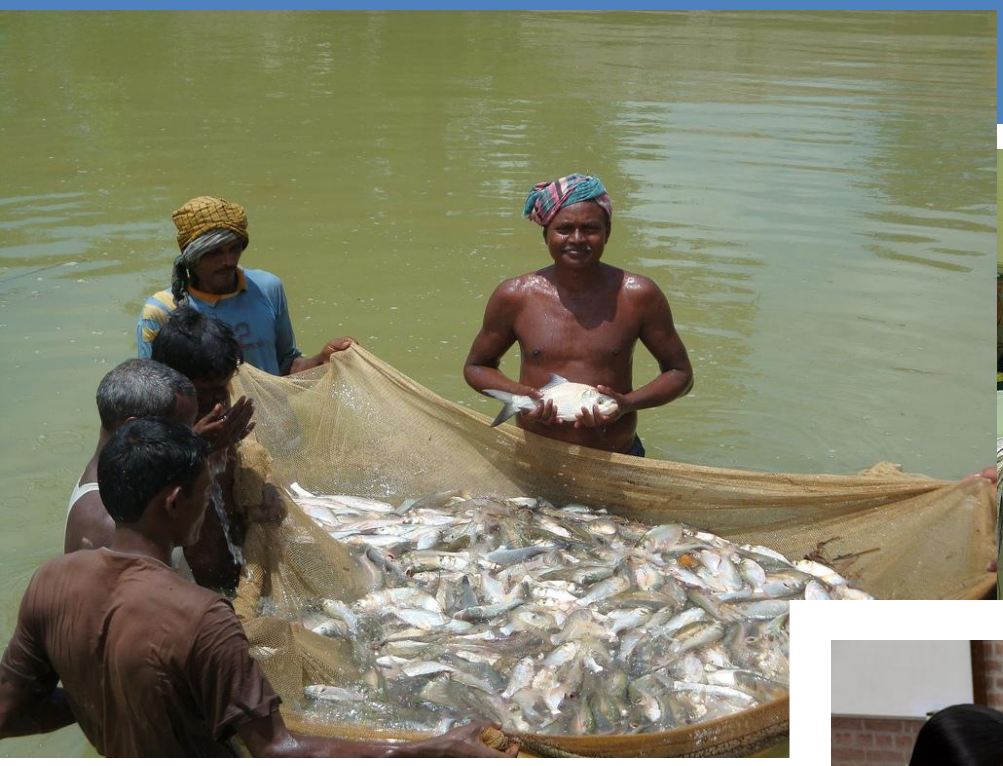
An Overview of Epidemiological Evidence on the Effects of Methylmercury on Brain Development, and A Rationale for a Lower Definition of Tolerable Exposure

December 2012



Prepared
by Edward Groth, PhD.
for

zero Hg
mercury working group

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This paper has been researched and prepared by Dr. Edward Groth, Groth Consulting Services, with all reasonable care and due diligence and acknowledges financial support of the European Environmental Bureau (Brussels) through a grant from the Sigrid Rausing Trust (UK). The EEB further acknowledges financial support from the European Commission. Sole responsibility lies with the authors and the donors are not responsible for any use that may be made of the information contained herein. The author has made every feasible effort to investigate objectively the relevant issues, and he is entirely responsible for the accuracy of the paper. Any third parties who rely on information contained in this document, or their own interpretation thereof, do so at their own risk.

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Introduction

It has been well known since about 1960 that methylmercury damages the developing brain. As research has progressed and methods have improved over the years, new evidence has consistently shown that harmful effects occur at lower levels of exposure than was previously recognized.

National and international government agencies have defined "tolerable exposure" limits, which are levels of intake of methylmercury believed, based on evidence available when they were set, to describe "safe" exposure, i.e., a level of intake sufficiently far below any exposure known to be harmful that it is reasonably certain to pose only a negligible risk, even to sensitive individuals and populations.

This document summarizes epidemiological research on the effects of methylmercury on the developing brain, beginning with severe pollution incidents in Japan that first documented methylmercury's effects, examining studies that found subtler but similar effects in island populations with high-fish diets, and reviewing recent studies that raise concerns that methylmercury has adverse effects even at exposures typical of ordinary fish consumption in most countries.

We then describe two current definitions of "tolerable exposure," and assess them in light of recent evidence that shows that neither definition currently provides an acceptable margin of safety. Finally, we propose a new definition of "safe" exposure based on all the evidence now available.

The health effects of fish consumption and research studying them are complicated by the fact that fish contains beneficial nutrients; fish consumption during pregnancy and by young children is essential for brain development. In research, beneficial effects of nutrients can hide the negative effects of mercury, and vice-versa. In risk management, women and children should not avoid fish or eat less fish (which could harm their health); instead they need guidance to choose low-mercury fish and shellfish.

Our proposed new definition of safe exposure balances these two important public-health concerns:

Encouraging consumption of widely available, popular low-mercury seafood varieties, while also keeping methylmercury exposure within acceptably safe limits.

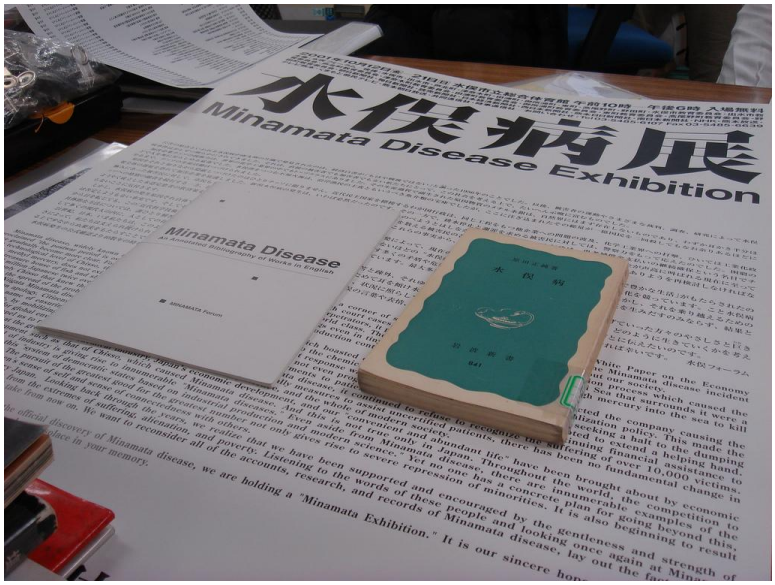
Early Evidence: Minamata and Niigata

In the 1950s, an acetaldehyde factory of the Chisso Chemical Company polluted Minamata Bay, Japan, with large amounts of methylmercury, and a similar operation polluted the ocean near Niigata. In both areas the mercury accumulated to very high levels in fish, and residents who ate locally-caught fish were exposed to extraordinarily high methylmercury doses. More than 2,200 people were officially diagnosed as severely poisoned; additional tens of thousands were exposed to high doses and were less severely affected (Yorifuji et al. 2012).

Although it was clear in 1956 that something toxic in the effluent from the factory [identified as methylmercury in 1959] was causing severe illnesses and deaths, the government chose to promote industrial growth, not require pollution control, and the company obstructed research and continued its discharges, until the plant was finally closed for economic reasons in 1968.

The people poisoned in these incidents suffered devastating damage to their nervous systems, now called "Minamata Disease." Adults experienced tingling in the hands, feet and face, tunnel vision and hearing loss, loss of coordination, a staggering gait. Their memories and speech were affected. Many died. But children whose mothers ate contaminated fish while they were pregnant suffered by far the worst damage, as methylmercury disrupted the intricate processes of brain development. Many children were born severely disabled, and could never walk, see, or speak normally or care for themselves (Yorifuji et al. 2012).

A study in Iraq in the 1980s involving consumption of methylmercury-contaminated wheat (Clarkson et al. 2003) also documented severe Minamata Disease. These early studies showed that methylmercury attacks the nervous system in myriad ways; that the developing brain is exquisitely sensitive to harm; and that mercury crosses the placenta, and affects the developing child before birth.



Studies of Island Populations with High-Fish Diets

In the 1980s, research sought to learn whether "background" methylmercury levels in ocean fish, from mercury entering the oceans over millennia from natural and human-made sources, rather than intense localized pollution, has milder but similar effects on the developing nervous system. Three major studies looked at island populations with seafood-rich diets and far above average exposure to methylmercury. They recruited pregnant women or those who had recently given birth, measured their mercury exposure, then tested their children for a variety of neurological functions. (Details of these and other studies are summarized in **Figure 1** and **Table 1**.)

Figure 1. Methylmercury Levels in Blood and Hair Associated with Adverse Neurodevelopmental Effects, 1960-2012

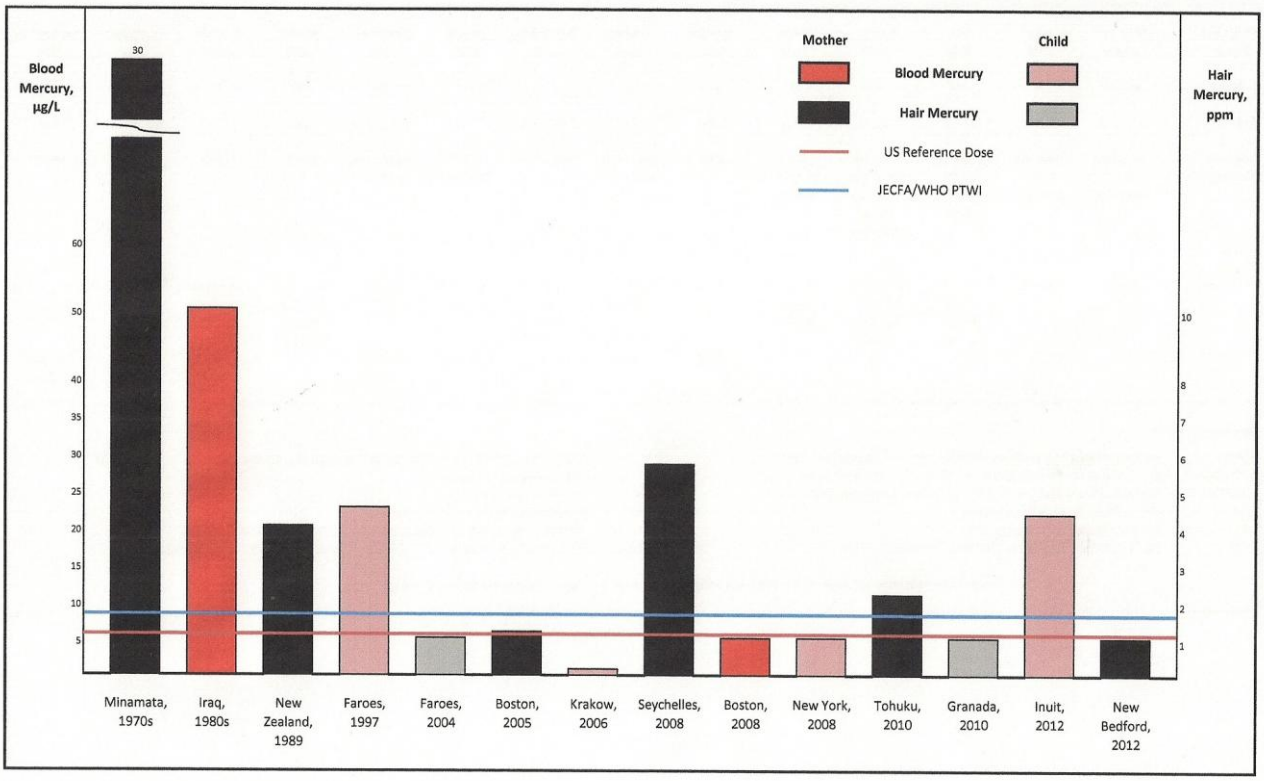


Table 1. Details of studies shown in Figure 1

Study Site & year	Minamata 1960s	Iraq 1980	N.Z. 1989	Faroes 1997	Faroes 2004	Boston 2005	Krakow 2006	Seychelles 2008	Boston 2008	New York 2008	Tohuku 2010	Granada 2010	Canada 2012	New Bedford 2012
Subjects	>2,000	70	237	917	882	135	233	228	341	151	498	72	279	421
Age	0 - 80+ yr	0 - 4 yr	4 - 7 yr	7 yr	14 yr	6 mo	1 yr	9 & 30 mo	3 yr	1, 2, 3, 4 yr	3 days	4 yr	School age	8 yr
Outcome Measure(s)	Multiple brain functions	Multiple brain functions	Academic TOLD MSCA WISC	Attention Language Memory Motor Eye-Hand	Brain auditory signals	VRM	BSID - PDI BSID - MDI	BSID -PDI	PPVT WRAVMA	BSID - PDI WPPSI-R	NBAS	MSCA	ADHD	ADHD
Size of Effects														
Mercury (-)	severe	severe	- 0.5 IQ point per ppm in hair	Each 2x Hg = 1.5 - 2 mo develop. delay	Delay in signal latency	-7.5	- 16.6 PDI - 10 MDI	-2.7	- 4.5, - 4.6	- 4.2 PDI - 3.8 IQ	Negative effect on motor cluster	- 6.6 general - 8.4 memory - 7.5 verbal	RR = 4	RR = 1.4 - 1.7
Fish (+)	n.a.	n.a.		n.a.		+ 4.0	n.a.	n.a.	+ 2.2, + 6.4	+ 8.7 PDI + 5.6 IQ				60% risk reduction

Outcome Acronyms

ADHD =	Attention Deficit/Hyperactivity Disorder, Standard Evaluation Protocol	RR =	Relative Risk. RR = 2 means high-exposed group had twice the risk of low-exposed group
BSID MDI =	Bayley Scales of Infant Development, Mental Development Index	TOLD =	Test of Language Development
BSID PDI =	Bayley Scales of Infant Development, Psychomotor Development Index	VRM =	Visual Recognition Memory
MSCA =	McCarthy Scales of Children's Abilities	WISC =	Wechsler Intelligence Scales for Children
NBAS =	Neonatal Behavioral Assessment Scale	WPPSI-R =	Wechsler Preschool and Primary Scales of Intelligence, Revised
PPVT =	Peabody Picture Vocabulary Test (measures verbal ability)	WRAVMA =	Wide Ranging Assessment of Visual Motor Abilities (measures fine motor coordination)

Note: Most outcomes are scored on a 100-point scale, so a score of - 5 suggests a 5 percent negative change

- A study in New Zealand found that children whose mothers had higher mercury exposure when pregnant scored lower on measures of academic achievement, language development, cognitive function and general intelligence (Kjellstrom et al. 1986, 1989; Crump et al. 1998).
- A study in the Faroe Islands, where the diet is rich in fish and includes high-mercury pilot whale meat, found that 7-year-old children with higher prenatal mercury exposure had lower scores for attention, language skills, memory, eye-hand coordination and other fine motor responses (Grandjean et al. 1997). Most of these effects were still present when the children were re-tested at age 14 (Debes et al. 2006).
- The Faroes investigators later re-analyzed their data to adjust for beneficial effects on brain development of fish the mothers ate while pregnant, found that there were some beneficial effects, and that the adverse effect of methylmercury was larger than they had earlier reported (Budtz-Jørgensen et al. 2003, 2007).
- A similar study in the Seychelles Islands initially did not find adverse effects comparable to those seen in the Faroes (Myers et al. 2003, Davidson et al. 2006). In 2001, the researchers began a second study to look for beneficial effects of the Seychellois women's very high consumption of fish (Myers et al. 2007, Davidson et al. 2008a, Lynch et al. 2011).
- This second study found a small but significant adverse effect of mercury on psychomotor development (Davidson et al. 2008b, Strain et al. 2008), which the researchers concluded had most likely been masked by beneficial nutritional effects in their earlier analyses. They also observed a small beneficial effect of maternal fish intake (Stokes-Riner et al. 2010). These recent results resolved a major source of confusion; it is now clear that the observations in the Seychelles are quite consistent with those from other studies.

Epidemiological Studies Since 2003

In the past decade, research has begun to focus on the next important question: If effects occur among women with high-fish diets, do smaller, subtler effects also occur in populations with ordinary, average fish consumption and mercury exposure? Using improved research methods developed in recent years, eight well-designed studies in six countries have focused on this question.

- In the Faroes, researchers observed a delay in transmission of auditory brain signals in 14-year-old subjects, not associated with their prenatal mercury exposure, but linked with the children's recent mercury exposure from fish in their own diets (Murata et al. 2004).
- A study in Boston found that 6-month-old infants' visual memory was adversely affected in children whose mothers had higher mercury exposure, while children whose mothers ate fish twice a week or more had improved scores on the same function (Oken et al. 2005).
- The same Boston investigators tested children at age three years for verbal development and fine motor coordination. Children of mothers with higher mercury exposure scored lower on both measures, while children whose mothers ate fish more than twice a week scored higher on both outcomes (Oken et al. 2008).
- A study in Krakow, Poland tested 1-year-olds for cognitive and psychomotor development and found substantially delayed development in children with higher prenatal mercury exposure (Jedrychowski et al. 2006).
- A study in New York City found that fish eaten during pregnancy had substantial beneficial effects on cognitive development in children tested at 12, 24, 36 and 48 months of age, while elevated prenatal

methylmercury exposure significantly adversely affected the same functions—psychomotor development, verbal and full IQ (Lederman et al. 2008).

- A study in Tohuku, Japan examined 3-day-old infants using tests for neurological functions in newborns. Motor functions were adversely affected by mercury exposure, and beneficially affected by high maternal fish consumption (Suzuki et al. 2010).
- A study in Granada, Spain assessed general cognition, verbal development, memory and motor development in 4-year-olds. Children with above-average methylmercury exposure scored lower on three outcomes (Freire et al. 2010). The children's own fish consumption, not maternal fish consumption during pregnancy, was associated with these effects.
- Two studies this year have linked prenatal mercury exposure to Attention Deficit/ Hyperactivity Disorder (ADHD). Boucher et al. (2012) evaluated Inuit children in northern Canada and found a higher risk for the inattention component of ADHD in those with higher mercury exposure. Sagiv et al. (2012) assessed 8-year-olds in New Bedford, Massachusetts (USA) and associated higher prenatal methylmercury exposure with a greater risk of both the inattention and the impulsivity components of ADHD, while high maternal fish intake reduced the risk of ADHD.

In most of these recent studies, the people studied were eating comparatively ordinary amounts of fish, and their exposure to methylmercury was only slightly above average for their countries. The Inuit study is an exception; their diet includes fish and marine mammals and is similar to the Faroese diet. But fish consumption in the other studies is typical of many diets around the world. For example, the Faroese teenagers, the 4-year-olds in Granada, and the women in the Boston studies all had an average hair mercury level around 1 part per million (ppm), and the New Bedford mothers' average hair mercury level was just 0.45 ppm, all well within the normal range. The average hair mercury level in most countries is below 1 ppm; in the US, for example, it is around 0.5 ppm, and only 10 to 20 percent of different subgroups have hair mercury above 1 ppm. The Japanese eat more fish than is common in most Western countries, and the average maternal hair mercury level in the Tohuku study was 2.22 ppm. People in many other Asian countries consume fish at rates similar to the Japanese.

The low levels of methylmercury exposure associated with adverse effects in recent studies can be contrasted with levels in Minamata, where hair mercury averaged 30 ppm, and in New Zealand, the Faroes and the Seychelles (average hair levels were 4, 4 and 5.9 ppm, respectively). (See **Figure 1**.)

These recent studies make it clear methylmercury exposure poses risks not just for populations with unusually high fish consumption; it is also a concern for people who eat everyday amounts of fish and have mercury exposure in the high region of the typical range. These studies provide no evidence of a threshold below which adverse effects are unlikely. The studies suggest that perhaps 10 percent of pregnant women and young children in the US and Europe, and undoubtedly a larger fraction than that in countries where fish is a more important part of the diet, are at risk for significant damage to the children's developing brains, from the methylmercury in the ordinary amounts of fish they eat.

Several published studies have found no adverse effects of methylmercury in populations with ordinary or even high seafood consumption. A few studies have associated improved cognitive performance with elevated methylmercury levels, suggesting that the beneficial effects of fish nutrients were greater than the adverse effects of mercury in those cases. For a more comprehensive review of most of the studies on this topic published in the past 40 years, see Julvez et al. (2012).

Several of the studies reviewed here also found beneficial effects of maternal fish consumption, in some cases larger than, in others smaller than and in others about the same size as the adverse effects of methylmercury. The relative size of beneficial and adverse effects is an important question that needs more research. Whatever their magnitude, benefits and risks are distributed differently. Benefits seem to occur broadly in everyone who eats enough fish, but most of the risk falls on a small fraction of the population who eat comparatively larger amounts of higher-mercury fish.

Government Definitions of Tolerable Exposure, 1999-2003

As research found that methylmercury in fish from unpolluted ocean areas can damage the developing brain in children whose mothers eat a great deal of fish, national governments and intergovernmental organizations (such as the World Health Organization [WHO]) took steps to define an upper limit of "safe" exposure. In fact, there is no "bright line" between safe and unsafe exposure to methylmercury; risk generally increases as exposure rises, and the dividing line between innocuous and harmful intake varies a great deal from one person to the next. Nevertheless, health authorities often find it useful to define an intake level that they consider "safe," as a reference point for comparison with various actual exposures. Two important examples are described here.

In 1999 the US Environmental Protection Agency (EPA), supported by an expert committee of the US National Research Council (NRC 2000), specified a Reference Dose (RfD) for methylmercury. The EPA used the best data available at the time, from the Faroes study (Grandjean et al. 1997), which showed a clear adverse effect in children whose average cord-blood mercury level at birth was 58 micrograms of methylmercury per liter of blood (58 µg/L). The EPA applied an "uncertainty factor" of 10 (i.e., divided the Faroes blood level by 10), yielding a Reference Level of 5.8 µg/L (Rice et al. 2003). Application of an uncertainty factor is a standard method for providing a margin between harmful exposure and a lower dose that should be safe; its main purpose is to take into account both known and unknown factors that make different individuals differentially sensitive to toxic effects.

The EPA then used a mathematical relationship between dietary intake and blood methylmercury to calculate the Reference Dose, a long-term dietary intake level of methylmercury that would produce an equilibrium blood level of 5.8 µg/L in an adult female. That RfD is 0.1 microgram of methylmercury per kilogram of body weight per day (0.1 µg/kg/day; Rice et al. 2003). National health surveys by the US Centers for Disease Control and Prevention have shown that the average blood mercury level in US women of childbearing age is about 0.9 µg/L, and roughly 6 percent of this subpopulation have levels above 5.8 µg/L (Mahaffey et al. 2009).

In 1978, following the events in Minamata, the WHO had adopted a limit called a Provisional Tolerable Weekly Intake (PTWI) for methylmercury, set at 3.3 µg/kg/week. (The US limit, on a weekly basis, is 0.7 µg/kg/week, so this early WHO PTWI was about five times as high as the later US RfD.) The 1978 limit was still in effect In 2001, when the Codex Alimentarius Commission, an international food safety body, asked that it be reviewed. The Joint Expert Committee on Food Additives (JECFA) did so in 2003 and recommended a lower PTWI, 1.6 µg/kg/week, which the WHO soon adopted. The current international exposure guideline for methylmercury intake is thus about 2.3

times as high as the US RfD, but JECFA explained in its report that this dose should produce an equilibrium maternal blood mercury level of about 8.7 µg/L, which is 1.5 times the US Reference Level.

JECFA used data from the Faroes and the Seychelles studies, which it combined. Neither the US EPA nor JECFA used the New Zealand data, and the Seychelles data in 2003 had not shown any statistically significant adverse effects of methylmercury. JECFA also used a smaller (6.4-fold, instead of 10-fold) uncertainty factor, explaining in its report that it felt this margin was sufficient and that the risks associated with decreased fish consumption needed to be taken into account when setting limits for mercury in fish (JECFA 2003).

The difference between these two exposure limits reflects many subjective scientific and value-laden judgments that experts make when developing such guidelines: Which data to use, how to interpret the data, how much precaution should be applied to account for uncertainties, and so forth. Neither the US RfD nor the JECFA PTWI is necessarily more "correct;" they are simply different.

A Revised Definition of Tolerable Intake is Needed

The US RfD and the JECFA PTWI are based on evidence from the Faroes and Seychelles studies, available a decade ago. But the substantial new evidence published since 2003, reviewed here, shows quite convincingly that neither limit is adequate to protect public health against methylmercury damage. The recent studies show both beneficial and adverse effects in people eating ordinary amounts of fish. But as **Figure 1** illustrates, the methylmercury doses associated with the adverse effects in recent studies are at least 5- to 10-fold lower than exposures found harmful a decade ago. As the figure makes clear, several studies have now reported adverse effects at mercury doses below the US RfD, and even farther below the JECFA PTWI.

For example, mothers with high mercury exposure in the Boston study had hair mercury levels at or above 1.2 ppm, which corresponds to a blood mercury level of about 5.2 µg/L; in the New York study, the babies' umbilical-cord-blood mercury was 5.05 µg/L; cord-blood in the Krakow study averaged just 1.05 µg/L. These blood levels are all below the US Reference Level of 5.8 µg/L. The Faroese 14-year olds, the Spanish 4-year-olds and the mothers in New Bedford had average hair mercury levels of 0.96 ppm, 0.96 ppm and 0.45 ppm, respectively, which also correspond to blood levels around or below 5 µg/L.

Progress in research has therefore made it clear that the RfD and the PTWI for methylmercury are no longer valid definitions of "safe" exposure. They provide no margin at all below harmful doses, and do not protect public health. In fact, new research has often led to downward revision of environmental health criteria, and it seems evident that the time has come to update official definitions of tolerable methylmercury exposure, to better align them with currently available epidemiological evidence.

But what should the new tolerable intake level be? Three concerns need to be balanced:

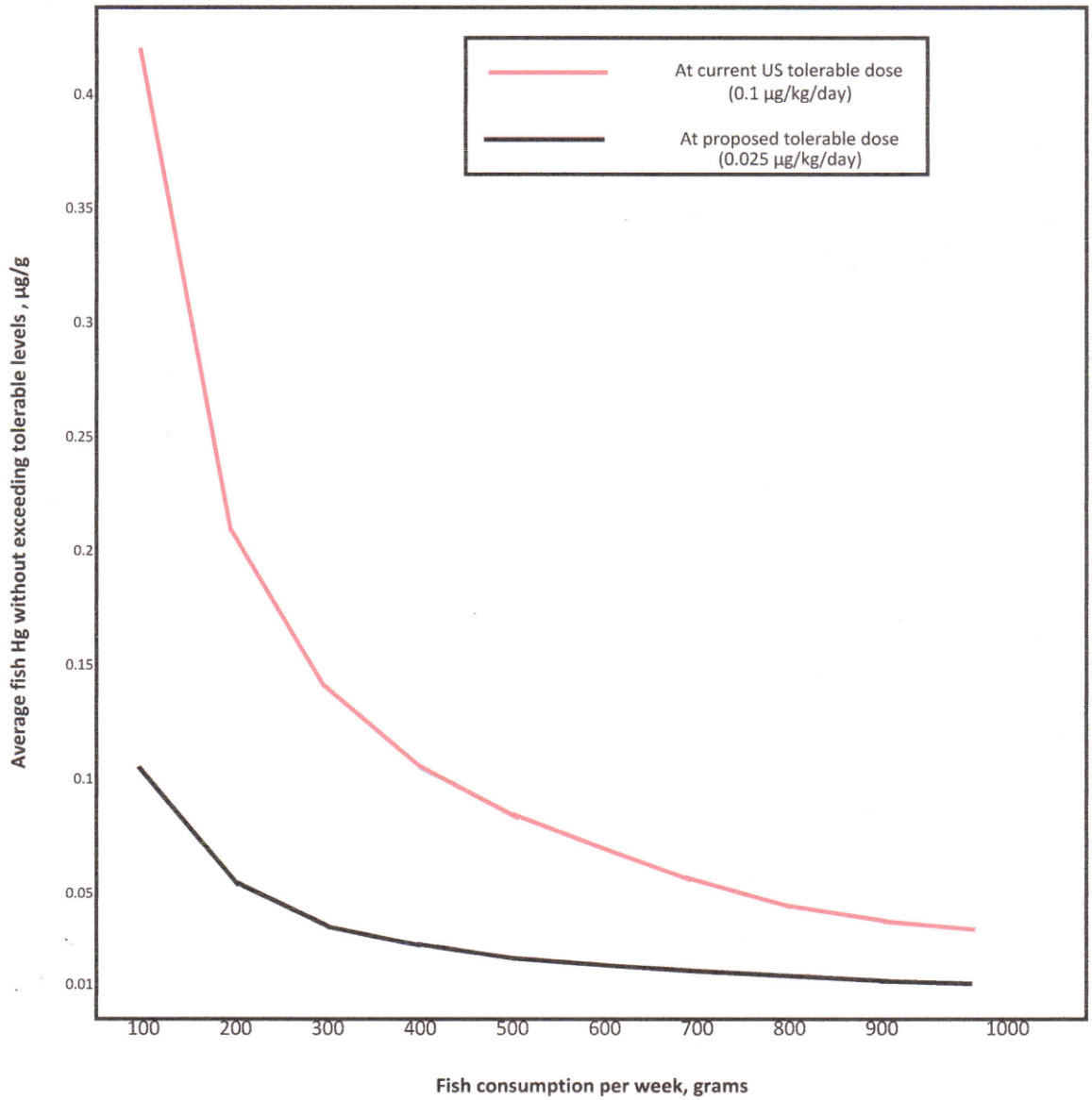
- First and foremost, the tolerable intake should be set low enough to provide an acceptable margin of safety below exposures that current evidence suggests are likely to be harmful.
- Second, the level must not be set so low that it restricts fish consumption; some degree of risk has to be accepted in return for the major public health benefits of eating fish. If efforts to avoid methylmercury exposure reduce fish consumption, counterproductive damage to public health seems likely. This risk must be given significant weight in managing the risk from mercury.
- Finally, tolerable exposure goals should be feasible to achieve; that is, most consumers should be able to attain safe exposure while eating familiar, widely available, economically affordable seafood. If an exposure guideline requires dramatic changes in most people's dietary patterns, it may be sound in theory but is likely to be nearly worthless in practice.

The approach the EPA used in 1999, starting with the lowest harmful dose level and applying an uncertainty factor of 10, might initially be considered. Since several recent studies reported adverse effects at blood mercury levels around 5 µg/L, roughly the Reference Level in blood associated with the current RfD, this approach would reduce the current US RfD by a factor of 10—to 0.01 µg/kg/day. However, we think such a low RfD would be very difficult to meet without substantially reducing fish consumption, to the overall detriment of public health.

We propose instead to replace both the US RfD and the JECFA/WHO PTWI with a new guideline of 0.025 µg/kg/day, i.e., one-quarter of the current US RfD. This dose level should be feasible to achieve for most people without restricting their overall seafood consumption; however, women and parents would need to learn to choose low-mercury species. **Figure 2** shows average methylmercury levels that fish consumed by a 60-kg (132-pound) woman would need to contain to keep weekly her mercury exposure within 0.025 µg/kg/day. As the figure shows, the average mercury level decreases as fish consumption increases. For women eating 100 to 500 grams of fish a week (about 1 to 5 servings), the average mercury level would range from about 0.1 to 0.02 ppm. For women consuming 1 kg of fish per week, the average would have to be 0.01 ppm.

A low average mercury level can be achieved if consumers have information about the mercury content of many different seafood items and choose wisely. For example, a majority of the most popular seafood choices and 70 percent of all seafood sold in the US have mercury levels below 0.1 ppm (Groth 2010). Low-mercury choices include shrimp, salmon, sardines, tilapia, scallops, clams and mussels, pollock, crabs, catfish, flounder and sole—all available, familiar, tasty and affordable. As global data indicate in the Biodiversity Research Institute 2012 report "*Mercury in the Global Environment: Patterns of Global Seafood Mercury Concentrations and their Relationship with Human Health"*, Figure 3, a wide variety of similar low-mercury choices is also available in many parts of the world. It therefore seems feasible for consumers—armed with reliable information—to keep their own methylmercury exposure within tolerable limits.

Figure 2. Average mercury levels in fish consistent with tolerable dose levels as fish intake increases.



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