidence of significant global adverse impacts from mercury and its compounds to warrant further international action to reduce the risks to human health and the environment. It is now developing a plan to raise global awareness of the critical need to sharply reduce human exposures to mercury.

These expert deliberations have reached consistent conclusions about methyl mercury toxicity by considering the increasing weight of evidence for methyl toxicity at low levels.

Approximately two weeks ago, The Lancet published an update of the Seychelles study. While the finding was negative, this paper sheds light on two of the possible reasons for inconsistencies between results from the Seychelles, Faroe Islands, and New Zealand work to date: the differences between the studies in age of testing, and endpoints used in neurotoxicological assessments.

Unfortunately, the reasons for the different results from these studies remain unclear. The NRC had identified random variability in outcome determination related to statistical power as the most plausible explanation for discrepancies among results. Such varying outcomes are by no means unusual in large-scale epidemiologic studies and remain a strong possibility. Since the most recent findings from the Seychelles reflect determinations on the same cohort as that evaluated in the studies reviewed previously by the NRC, the same limitations due to statistical power would be expected in the follow-up. Misclassification of exposure, stemming from both the use of maternal hair as an exposure measure and the recruitment of women into the study six months post partum, by necessity, also remains an issue in the recent update, as well as questions which have been raised about cultural differences and language issues that could have limited the accuracy of a key neurotoxicological endpoint measurement, the Boston Naming Test.

While both the Seychelles and Faroe Islands studies are well designed and well executed, the NRC concluded on the basis of careful consideration that the positive findings of the Faroe Islands and other works could not properly be discounted by the negative findings of the Seychelles study. Nothing in the Seychelles update changes the balance for this conclusion.

Furthermore, prudent public health practice dictates that when authorities are confronted with both positive and negative studies and there are irresolvable uncertainties as to which results are more generally applicable, guidance should be derived from the studies showing adverse outcomes rather than from negative studies. In the case of methyl mercury, indications of adverse effects are buttressed by the positive findings from the New Zealand study as well as in studies from French Guiana and the Amazon. The weight of evidence on methyl mercury is enhanced by a large docket of in vivo and in vitro results, as well as by recent epidemiological studies concerning potential adverse cardiovascular effects at relatively low levels of exposure.

We believe that the time is ripe for JECFA to reduce the Provisional Tolerable Weekly Intake for methyl mercury at its upcoming meeting in Rome. We suggest that the science strongly supports the determination by the U.S. EPA of a reference dose of 0.1 ug/kg body weight per day, which is consistent with recommendations that whole blood mercury levels not exceed 5.8 µg/L (ppb) or the hair level not exceed 1.0 ppm. We urge JECFA to recommend exposure limitations consistent with these indices.

Attached is a more detailed summary of the most important developments on mercury toxicity that have come to light since JECFA last met to discuss methyl mercury in the diet. We hope that this information proves useful to your deliberations.

Sincerely,

Attached Signatories

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Attachment

Important Developments in Scientific Evidence on Methyl Mercury Toxicity and Exposure, and Policies on Permissible Exposure Levels, 2000-2003

Introduction

Methyl mercury poisoning incidents, particularly the well-known incident in Minamata, Japan, have documented links between exposure and neurotoxicological effects.ⁱ Three prospective epidemiological studies, in the Faroe Islands, the Seychelles, and in New Zealand, have been singled out over the past five years for the development of dose response calculations. The study in the Faroe Islands documented subtle deficits of several functional domains at prenatal methyl mercury exposure levels previously thought to be safe.ⁱⁱ This finding was in agreement with a prospective study in New Zealandⁱⁱⁱ as well as cross-sectional epidemiological studies in French Guiana^{iv} and the Amazon^v that also showed effects but do not lend themselves to dose response analysis. However, results from the Seychelles have not been concordant; to date, this prospective study has not shown effects^{vi, vii}. There have been hundreds of toxicological studies delineating toxic impacts of methyl mercury on animals and in vitro over the past decades, as well as additional epidemiological studies suggesting toxic effects beyond developmental neurotoxicology .

Important Recent Evidence on Methyl Mercury Toxicity

Some scientific issues related to the Faroe Islands study, particularly the possibilities of PCB confounding and bolus exposures to mercury, have been resolved.

Questions have been raised about confounding factors in the Faroe Islands studies that could have affected observed associations between exposure to methyl mercury and neurodevelopmental outcomes in the latter study. The National Research Council performed analyses that addressed this issue specifically with regards to the Faroe Islands study and concluded that although there were effects associated with both PCBs and methyl mercury, these effects are independent.^{viii} The Faroe Island researchers have subsequently found "...PCB-associated neurotoxicity could be latent in this population and may be unmasked at increased methyl mercury exposures. Parallel calculations for mercury showed remarkably different results. The mercury-associated neurobehavioral deficits were quite similar within the three-tertile PCB concentration groups with the mercury regression coefficients in the lowest PCB tertile tending to be the greatest. ...These results indicate that the mercury-associated effect is unlikely to be affected by PCB exposure to any great extent."^{ix}

Concerns had been raised regarding confounding of maternal age and the presence of older siblings at home. However, a detailed analysis has indicated that these

parameters will not alter the analysis, and results obtained with these two covariates along with 18 others did not affect the results.^x

Finally, it has been suggested that the Faroe Islands study reflected only the effects of “bolus” (acute, intermittent) doses of mercury, while the Seychelles captured chronic exposure more typical of dietary intake in many cultures. However, an analysis of hair-mercury profiles has since suggested that the pattern of mercury exposure rates over time in the Faroe Islands and the Seychelles studies are similar. Additionally, an analysis eliminating the infants of women with the most highly variable hair mercury levels resulted in a stronger association between mercury exposure and adverse neuropsychological outcome.^{xi} Furthermore, and perhaps more importantly, a recent article by Hightower et al. (2003) has demonstrated that many Americans are exposed to “bolus” mercury consumption through commercial fish such as Ahi or other tuna steaks, Sushi, and swordfish. Mercury levels in these fish species raised blood mercury levels several fold in individual subjects who consumed them. Some blood mercury levels observed by Hightower et al. were higher than the levels seen in both the Seychelles and Faroe Islands studies^{xii}.

Also in the past three years, new information has become available on neurological status at two weeks of age in the Faroese Cohort 2, born in 1994-1995 and originally reported in Steuerwald et al. (2000).^{xiii} This study examined 182 infants born in the Faroe Islands, along with corresponding levels of mercury in maternal serum, hair, milk and umbilical cord blood. This study found that the neonatal neurological status (measured in the Neurological Optimality Score, or NOS) was significantly poorer at higher blood-mercury concentrations. The authors report that, “exposures to methyl mercury and polychlorinated biphenyls were increased in relation to maternal seafood intake... After adjustment for confounders, including PCB body burden, a 10-fold increase of the cord-blood mercury concentration was associated with a decreased neurologic optimality score of 2.0 ($P = .03$). This effect corresponds to a decrease in gestational age of about 3 weeks.” The neonatal NOS assessment has been used as an important predictor of neurological risk later in childhood, and extensive results from a project in Groningen in the Netherlands have shown that the neonatal NOS has a high specificity (but a low sensitivity) for subsequent development of minor neurological dysfunction.^{xiv} These findings support the validity of the neonatal assessment using the NOS methodology, and they are in accordance with the exposure-associated effects seen in older children.

Finally, the impact of mercury on overall growth and development has been further supported by data published since 2000. In the Faroese Cohort 2, pre and postnatal methyl mercury exposure was found to be associated with decreased postnatal growth, particularly before 18 months of age. The authors found that, “irrespective of duration of breast-feeding, a doubling of the mercury concentration in cord blood was associated with a decrease in weight and height.”^{xv}

Tests on the Faroe Islands children's cohort have continued as the children have matured, providing additional information on neurological and other impacts beyond seven years of age.

The Faroese study has been updated to include state of the art neurological testing administered to the cohort of children under study as they have matured. In the 1997 report of the Faroes study, examinations of children at age 7 had included several probes into CNS-mediated functions such as past achievement of developmental milestones, plus sensitive measures of neurological function, such as evoked potentials, visual and auditory acuity, and neuropsychological functions.^{xvi} Subsequently, during re-examination of the same cohort of children at age 14, these measures were broadened to include social adjustment and measures of academic knowledge and achievement; a pilot study has also been done with a subset of the children at age 16 using functional and structural neuroimaging techniques to probe CNS correlates of methyl mercury exposures. In a lecture delivered at the International Joint Commission for the Great Lakes in February, 2003, the principal investigator of the Faroes study, Dr. Philippe Grandjean, reported that the results of the 14-year follow-up were in agreement with the earlier findings of developmental effects (1997). The authors now find that results of mercury exposure include delays of the brainstem auditory evoked potentials, a neurophysiological measure of neurotoxic effects known to be independent of socioeconomic confounders.

Additional evidence of increased risk of coronary heart disease due to mercury exposure, first reported in 1995, has emerged with the publication of additional studies.

Several studies have linked mercury exposure to cardiovascular disease. These studies are important because consumers are advised to eat fish to protect against heart disease. Some fish species contain beneficial omega-three fatty acids, and fish is a low-fat source of protein. However, recent studies raise the possibility that moderate mercury content in fish may in fact diminish the cardio protective effect of fish intake. Salonen et al. (2000) reported an association between moderate hair mercury content and accelerated progression of carotid arteriosclerosis (determined by ultrasonographic assessment of common carotid intima-media thickness), in a prospective study among 1014 men aged 42-60 years in Finland. Hair mercury levels greater than 2 ppm (well within the range of the U.S. adult population) showed a doubling of the risk of cardiovascular mortality in this study.^{xvii}

Recently, Guallar et al. (2002) reported in the New England Journal of Medicine that toenail mercury level (an indicator of exposure) was directly associated with the risk of myocardial infarction.^{xviii} This case-control study was conducted in eight European countries and Israel, and studied 684 men with a first diagnosis of myocardial infarction. The authors report that the mercury levels in the patients were 15 percent higher than those in controls (95 percent confidence interval, 5 to 25 percent). The risk-factor-adjusted odds ratio for myocardial infarction associated with the highest as compared with the lowest quintile of mercury was 2.16 (95 percent confidence interval, 1.09 to

4.29; P for trend=0.006). The authors suggest certain mechanisms that may be contributing to this effect, including inactivating the antioxidant properties of glutathione or catalase, inducing lipid peroxidation, promoting platelet aggregability and blood coagulability, and affecting the inflammatory response, among several others.

A third study on cardiovascular health was unable to replicate the findings of Guallar et al. However, the study population consisted largely of dentists who had an occupational exposure to elemental mercury. Since mercury exposure measurements in this study were based on total mercury, the elemental mercury exposure could have confounded detection of a methyl mercury effect. In fact, when the dentists were removed from the study, an association with cardiovascular outcomes (albeit not statistically significant, probably due to the smaller sample size) was seen with mercury exposure.^{xix}

The posited association between methyl mercury and heart disease suggests that long-term mercury exposure, even at very low levels, may contribute to a disease that is responsible for one third of all deaths globally in 2000. In that year the World Health Organization predicted that heart disease would be the number one cause of death in developing countries by 2010.^{xx} It was the number one killer of Americans in 2000, causing 257.9 deaths per 100,000 population in the U.S. The medical and social costs of heart disease are staggering. We believe the emerging evidence of an association between chronic low-level mercury exposure and this major modern cause of death deserves to be given significant weight in JECFA's review.

Important Recent Evidence on Methyl Mercury Exposure

New evidence has come to light that exposure to methyl mercury is widespread and occurring at levels exceeding health-based recommended limits. Just a month ago, for example, the Journal of the American Medical Association (JAMA) published results from an extensive survey of the U.S. general population that bolsters previous findings of concern about blood mercury levels in fish-consuming subpopulations including recreational anglers, subsistence fishers, and American Indian and Alaskan Native groups.

Although it has long been recognized that mercury is widespread in the environment and that exposure occurs primarily through consumption of fish and shellfish which have bioaccumulated methyl mercury, information about the distribution of blood mercury levels in the general population has been lacking, and hence it has been difficult to fully evaluate the public health significance of the mercury problem. Exposure information for women of childbearing age has been particularly urgently needed, since fetal exposure is known to be a critical window of exposure to the compound.

In the April 2003 issue of JAMA, Schober et al. reported the results of the first 2 years of the U.S. NHANES (National Health and Nutrition Examination Survey,

conducted by the US Centers for Disease Control and Prevention) study, which was measured blood mercury levels of 1709 women of child-bearing age and 705 children in the general population from across the country.^{xxi} Eight percent of reproductive-aged women had blood mercury levels higher than 5.8 µg/L, below which exposures are considered to be without adverse effect by US EPA. Mercury levels were 3 times higher in women than in young children, which the authors speculate may be due to differences in toxicokinetics, dose-body size relationships, dose frequency, or unknown sources of mercury exposure in adults. Blood mercury levels were associated with self-reported fish consumption in the past 30 days for both children and women; among women, blood mercury levels were almost 4-fold higher in women who reported eating 3 or more fish meals in the past month, compared with those who ate no fish over the same time period. The authors expressed particular concern for those women who are pregnant, or who may become pregnant.

A 2001 publication of Stern et al. (2001) also found widespread exposure to mercury in the general population. These authors determined hair and blood mercury levels in mainly first-trimester pregnant women in New Jersey and found that approximately 10 percent had levels exceeding the USEPA RfD and that 1 to 2 percent of the women had hair mercury levels exceeding 4 µg/g, “in the range of possible concern for adverse developmental effects”.^{xxii}

Finally, Hightower et al. (2003) recently published a study finding that 89 adult patients in San Francisco who reported diets high in fish consumption had mean blood mercury level of 14.5 µg/L (ppb) and a median of 11.2 µg/L. The mean level for women in this survey was 10-times higher than the U.S. national mean of 1.3 µg/L (NHANES, CDC).^{xxiii}

These three publications, taken together, confirm that the general population, at least in the U.S., is routinely exposed to mercury doses higher than those presumed to be safe. The recent data are notably in accordance with a prediction by a committee of the National Research Council of the U.S. National Academy of Sciences, which assessed methyl mercury exposure and toxicity in 2000. The growing evidence of relatively widespread excessive exposure lends urgency to the JECFA re-evaluation at this time.

Emerging Consensus Among National and International Authorities

Following extensive study and *de novo* analysis, the US National Research Council (NRC) concluded that the Faroe Islands study provided the single best basis for evaluating the toxicity of methyl mercury. Significantly, integrative analysis using all three studies also supported this conclusion. Furthermore, NRC concluded that EPA’s RfD for methyl mercury (0.1 ug/kg per day) was scientifically justified.

In 2000, an expert committee convened by the U.S. National Research Council (NRC) reviewed methyl mercury exposure and toxicity with regard to identifying appropriate methods for setting a reference dose. The NRC assessment concluded that certain strengths of the Faroe Islands study – its large study population, its use of two

measures of exposure (maternal hair and cord blood), its extensive peer review in the epidemiological literature, and the re-analysis of its raw data in response to questions the NRC itself had submitted to the researchers -- made the Faroe Islands study the most appropriate basis for deriving an RfD.^{xxiv}

The NRC committee recognized that the Faroe Islands population had been exposed to relatively high levels of PCBs and agreed that this was a potential issue of concern. Consequently, it undertook its own reanalysis of the data. It concluded that the adverse effects found in the Faroe Islands study were not solely attributable to PCB. Moreover, the NRC committee noted that the results from New Zealand demonstrated neurological effects associated with methyl mercury exposure at similar levels to the Faroe Islands study, and without the potential for co-exposure to PCB's.^{xxv}

Although the NRC committee recommended that quantitative risk assessment be based on the Faroe Islands study, it also explored a weight-of-evidence approach based on an integrative analysis that allowed a quantitative synthesis of information across all three epidemiological studies. This is consistent with US EPA practice to consider the weight of evidence of the available literature when deriving the basis for an RfD. To do this, the NRC relied upon a hierarchical random effects model designed to take proper account of appropriate study-to-study and outcome-to-outcome heterogeneity across the studies. Such a model provided a useful tool for separating random versus systematic variation and thereby provides more stable estimates of study-specific and outcome-specific benchmark doses. The effect of the hierarchical modeling was to smooth away much of the random variability observed in the original data, particularly the more extreme values. Significantly, the integrative analysis resulted in a point of departure of 32 ug/l in blood, lower than the 58 ug/l for the Boston Naming test in the Faroe Islands study.

After reviewing and taking into consideration the evidence on carcinogenicity, immunotoxicity, reproductive effects, renal toxicity, cardiovascular effects, and central-nervous-system toxicity which was available in many studies outside of the Seychelles and Faroe Islands epidemiological works, selecting an end point for the RfD, examining the critical studies for the RfD, and assessing the need for uncertainty factors, the NRC committee concluded that EPA's RfD of 0.1 ug/kg per day was scientifically justifiable for the protection of public health. The committee further estimated based on the data that over 60,000 children are born in the U.S. each year at risk for adverse neurodevelopmental effects due to *in utero* exposure to methyl mercury.^{xxvi}

The U.S. Environmental Protection Agency (EPA) developed a reference dose (RfD) of 0.1 mg/kg body weight per day for methyl mercury. This is calculated to correspond to a whole blood mercury level below 5.8 mg/L (ppb) or a hair level below 1.0 mg/g (ppm). EPA has also issued a general fish consumption advisory for methyl mercury based on its RfD, advising women who are or may become pregnant, nursing mothers and young children to limit consumption of freshwater fish to one 6-8 ounce meal per week for adults and one 2-3 ounce meal for young children.

In 2001, the U.S. Environmental Protection Agency derived a reference dose (RfD) for methyl mercury, which is a daily intake that is likely to be without appreciable risk of deleterious effects during a lifetime. This derivation used a series of benchmark dose (BMD) analyses provided by the National Research Council (NRC). Analyses were performed for a number of endpoints from all three of the longitudinal cohort studies of the neuropsychological consequences of in utero exposure to methyl mercury: the Faroe Islands, Seychelles, and New Zealand studies, as well as from the integrative analysis that NRC had undertaken. The EPA applied a total uncertainty factor (UF) of 10 for intrahuman toxicokinetic and toxicodynamic variability and uncertainty while setting this RfD. Dose conversion from cord blood mercury concentrations to maternal methyl mercury intake was performed using a one-compartment model. EPA identified cardiovascular consequences of methyl mercury exposure and delayed neurotoxicity during aging as a result of previous exposure as significant areas requiring future attention.^{xxvii}

The European Commission endorsed the US EPA's reference dose as the appropriate methyl mercury standard

In October 2002, the European Commission (EC) released a report on mercury, entitled "*Ambient Air Pollution by Mercury (Hg). Position Paper.*"^{xxviii} The EC report identifies "exposure to methyl mercury via diet is the critical mercury problem for Europe, the reduction of potential exposure to this mercury species should be the focus for the steps to be taken in Europe...shares the recent evaluations by the US EPA and NRC (National Research Council)" and considers the US EPA's reference dose to be appropriate for Europe.

The British Food Standards Agency issued a new fish consumption advice for methyl mercury for sensitive populations based on a more protective standard

The British Food Standards Agency (FSA) began in February 2003 to advise pregnant and breastfeeding women, and women who intend to become pregnant, to limit their consumption of tuna to no more than two medium-size cans or one fresh tuna steak per week.^{xxix} The new safety guideline for pregnant and breastfeeding women and women intending to become pregnant is almost five times lower than that for the general population.^{xxx}

The United Nations Environmental Programme (UNEP) recognized the critical public health importance of sharply reducing public exposures to methyl mercury.

At the United Nations Environment Programme (UNEP) Governing Council meeting in Nairobi, Kenya in February 2003, the Global Environmental Ministers endorsed the December 2002 UNEP Global Mercury Assessment Report, which recognized the serious global health threats from methyl mercury:

“Methyl mercury is adversely affecting both humans and wildlife. This compound readily passes the placental barrier and the blood-brain barrier, and is a

neurotoxicant, which may in particular cause adverse effects on the developing brain. Studies have shown that methyl mercury in pregnant women's diets can have subtle, persistent adverse effects on children's development as observed at about the start of school age. Moreover, some studies suggest small increases in methyl mercury exposure may cause adverse effects on the cardiovascular system. Many people (and wildlife) are currently exposed at levels that pose risks of these, and possibly other adverse effects."^{xxxii}

In its decision, the Governing Council agreed that "there is sufficient evidence of significant global adverse impacts from mercury and its compounds to warrant further international action to reduce the risks to human health and the environment."^{xxxii} They recognized that mercury is a serious global pollutant warranting immediate action to alert the public to the exposure risks from mercury, especially vulnerable groups such as pregnant women, the fetus, the newborn and young children because of the sensitivity of the developing nervous system. The Governing Council charged UNEP with "developing strategies for enhanced outreach and risk communication activities to reach at-risk populations, including sensitive populations," affected by methyl mercury, implementing a plan to raise global awareness of the critical need to sharply reduce human exposures to mercury, and reporting on progress in implementation at the next Governing Council meeting in South Korea in 2005.^{xxxiii}

CONCLUSIONS

As detailed in this paper, there is a very large body of literature on the toxic effects of exposures to low levels of methyl mercury. Three prospective epidemiological studies, in the Faroe Islands, the Seychelles, and in New Zealand, have been singled out for the development of dose response calculations, and two additional cross-sectional epidemiological studies lent weight to the analysis. These studies have looked at a wide range of endpoints, including neurological function, memory, attention, visuospatial ability, IQ, age at achieving developmental milestones, and sensory function. Other studies provide strong emerging evidence that chronic low-level methyl mercury exposure is associated with a substantially increased risk of coronary heart disease. Additional evidence developed in the past three years demonstrates that significant numbers of consumers are routinely exposed to methyl mercury doses of public health concern, primarily through their diets.

Setting aside remaining points on which the three studies of prenatal neurobehavioral toxicity appear to disagree, the weight and the convergence of evidence that methyl mercury poses a substantial threat to public health is increasingly compelling.

We urge JECFA to take stock of the literature and of the deliberations by food safety authorities that have occurred since 2000, described here and to recommend a health protective exposure limit for methyl mercury. We respectfully suggest that the science supports a lowering of the Provisional Tolerable Weekly Intake to levels

consistent with the determination by the U.S. EPA and other international bodies of an RfD no greater than 0.1 µg/kg body weight per day.

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