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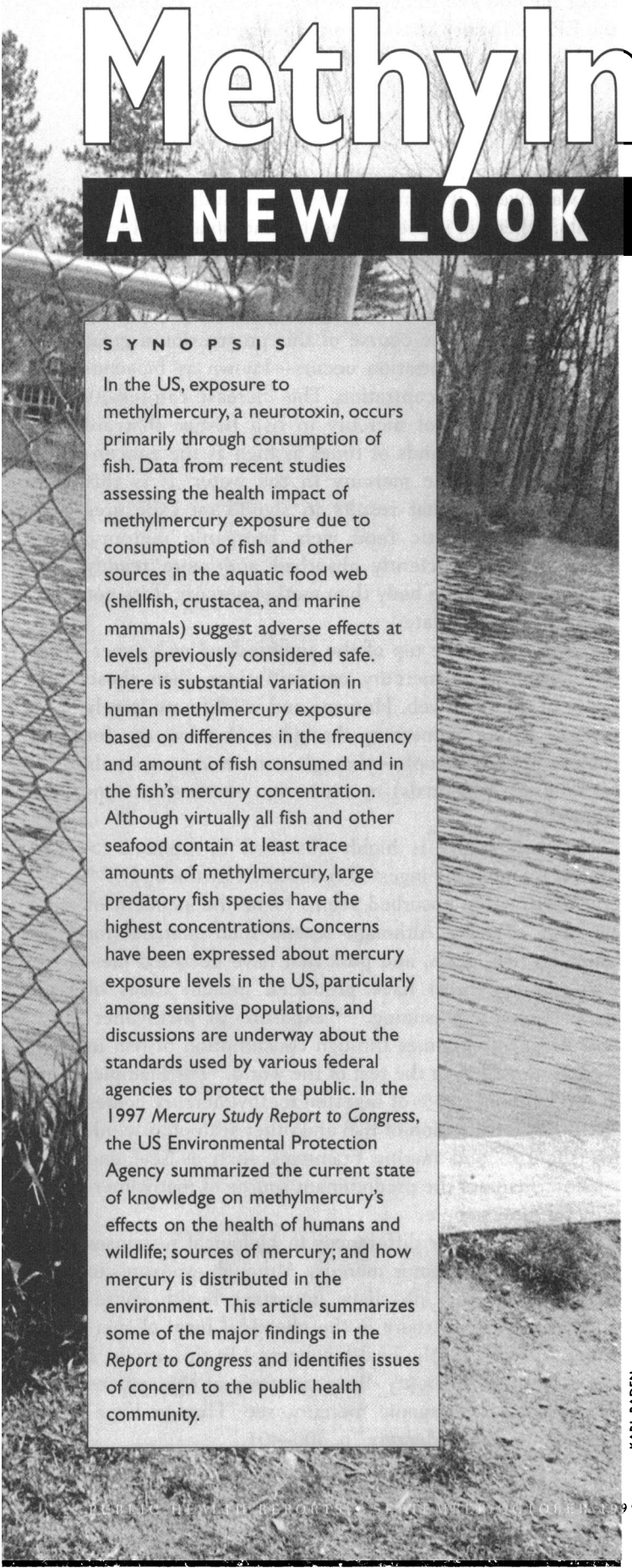
Kathryn R. Mahaffey, PhD

Methylmercury: A NEW LOOK AT THE RISKS



SYNOPSIS

In the US, exposure to methylmercury, a neurotoxin, occurs primarily through consumption of fish. Data from recent studies assessing the health impact of methylmercury exposure due to consumption of fish and other sources in the aquatic food web (shellfish, crustacea, and marine mammals) suggest adverse effects at levels previously considered safe. There is substantial variation in human methylmercury exposure based on differences in the frequency and amount of fish consumed and in the fish's mercury concentration. Although virtually all fish and other seafood contain at least trace amounts of methylmercury, large predatory fish species have the highest concentrations. Concerns have been expressed about mercury exposure levels in the US, particularly among sensitive populations, and discussions are underway about the standards used by various federal agencies to protect the public. In the 1997 *Mercury Study Report to Congress*, the US Environmental Protection Agency summarized the current state of knowledge on methylmercury's effects on the health of humans and wildlife; sources of mercury; and how mercury is distributed in the environment. This article summarizes some of the major findings in the *Report to Congress* and identifies issues of concern to the public health community.

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CLINICALLY EVIDENT METHYLMERCURY poisoning due to consumption of contaminated fish has occurred in such diverse regions of the world as Japan and the Amazon River Basin. Exposure to high levels of methylmercury has produced fatalities as well as devastating neurological damage among adult survivors. Fetuses are more sensitive than adults. In Minamata and Niigata, Japan, mothers who themselves had only mild symptoms gave birth to infants who had severe in utero methylmercury poisoning, resulting in a condition resembling cerebral palsy but also accompanied by blindness and deafness.[1] Lower methylmercury exposures can produce changes in visual function, altered sensory and motor nerve function, and developmental delays that reflect *in utero* damage to the fetal nervous system.[2] Whether exposures sufficiently high to cause symptoms of subtle mercury toxicity are occurring in the US is currently being evaluated by public health and environmental organizations.

Virtually every human being has at least trace amounts of mercury in his or her tissues, resulting from environmental exposures, mercury-silver amalgams in dental restorations, occupational exposures, or exposure to often overlooked sources such as pharmaceuticals. Mercury in pharmaceuticals is a newly identified problem. Mercury has been shown to be an ingredient in some folk remedies and cosmetics that fall outside of government regulatory control. Within the past few months, use of mercury-containing preservatives in vaccines has been reviewed by the American Academy of Pediatrics and the US Public Health Service. *[Ed. note: see related News & Notes item on p. 393.]*

Many readers will remember seeing striking photographs of people with mercury poisoning in Japan in the 1960s. In the US in recent years, concerns have been raised about the amount of methylmercury in the fish supply, and discussions have arisen over the standards used by various federal agencies to protect the public's health.[3] In the 1997 *Mercury Study Report to Congress*, the US Environmental Protection Agency (EPA) summarized the current state of knowledge on methylmercury's effects on the health of humans and wildlife; sources of mercury; and how mercury is distributed in the environment.[4] In what follows, I give a brief summary of some of the major findings in the *Report to Congress* and identify issues of concern to the public health community.

How Is Mercury Distributed in the Environment?

Mercury is widely distributed around the earth. One of the elements on the Periodic Table, mercury cannot be destroyed; the total amount present on the planet will always be the same. Mercury cycles in the environment as a result of natural phenomena and human activities.

Natural phenomena such as volcanoes cause mercury to be released to the air. Mercury releases also occur as a result of industrial processes and of combustion of mercury-containing wastes and fuels. Mercury has been widely used in industrial processes because of its chemical and physical properties (for example, it conducts electricity, it responds to temperature and pressure changes, and it forms alloys with many metals). Mercury is released from industrial processes as air emissions or as water discharges. Mercury-bearing wastes from industrial processes or from eventual disposal of mercury containing products are either disposed of or burned, which can also result in releases to the air or water. Combustion of fuel, especially coal, is another important source of mercury releases. The US Environmental Protection Agency (EPA) estimates that these anthropogenic releases (that is, releases resulting from human activity) have increased to a level two to five times those of pre-industrial times.[4] (An in-depth analysis of the fate and transport of mercury can be found in the EPA's *Mercury Study Report to Congress*.[4])

Mercury in the atmosphere has a complex fate. (See Figure 1.) The mercury that is released into the air is mercury vapor or inorganic mercury. Mercury released into the atmosphere as a gas ultimately redeposits on the earth with precipitation. Once on the earth or in the waterways, it is incorporated into sludges or sediments, where it is methylated by microbial or abiotic processes into methylmercury. The plant and sedimentary materials are consumed by small fish that are consumed by progressively larger fish and finally by humans. During the course of this progression a great increase in concentration occurs—known as bioaccumulation or bioconcentration. This increase can results in concentrations of mercury in fish tissues that are hundreds of thousands of times as high as the concentration of inorganic mercury in the water. It is this bioaccumulation that results in significant exposures through the aquatic food web. Inorganic mercury, which is less efficiently absorbed and more readily eliminated from the body than methylmercury, does not tend to bioaccumulate.

Predators at the top of the aquatic food web generally have higher mercury concentrations than those lower in the food web. Humans and wildlife are largely exposed to methylmercury through eating fish or—for some groups of people—through consuming mammals (usually sea mammals) or birds that themselves consume fish.

Methylmercury is highly absorbed by humans (> 95% of the mercury ingested is absorbed by the body),[5–8] and the fraction absorbed seems to be independent of the type of food. Although several food sources (for example, fish, grain, and pork that have been fed mercury-treated grain) have produced human cases of methylmercury poisoning,[9–11] exposure to methylmercury most often comes through consumption of fish in the US as well as in the rest of the world.[12] For example, in the US about 95% of ingested methylmercury comes from the consumption of fish and other seafood (including shellfish and marine mammals such as seal and whale).[7] Fish are the predominant source of methylmercury for most people.[7]

There are major differences in biological responses to inorganic and organic mercury. Although exposures to inorganic mercury also have important health consequences, methylmercury is the chemical form of mercury of greatest public health concern.[4] In this article, I focus on methylmercury; for a summary of the sources of exposure to inorganic mercury, see "Human Exposures to Inorganic Mercury," p. 400–401.

ADVERSE HEALTH EFFECTS OF METHYLMERCURY

Methylmercury at high doses is extremely well documented as a human neurotoxin, with effects mainly on the motor and sensory systems, especially in the area of sensory-motor integration. As with all chemicals, the amount of exposure and susceptibility of the host determine the effects.

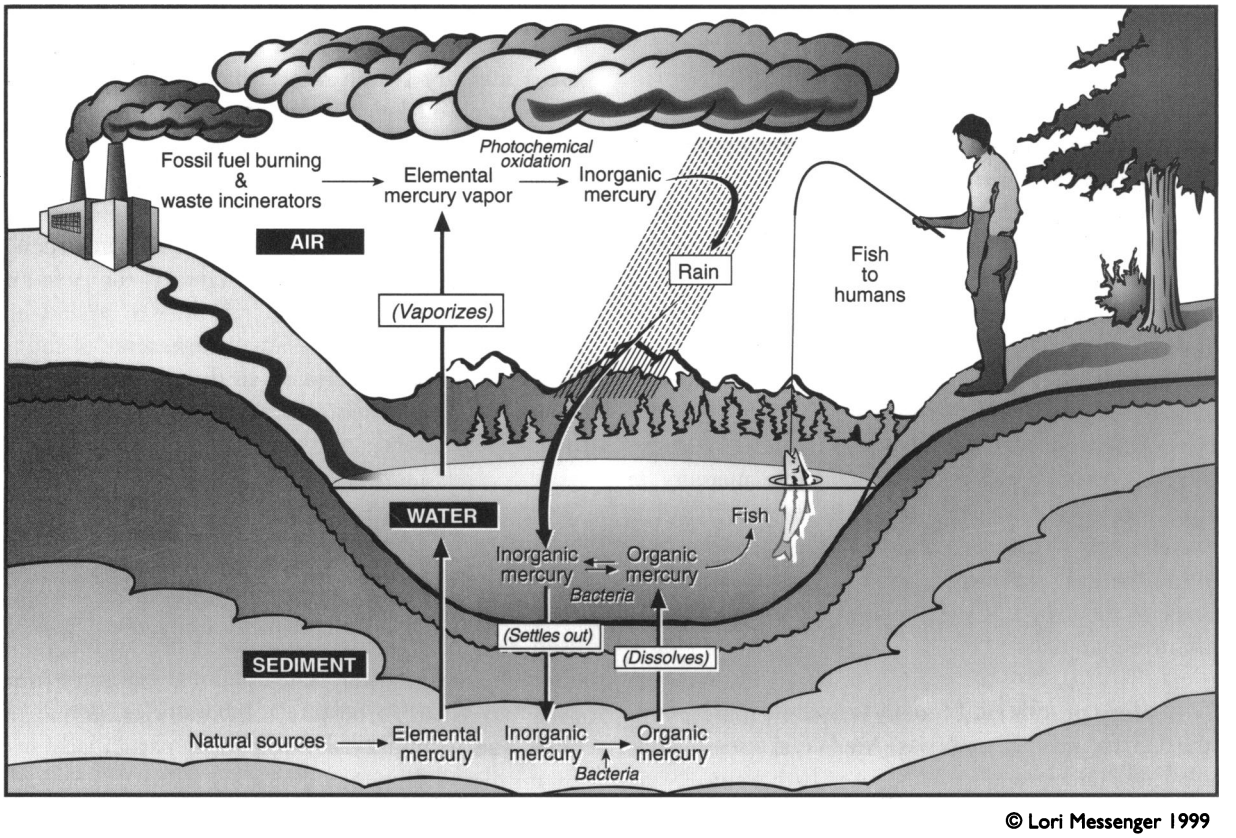
Epidemics of methylmercury poisoning have occurred in this century in various parts of the globe, producing health problems for humans, wildlife, and domestic animals. During the 1950s and 1960s, major epidemics of methylmercury poisoning in Japan, resulting in deaths and severe neurological damage, were caused by consumption of seafood in Minamata and freshwater fish in Niigata.[13] Domestic animals such as cats that consumed fish also developed neurological problems. Epidemics of methylmercury poisoning resulting from consumption of methylmercury used as a fungicide on grain occurred in Iraq in the 1960s and 1970s.[10] (Use of mercury-containing fungicides on seed grain has since been banned in many countries.) These epidemics, and a number of case reports, including one from the United States,[11] provide the strongest possible evidence linking exposure to methylmercury with human fatalities and neurological disease.

Methylmercury's effects on the nervous system follow a sharp dose-response curve. A clear demonstration of the steepness of the dose-response curve for methylmercury and neurological changes was shown by Wobesser's investigations with mink.[14] A diet containing methylmercury at 1.1 micrograms of mercury per gram (μg/g) of food produced histopathological abnormalities in the central nervous system with no clinical symptoms, but 1.8 μg/g produced anorexia, posterior ataxia, and other neurological symptoms. At 4.8 μg/g, death occurred within 26 to 36 days, and at 8.3 μg/g, within 19 to 26 days.

Nervous system effects in adults have been used in establishing limits aimed at protecting the public's health. The development of paresthesia has been considered an early indicator of neurological damage in adults following methylmercury exposure.[12,15,16] Until recently, such changes were thought to occur when mercury concentrations in hair are greater than 50 parts per million (ppm).[12] Adverse effects on neuromotor function and visual contrast sensitivity have been reported among adults whose hair mercury concentrations were lower than 50 ppm.[17] These newer data suggest adverse nervous system at a

(continues on p. 402)

Figure. Mercury in the environment



dose below that previously considered the threshold for clinical effects among adults.

Following the birth in Japan of severely damaged infants to mothers who themselves had minimal symptoms of methylmercury poisoning,[18] the increased sensitivity of the fetus was recognized. The fetal nervous system is currently considered to be the organ system most vulnerable to the effects of methylmercury.[4,12] Recent publication of epidemiology data associating changes in children's blood pressure with maternal hair mercury levels <10 ppm[19] suggest health outcomes in addition to delays in neurological development may be used in setting standards aimed at protecting public health (such as EPA's Reference Dose). Because development of the fetal nervous system is more sensitive to methylmercury than the mature nervous system, the maternal-fetal pair is considered to be the most sensitive human subpopulation. The German *Kommission "Human-Biomonitoring"* (Human Biomonitoring Commission) of the *Umweltbundesamtes* (Federal Environment Office) judged the fetus to be five to ten times more sensitive to methylmercury than adults.[20] Government recommendations to limit mercury exposure are increasingly based on protection of the fetal nervous system. Although the dose of methylmercury regarded as "safe" varies with specific recommendations, there is a consensus that at high exposures the developing nervous system can be disastrously damaged and that fetuses are more sensitive to methylmercury than adults. Most recent changes in recommended levels for methylmercury aim to protect the fetus. Currently it is thought that adverse effects can be identified in the child when the pregnant woman's exposures result in maternal hair concentrations between approximately 5 ppm for subtle developmental changes[20] to a range of 10 ppm to 20 ppm for clinically obvious changes such as delayed walking.[12]

Is there evidence of methylmercury toxicity in the United States? Fortunately, clinically evident, severely debilitating neurological damage of the type produced by methylmercury in Japan and Iraq has not been found in the United States, with extremely rare exceptions.[11] In the US, hair mercury concentrations are usually lower than 3 ppm and typically lower than 1 ppm, according to a variety of data sources (for a summary of these data, see EPA's *Mercury Study Report to Congress*.[2,7]) A number of reports involving small numbers of subjects have identified adults with hair mercury in the range of 3 ppm to 10 ppm.[21–23]

Among women, hair mercury concentrations ≥10 ppm are of concern because of potential risks to developing fetal nervous systems, according to the World Health Organization.[12] The number of US women of childbearing age whose hair mercury is ≥10 ppm is simply not known, although such cases have been reported[24] (Personal communications, C. Greg Smith, MD, North Carolina Department of Environmental Health and Natural Resources, and Michael Gochfeld, MD PhD, Department of Environmental and Community Medicine, UMDNJ–Robert Wood Johnson Medical School, August 1999).

One occasionally hears the statement that mercury poisoning doesn't happen in the United States. While cases of clinically evident mercury toxicity are rare or nonexistent in this country, subtle methylmercury toxicity may be another matter. Would subtle methylmercury toxicity be recognized? If we focus on the classical, clinically evident signs of methylmercury intoxication, will we fail to recognize the sensitive, but nonspecific, symptoms of subtle methylmercury toxicity? Many of the symptoms produced by mild to moderate methylmercury toxicity (for example, delayed neurological development, impaired cognitive skills) can also be caused by a number of other factors.

Recognizing that exposures we routinely live with may be harmful is easier if there are examples of other chemical exposures to provide a frame of reference. Within the field of environmental health, pediatric lead toxicity is an example. Over the past 20 years, national estimates of blood lead levels for the United States population have showed mean values[25] that are now recognized as harmful to children's cognitive[26–29] and behavioral development.[30,31] During the period from 1960 through 1985, the blood lead level for children considered acceptable by the US Public Health Service dropped from 40 µg/dL to 10 µg/dL.[32] Considerable controversy was voiced during that period over the validity of the findings of reduced cognitive ability with increasing blood lead in the range of 10 µg/dL to 30 µg/dL. Long-term follow-up of children in two of the major cohorts has demonstrated that blood lead levels considered "normal" in the 1970s are associated with impaired intellectual function and behavioral function.[28,30,31] Regarding the *in utero* effects of moderate exposure to methylmercury, we are still in the period of controversy. The outcome remains to be seen.

WHAT LEVEL OF METHYLMERCURY EXPOSURE IS ASSOCIATED WITH NEURODEVELOPMENTAL EFFECTS?

Recently there has been a lot of focus on the part of public health and environmental groups on what levels of exposure to methylmercury can be considered safe.[33–35] Although the epidemics in Minamata and Niigata made clear that severe neurological damage can result from consumption of contaminated fish, the dose-response data on which many recommendations for limits on methylmercury exposure are based on data from the Iraqi epidemic.[10,36] Because the exposures in Iraq were of about six months' duration, there have always been questions about extrapolating the effects of this exposure period to longer-

Table 1. Comparison of government-recommended limits on methylmercury exposure

Government agency	*Date*	*Recommended limit*	*Critical effect and target group*
US Food and Drug Administration	1970s	Acceptable Daily Intake = 0.4 µg/kgbw/day	Paresthesia in adults
US Joint Expert Committee on Food Additives	1989	0.48 µg/kgbw/day	Paresthesia in adults
		Maternal hair mercury levels in the 10 ppm–20 ppm range	5% risk of neurological deficits in the child following fetal exposure secondary to maternal ingestion of methylmercury sufficient to produce maternal hair mercury levels in the 10 ppm–20 ppm range
World Health Organization	1990	0.48 µg/kgbw/day	Paresthesia in adults
		Maternal hair mercury levels in the 10 ppm–20 ppm range	5% risk of neurological deficits in the child following fetal exposure secondary to maternal ingestion of methylmercury sufficient to produce maternal hair mercury levels in the 10 ppm–20 ppm range
US Environmental Protection Agency	1995	Reference Dose = 0.1 µg/kgbw/day	Maternal/fetal pair
US Agency for Toxic Substances and Disease Registry	1999	Minimal Risk Level = 0.3 µg/kgbw/day	Maternal/fetal pair
Health Canada	1998	Provisional Tolerable Daily Intake = 0.2 µg/kgbw/day	Maternal/fetal pair
Kommission "Human-Biomonitoring" des Umwelbundesamtes (Germany)	1999	Recommended limit values for inorganic and organic mercury for general populations, occupationally exposed groups, and sensitive subpopulations	Fetal nervous system
		HBM I of 5 µg/L for organic mercury among women of reproductive age; corresponds to maternal hair mercury concentrations of 1.5 µg/g using a 1:300 conversion	Women whose blood mercury exceeds these levels are advised to restrict fish consumption and/or restrict the use of methylmercury-containing pharmaceuticals

kgbw = kilogram of body weight

duration exposures. Extrapolations from high dose to low dose exposures have also been questioned. At much lower exposures than produced clinically obvious disease in the mercury poisoning epidemics in Japan and in Iraq, more subtle indications of methylmercury toxicity have been found in several groups of children.[37–40] Indications of subtle adverse effects of mercury on the developing nervous system have been noted in reports from New Zealand and Canada. In New Zealand, an inverse correlation was observed between IQ in children and maternal hair mercury level.[37] Maternal hair mercury levels have been correlated positively with abnormal muscle tone in male Cree Indian children in Northern Quebec.[38] And recent cross-sectional studies have identified decrements in motor function, attention, and visuospatial performance among Amazonian children consuming methylmercury-contaminated fish.[39] In the Madeira Islands, children whose mothers had hair levels of methylmercury ≥ 10 ppm showed changes in evoked auditory and visual potentials (electrical potentials that reflect the functioning of the neuronal circuits that generate them).[40]

To fill some of the data gaps, additional studies were undertaken about a decade ago to look at the association between indicators of subtle neurodevelopmental dysfunction and exposure to methylmercury from fish. Two major prospective, longitudinal cohort studies—in the Seychelle and Faroe Islands—have evaluated far more subtle endpoints of neurotoxicity than were assessed in either the epidemics in Minamata and Niigata or the Iraqi poisoning epidemic. The two cohort studies have the advantage of larger numbers of subjects than in the New Zealand and Canada studies. Their prospective design provides a greater chance to determine at what stage the developing brain is particularly vulnerable to methylmercury than cross-sectional studies of the types reported by Grandjean et al.[39] and Murata et al.[40]

THE SEYCHELLOIS AND FAROESE COHORT STUDIES

Located in widely separate geographic areas, two major cohort studies are currently underway: one in the Seychelle Islands, which are located in the Indian Ocean,[41] and the other in the Faroe Islands, in the North Atlantic.[42] Initial findings have been published, and additional reports from these two cohorts will be published in the near future. Both studies are prospective, longitudinal studies of child development in which mothers were enrolled during pregnancy and their children's development followed into early elementary school. Among the Seychellois, reef fish and deep sea fish are major components of the diet and contain methylmercury typically at concentrations lower than 0.3 ppm.[41] In the Faroes, mercury exposures come from eating both fish and pilot whale muscle.[42]

Investigators used standardized measures of neurobehavioral function to evaluate developmental status in both the Seychellois and Faroese cohorts. The tests differed in that those used by the Seychelles investigators were more global, while those used to assess the Faroese cohort focused on multi-focal, domain-related assessments, that is, more specialized tests of nervous system function. The Seychellois children were tested at multiple ages—6 months, 29 months, 66 months, and 84 months—and were evaluated with global developmental measures such as the Denver Developmental Screening Test or the McCarthy Scales of Child Development as well as tests of overall IQ. By contrast, the Faroese children were evaluated at 84 months of age using a number of neuropsychological tests that assess domain-related function. In early 1999, additional testing in the Seychellois cohort was undertaken using a test battery similar to that used by the Faroese investigators.

As measured by average hair mercury concentrations, the body burden of methylmercury was comparable for these two populations. The arithmetic mean maternal hair mercury concentration among the Faroese cohort was 5.6 ppm (range 0.2 ppm to 39.1 ppm); among the Seychellois cohort the arithmetic mean was 6.8 ppm (range 0.5 ppm to 27 ppm). The Faroe Islands investigators also reported additional biomonitoring data including umbilical cord mercury concentrations, which showed the closest association with adverse effects.

To date, a somewhat different picture has emerged from these two cohorts. Based on the global assessments of child development used in the Seychelles, methylmercury does not appear to have adversely affected child development in this cohort under conditions present in the Seychelle Islands. However, among the Faroese children tested at 84 months of age, domain-related deficits were identified. In the Faroese cohort, maternal hair mercury concentrations in the range of 3 ppm to 10 ppm were associated with neuropsychological dysfunction among the children that was most pronounced in the domains of language, attention, and memory, and to a lesser extent in visuospatial and motor functions.[42] The Seychelles investigators also administered the domain-related McCarthy subscales, which also showed no association between neurobehavioral functioning and level of methylmercury exposure.[43]

In evaluating the risk to human populations and setting standards for "safe" levels of exposure, public health and environmental organizations (including federal agencies in the US, international organizations, and advocacy groups) have sought to understand the implications of the two major cohort studies. Policy decisions have been based on each agency or organization's understanding of the implications of these studies' findings. The Seychelles investigation did not show effects that were established in earlier research, suggesting that mercury is less toxic than previously thought, while the Faroe

Islands investigation showed effects at lower levels than those shown in earlier studies.

Understanding the differences between the two cohort studies. A number of explanations have been offered for the different outcomes from these two cohorts; these have been looked at previously.[43,44] They include:

- Age of the children at the time of testing. Testing children who are older than 66 months may offer a better opportunity to detect subtle differences because the testing instruments are more diverse and the children are able to participate in more extensive testing. Also developmental assessments are likely to be less sensitive in detecting subtle neurotoxic effects during a period of rapid change which characterizes the period covering 60 to 72 months.[43]
- Differences in the test batteries utilized to assess developmental status.
- Ethnic differences in the populations studied. This is acknowledged as a possible explanation in part because genetically different strains of the same animal species (for example, mice) have shown marked differences in tissue levels of methylmercury associated with a particular exposure[45–47] and in the effects produced.[48]
- Potential differences in the patterns/timing of methylmercury exposures even if mean maternal hair concentrations are comparable.
- Exposure to fish and other seafood containing substances that are either beneficial or harmful to neurodevelopment may have differed between the two cohorts. The intake of omega-3-fatty acids was high for both groups because of the high consumption of seafood. The Faroese children had more exposure to PCBs than the children in the Seychelles. The influence, if any, of these substances in the marine diet on the outcome of the studies remains to be established. Within the cohort of Faroese children, the tercile of subjects with the lowest PCB exposure showed the strongest adverse effects of methylmercury.[49]
- Some other, yet unknown, difference may be the reason the two cohorts yielded different results.

The National Academy of Sciences convened a committee to evaluate the results reported from these cohorts as well as other health data on methylmercury toxicity. A report from the NAS panel is expected to be completed in May 2000. EPA will use the findings of the NAS committee in reassessing its methylmercury standard.

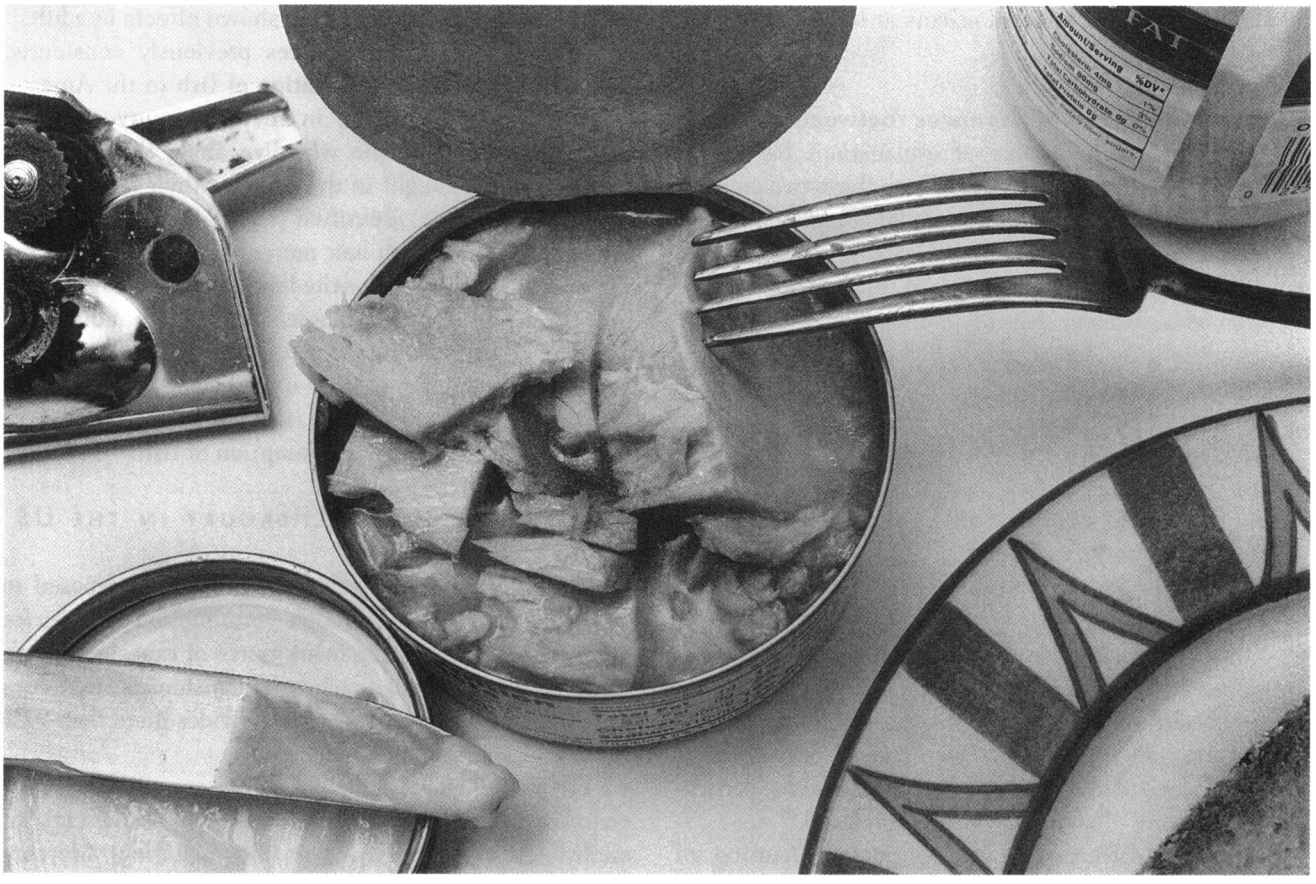
Putting the results from the two major cohort studies into perspective may be made easier as the results from additional cross-sectional studies on the effects of methylmercury on child development are published. Recently published cross-sectional studies of geographically separate populations have shown effects in adults[17] and children[39,40,42] of exposures previously considered safe. For example, contamination of fish in the Amazon River Basin has resulted in methylmercury exposure among groups of people who live along the river and depend on fish caught in the river for their food supply; Lebel et al. have identified visual and neurological effects associated with hair mercury concentrations less than lower than 50 ppm—the level usually thought to be the threshold for neurological effects in adults[12]—among adults in an Amazon community.[17] A report is expected in September 1999 on the neuropsychological assessment of children in Guyana exposed to methylmercury through consumption of fish.

EXPOSURE TO METHYLMERCURY IN THE US

In the US, as well as worldwide, people are exposed to methylmercury mainly through consumption of fish; for some subpopulations, the main source of exposure is consumption of mammals (such as sea mammals) that consume fish. The aquatic food web provides more than 95% of humans' intake of methylmercury.[7]

For an individual, mercury exposure can be approximated by measuring the concentration of mercury or methylmercury in blood or hair (biomonitoring). Mercury exposures for members of a group can also be estimated from dietary survey data and information on the average mercury concentrations in a specific fish species. The estimated methylmercury intake for a population or subpopulation can be calculated from how much fish people eat, how often they eat it, and the mercury concentration of the fish consumed. Although some population groups eat marine mammals, which often have higher mercury concentrations than fish, fish are the main sources of methylmercury exposure in this country.

Fish consumption in US: how often do people eat fish? In the US population, fish consumption is highly variable. According to a mid-1990s dietary survey referenced in the 1997 *Report to Congress*,[7] approximately 1% to 2% of the US population eat fish daily, whereas a little more than 10% of people rarely consume fish. EPA estimates that about 85% of people in the US eat fish or shellfish over the course of a month, with about 60% consuming fish four or more times a month or, on average, at least once a week.[2,7] Within the general population, there are subpopulations who consume fish much more frequently than the national average (Table 2). In general, members of minority groups eat fish more often than the general population and eat larger amounts of fish.[2,7] US residents of Asian/Pacific Islander[50] and Caribbean ancestry and some Native American groups consume fish at higher levels than other subpopulations in the US. Recreational and



KARL BADEN

subsistence fishers—including members of some Native American tribes—consume fish at levels substantially higher than those among the general US population.[51–54] Communities in some remote geographic regions such as subsistence fishing villages in Alaska also have very high levels of consumption of fish and other seafood.[55]

Fish consumption in US: how much fish do people eat? Within the general population EPA has estimated that approximately 1% to 5% of women of childbearing age (15–44 years old) eat 100 grams or more of fish or shellfish per day.[2] The range reflects the results of different dietary surveys. According to EPA's analyses, there are somewhat more than 58 million women ages 15–44 years in the United States, and approximately 9.5% of women in this age group are pregnant in any one year. The number of women in this age group eating enough fish to raise concerns about the amount of methylmercury they consume has been variously estimated as from 52,000 to as high as 277,000.[2]

Mercury concentrations vary by type of fish. Estimates of methylmercury intake for the general and specified subpopulations depend on the amount and type of fish consumed, in addition to the frequency of fish consumption. Fortunately, the most commonly consumed fish species in the United States are comparative low in methylmercury—shrimp, Alaska pollock, most tuna, and salmon. In its *Report to Congress*, EPA estimated based on dietary surveys that the average concentration of methylmercury in fish and shellfish in the US was 0.12 ppm to 0.14 ppm mercury.[4] In fact, the 10 most commonly consumed species usually contained less than 0.2 ppm mercury.[4]

Although the most popular species of fish are comparatively low in methylmercury, it is important to recognize that there are also fish species with considerably higher average concentrations. Shark and swordfish average approximately 1 ppm or higher.[7] Other species often in the range of 0.5 ppm and higher include various bass, king mackerel, orange roughy, pike, and porgy.[7] Typically, large, predatory fish at the upper end of the aquatic food chain are high in mercury.

There is some limited evidence that mercury in water also threatens the health of the fish themselves. The top predator species, highly valued in the commercial fish market, are already sufficiently threatened by overfishing that the National Marine Fisheries Service has tightened fishing restrictions on shark, marlin, and tuna.

Because the mercury concentration varies with the conditions in which the fish is raised, its hard to predict mercury levels for a specific species of fish. These predictions are even more complicated because of introduction into the market of some species of farm-raised fish. Usually farm-raised fish are lower in mercury concentrations than comparable species and sizes of wild-caught fish.

Fish advisories. Freshwater fish can be found with concentrations greater than 0.5 ppm if they swim in contaminated waters. Fishing advisories based on mercury contamination have been issued by 40 states, with 10 states advising limitations on fish consumption from all water bodies (see URL: **http://www.epa.gov/ost/fish/**). Five coastal states have advisories to limit consumption of marine fish. Data from the Northeast states collected in the mid-1990s showed average mercury concentrations > 0.5 ppm in 20% to 100% of fish samples of some species, and >1 ppm in 2% to 25% of samples of some species depending on location.[56] In Wisconsin, the most commonly sought-after game species, walleye, averaged approximately 0.5 ppm, with individual values > 3 ppm, in a 1998 study (Personal communication, J. Amrhein, Wisconsin Department of Natural Resources, July 1998).

RECOMMENDED LIMITS ON METHYLMERCURY EXPOSURE

State and national governments, as well as international organizations, have recommended acceptable levels of mercury exposure that are thought to be protective against adverse effects. Most of the recommended limits are based on neurological damage as the critical effect. A major difference between current recommendations is whether the limits are set to be protective of the general adult population or to be protective of pregnant women and their fetuses. The second area of difference is based on how the results of the two major cohort studies are interpreted—that is, whether the exposure level thought to be safe is predominantly based on the Faroese data, which showed effects at levels previously considered "safe," or the Seychelles study, which did not show adverse effects at typical exposure levels found in the Seychelles.

The choice of "uncertainty factors" used to translate from the lowest doses that are observed to produce adverse effects to doses that are considered to be without adverse effects is another of the reason for differences in the health standards promulgated by various agencies and organizations. These values are small, typically five[57] to ten.[16] Uncertainty factors convey how confident risk assessors are about making an estimate of a safe exposure level. Factors such as person-to-person variability in susceptibility to adverse effects, in metabolism, or in tissue distribution of mercury influence the choice of uncertainty factors. The greater the numerical value of the uncertainty factor, the less certain the assessor is about the prediction of a safe exposure level from the available data. What may seem small differences between these uncertainty values are important because of the narrow range between no effect and effect levels. As noted above, methylmercury's effects on the nervous system follow a sharp dose-response curve.

Table 2. Frequency of fish and shellfish consumption among males and females ages 11 years and older, NHANES III, as analyzed in EPA's 1997 *Mercury Study Report to Congress*[7]

Frequency of fish/shellfish consumption	*Percentage of participants ages 11 and older*
None	12
Once a month or more	88
Once a week or more	58
Twice a week or more	23
Three times a week or more	13
Approximately daily (6 times per week)	3

NHANES = National Health and Nutrition Examination Survey

World Health Organization (WHO). Based on an evaluation of the risks of adverse effects in adults (specifically paresthesias), in 1990 WHO concluded that daily consumption of 0.46 µg methylmercury per kilogram of body weight (kgbw) per day would not result in detectable adverse effects on the adult nervous system.[12] The WHO evaluation also recognized that the fetus differs from the adult in sensitivity to methylmercury, concluding that maternal hair mercury in the range of 10 ppm to 20 ppm is associated with a 5% risk of neurological deficits (clinically evident developmental delays) in the young child due to *in utero* exposure. WHO also concluded that in populations consuming large amounts of fish (in the range of ≥100 grams per day), the hair levels of methylmercury in women of childbearing age should be monitored as a preventive health measure.

US Food and Drug Administration (FDA). The FDA develops action levels that enable the agency to regulate the sale of fish and other seafood in interstate commerce based on mercury concentrations. The FDA's action level of 1 ppm, established in 1979, is based on consideration of the tolerable daily intake (TDI) for methylmercury as well as information on seafood consumption. The TDI is defined as the amount of methylmercury that can be consumed daily over a long period of time with reasonable certainty of no harm. The FDA has established a weekly TDI of 0.3 mg/week (300 µg/week) total mercury, of which no more than 0.2 mg/week (200 µg/week) present as methylmercury. These amount are equivalent to 5 µg total mercury and 3.3 µg/kgbw. This tolerable level would correspond to approximately 230 µg/week of methylmercury, or 33 µg/day, and is based on adverse neurological effects in adults. The FDA's Acceptable Daily Intake, essentially equivalent to the TDI, is overall 0.4 µg/kgbw/day.

Based on observations from the poisoning event in Iraq, the FDA has acknowledged that fetuses may be more

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sensitive than adults to the effects of mercury.[58–60] Recognizing these concerns, the FDA has provided advice for pregnant women and women of childbearing age to limit their consumption of fish species known to have high levels of methylmercury.[60] The FDA believes, however, that given existing patterns of fish consumption, fewer than 1% of women eating such high mercury fish will experience a lower margin of safety, or stated another way, that fewer than 1% of women will take in more than the ADI.

EPA. EPA's risk assessments follow the paradigm established by the National Academy of Sciences.[61] In an effort to provide quantitative estimates of levels that produce adverse effects, EPA developed the reference dose approach. A reference dose, or RfD, is an estimate of daily exposure for the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Scientists who assess the data leading to the development of an RfD recognize that there is an uncertainty in each estimate of a level that produces adverse effects. The uncertainty factor is usually conceptualized as spanning an order of magnitude around the actual value. An RfD is calculated by estimating a No Observed Adverse Effect Level (NOAEL) or a Lowest Observed Adverse Effect Level (LOAEL) that is adjusted by a specified uncertainty factor. Even if data from human subjects are available, uncertainty factors incorporate adjustments for such issues as extrapolation from high dose to low dose, person-to-person variability in susceptibility, and extrapolation from comparatively short-term exposures to chronic or lifetime exposures.

Given the limitations associated with the NOAEL and LOAEL approaches, EPA has used alternative methods such as the benchmark dose, a statistically based method for establishing a dose that is the starting point for setting the RfD, rather than simply using a NOAEL or LOAEL. For developmental toxins, a threshold value (that is, a level below which effects are thought not to occur) is assumed in order to justify setting an RfD. (There have been exceptions, such as inorganic lead, for which no exposure is thought to be without adverse effect and consequently there is no RfD.) The benchmark dose approach is based on the use of a mathematical model to derive an estimate of the dose (the BMD) that is associated with a selected prevalence level (for example, 1%, 5%, or 10%) of the selected health effect in the population and the confidence limits around this dose; the 95% lower bound is called the benchmark dose level (BMDL). The BMDL is divided by an uncertainty factor or factors to estimate an RfD. The BMDL may also be divided by what is called a modifying factor, which accounts for the degree of confidence in the data for the agent being evaluated.

EPA's mercury RfD. The current RfD for methylmercury is 0.1 µg/kgbw/day.[16] This RfD was developed in 1994 based on the findings for 81 mother/child pairs identified in the Iraqi poisoning epidemic[36] and before any of the data from the Seychelles and Faroes were published. The BMDL based on maternal hair mercury was 11 µg/g hair with an uncertainty factor of 10. This BMDL is the lower bound of a dose that corresponds to a 10% prevalence of clinically overt effects in a population whose exposure to methylmercury was through consumption of contaminated grain. The choice of 10 as the uncertainty factor reflects such uncertainties as person-to-person differences in tissue distribution or kinetics of methylmercury, and extrapolation from shorter to chronic exposures. Earlier, EPA had an RfD of

0.3 µg/kgbw/day based on the development of paresthesia in adults in the Iraqi epidemic. Biokinetic data were used to "translate" hair mercury concentrations to dietary intake and included information such as the proportion of ingested mercury that is absorbed from the gastrointestinal tract and the half-life of mercury in humans. These data were obtained from metabolic studies in humans in which methylmercury in fish was the source of mercury.

The RfD is sometimes used as a screening value to assess the "safety" of exposures to mercury (for example, as the basis for some fish advisories or in screening "safe" levels of mercury in pharmaceuticals such as vaccines). When comparing exposures with the RfD, three cautionary notes must be kept in mind. First, the RfD is not a "bright line" below which there is safety and above which adverse health effects will immediately occur. However, as exposures become multiples of the RfD, there is progressively greater concern on the part of medical and public health personnel that adverse health effects can occur. Second, methylmercury is retained in the human body with a half-life generally considered in the range of about 50 days[62,63] to 70 days.[64] A half-life of this length means that each day's ingestion of methylmercury contributes to bioaccumulation of methylmercury in tissues. Third, the duration of exposures is an important consideration. In the definition of the RfD, the exposure period considered is a lifetime of exposure. With developmental toxins, scientists recognize that there are critical developmental windows during which there is much greater vulnerability of the fetus to adverse effects. In terms of potential developmental problems caused by maternal exposure to methylmercury, short-term peak exposures are considered important. At the federally sponsored Mercury Workshop held in November 1998, members of the Experimental Animals Panel concluded that even a few days to a week of exposure would have a potentially adverse impact on fetal development if these exposure occurred during a critical period of fetal brain development.[43]

The mercury exposure estimates used in the *Mercury Study Report to Congress* in assessing the risk of developmental deficits were based on estimates of month-long dietary intake for women ages 15–44[7] (see Table 3). These were derived from fish intake data from national dietary surveys conducted in the mid-1990s (including the National Health and Nutrition Examination Survey [NHANES] III). These exposure estimates suggested that approximately 7% of US women of childbearing years consume more mercury than the RfD of 0.1 µg/kgbw/day.[7] A question raised in response to the *Report to Congress* concerned the appropriate exposure period for assessing the effects of a developmental neurotoxin. In view of the observations reported at the 1998 federal Mercury Workshop,[43] a month may be too long a period.

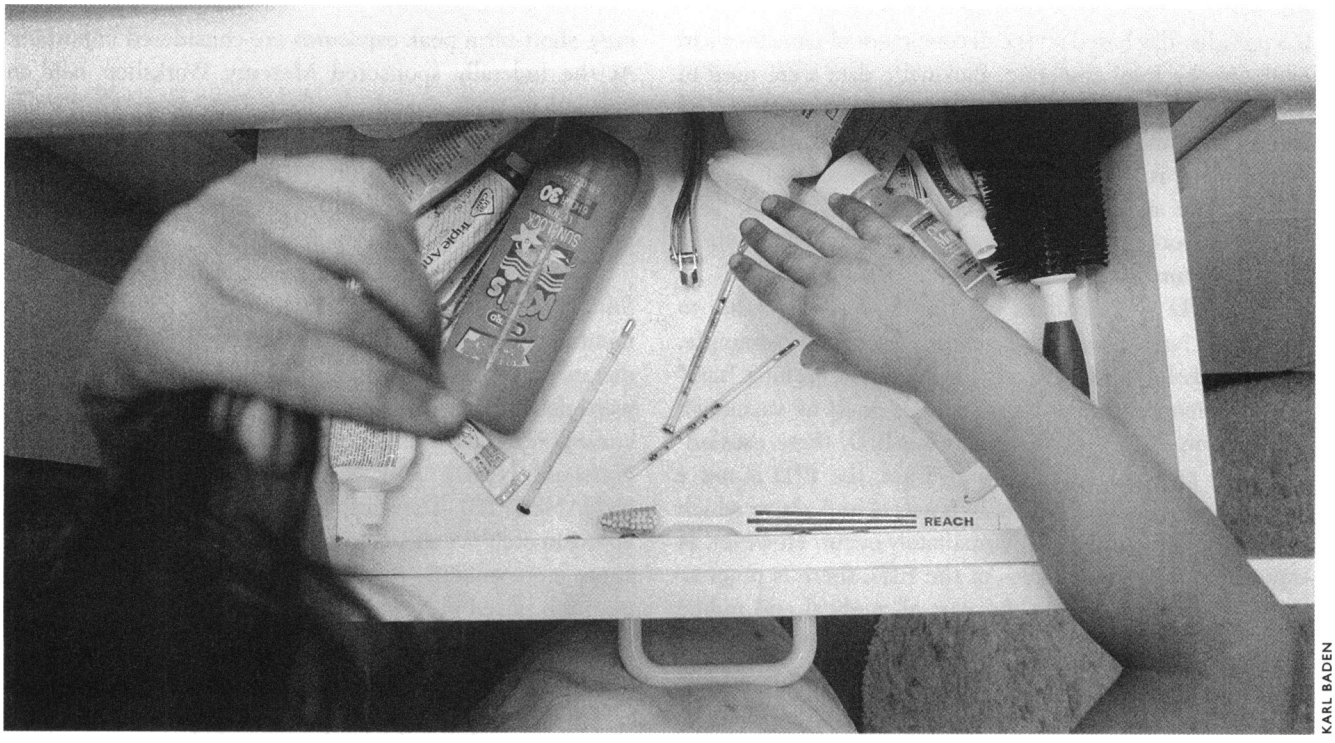
Fortunately, the *Mercury Study Report to Congress* also included data on single-day estimates for those women who reported eating fish in the surveys reviewed. Based on this short time frame, EPA estimated that the mercury exposure of the top 5% of fish consumers is five times the RfD.[2,7] It is still unclear which of these time frames is the most relevant for developmental toxins. Single-day exposures may not be representative of usual fish consumption unless the person is a frequent fish consumer. Patterns of

Table 3. Estimated mercury exposure due to consumption of fish and shellfish of US women ages 15–44 years

Exposure period	*Estimated fish/shellfish consumption (g/day)*	*Estimated mercury exposure (µg/kgbw/day)*
Per user based on estimated single-day intake[a]		
50th percentile	68	0.10
75th percentile	122	0.20
90th percentile	210	0.38
95th percentile	278	0.53
Per user based on estimated month-long intake (µg /kgbw/day)[b]		
50th percentile	9	0.01
75th percentile	21	0.03
90th percentile	46	0.08
95th percentile	78	0.13

kgbw = kilogram of body weight

[a]Women ages 15–44 years, summary of single-day intake data as analyzed in EPA's 1997 *Mercury Study Report to Congress*[2,7]
[b]Women ages 15–44 years, National Health and Nutrition Examination Survey (NHANES) III, as analyzed in EPA's 1997 *Mercury Study Report to Congress*[7,8]



KARL BADEN

consumption among less frequent fish consumers are somewhat better captured by month-long intakes and frequency data. What is unclear is whether high levels of methylmercury exposure need to be sustained for a month to have an effect on developmental processes.

After the mother/fetal pair, the second group of concern is young children, particularly those younger than 6 years of age. Because the RfD is specific for methylmercury effects on the developing fetus, it may not be appropriate to apply it to young children. It is uncertain whether the young child's vulnerability to methylmercury is more similar to that of the adult or that of the fetus. Young children have a higher caloric need relative to body weight than adults. Analyses of dietary surveys have shown that on a µg/kgbw basis, children ages 3–6 years are exposed to methylmercury at levels two to three times adult exposures (Table 4). The significance of these exposures to the young child's developing nervous system are yet undetermined.

Health Canada. The Bureau of Chemical Safety in the Food Directorate of Health Canada uses 0.47 µg/kgbw/day as the current provisional Tolerable Daily Intake (pTDI) for the general population. This value of 0.47 µg/kgbw/day is that same as an earlier standard for adults established by the Joint Food and Agriculture Organization/World Health Organization Joint Expert Committee on Food Additives (JECFA) in 1972. JECFA kept the recommendations in 1989 but, while this level was recommended for the general population, JECFA raised the concern that pregnant and nursing mothers were likely to be at greater risk from adverse effects of methylmercury.[15] In 1998, Canada adopted a more protective standard for fetuses and infants.[57] For pregnant women, women of childbearing age, and infants, the Canadian Bureau of Chemical Safety of the Food Directorate has a pTDI of 0.2 µg/kgbw/day utilizing EPA's "benchmark dose" of 11 ppm mercury in maternal hair as the reference, but with a five-fold uncertainty factor. The EPA utilized an uncertainty factor of 10 to establish its RfD of 0.1 µg/kgbw/day, resulting in a standard that is more restrictive than the Canadian value. Like the EPA, the Canadian scientists regard their pTDI value for protection of the maternal/fetal pair and infants as provisional, recognizing that additional data are forthcoming from the Seychellois and Faroese cohort studies.

The Canadians use an action level of 0.5 ppm methylmercury in fish and seafood to remove items from commerce. (Swordfish, shark, and fresh and frozen tuna are exempted on the basis that these are "gourmet" food products not consumed in substantial amounts in Canada.) By contrast, the FDA utilizes the higher value of 1 ppm, as discussed in more detail below.

German government's *Kommission "Human Biomonitoring" des Umweltbundesamtes.* The German *Kommission "Human-Biomonitoring" des Umweltbundesamtes* (Human Biomonitoring Commission of the Federal Environmental Office) develops reference values for concentrations of chemicals in hair and blood, which are essentially the upper limits for "safe" exposures.

Both the Canadians and the Germans reviewed both the Seychelles and Faroes data in setting their latest limits for mercury, setting lower limits based on their acceptance of the Faroese data as significant.

The Commission's recommendations reflect a two-tiered

approach with specified interventions at each level. Based on the neurodevelopmental deficits observed among the Faroese cohort as well as the developmental data from the Seychellois cohort, adverse effects in children are judged to occur when during pregnancy the mother's blood contains more than 15 µg/L mercury, roughly equivalent to 4–5 ppm in hair. To provide added protection, if a woman of childbearing age has a blood mercury level in excess of 5 µg/L or a hair level of approximately 1.5 ppm mercury, it is recommended that a history be taken to see if the woman is consuming fish containing organic mercury or mercury-containing medicines. If the woman consumes a lot of fish and she consumes species high in mercury, reduction of fish consumption is advised. If medicines containing mercury are used, replacement with mercury-free products is recommended. Additional interventions are recommended if the HMB II of 15 µg/L is exceeded.

US Agency for Toxic Substances and Disease Registry (ATSDR). One of the US agencies responsible for protecting the public from harmful chemicals, ATSDR, develops Minimal Risk Levels (MRLs) for chemicals. These are considered conceptually comparable to EPA's RfDs. The MRL is an estimate of the level of human exposure to a chemical that does not entail appreciable risk of adverse non-cancer health endpoints. These are guidance values established by ATSDR and can be use by public health officials as tools when screening for potential human exposure at hazardous waste sites. MRLs are not intended for use in determining clean-up levels or for other regulatory purposes.

The MRL for methylmercury had been 0.1 µg/kgbw/day in a toxicology profile released in 1994. Earlier this year, ATSDR released a profile raising the MRL to 0.3 µg/kgbw/day based on its interpretation of data from the Seychelles and Faroes cohort studies.[65] This is less stringent than the previous standard and three times less stringent than the EPA's RfD. The current MRL of 0.3 µg/kgbw/day was based on a No Observed Adverse Effect Level (NOAEL) of 15.3 ppm for the highest exposure group (quintile) in the 66-month-old children's data from the Seychelle Island cohort study. This contrasts with an estimated 5% risk of neurological deficits in young children when maternal hair mercury concentrations are 10–20 ppm based on an assessment of the Iraqi data.[12]

WHAT IS EPA DOING TO REDUCE ENVIRONMENTAL EXPOSURES TO MERCURY?

EPA has undertaken a number of actions designed to help reduce mercury pollution of the environment, including issuing regulations for industries that significantly contribute to mercury pollution. Some manufacturers are already shifting away from mercury use. For example, the Chlorine Institute announced in April 1999 that it has a goal of zero release of mercury from chlor-alkali plants, which manufacture chlorine using a mercury-based process. Looking broadly, domestic demand for mercury decreased more than 75% from 1988 to 1996.[4]

EPA has issued standards for mercury emissions from municipal waste combustors and medical waste incinerators as well as standards for mercury releases from industrial, commercial, and institutional boilers; process heaters; industrial, commercial, and other non-hazardous solid waste combustors; gas turbines; and stationary internal combustion engines. EPA is also in the process of developing new human health water quality criteria for mercury based on current toxicity assessments, more appropriate estimates of fish consumption, and more accurate estimates of bioaccumulation. EPA-required reports of releases of mercury compounds are listed on the Toxics Release Inventory, which identifies facilities that release mercury into the environment (for more information: **http://www.epa.gov/opptintr/tri/whatis.htm**).

Table 4. Estimated mercury exposure due to consumption of fish and shellfish in children ages 3–6 years, NHANES III, as analyzed in EPA's 1997 *Mercury Study Report to Congress*[7,8]

Exposure period	*Estimated fish/shellfish consumption (g/day)*	*Estimated mercury exposure (µg/kgbw/day)*
Per user based on estimated single-day intake		
50th percentile	43	0.28
90th percentile	113	0.77
95th percentile	151	1.08
Per user based on estimated month-long intake (µg /kgbw/day)		
50th percentile	5	0.03
90th percentile	25	0.17
95th percentile	39	0.28

NHANES = National Health and Nutrition Examination Survey
kgbw = kilogram of body weight

EPA has taken a significant role in a number of initiatives, including the Great Lakes Binational Toxics Strategy, the North American Agreement on Environmental Cooperation's Mercury Action Plan, and the New England Governors/Eastern Canadian Premiers' Mercury Action Plan. (See "Mercury: A Regional Problem Requires Collaborative Efforts," p. 414–415.)

CONCLUSION

In the short term, if consumers have adequate information on levels of toxic chemicals, including methylmercury, that bioaccumulate in fish, they can make individual choices on how to control mercury exposures. Medical professionals frequently recognize the benefits of fish consumption for cardiovascular health. While these benefits are important, medical professionals also recognize that women of childbearing age (specifically during the periods of pregnancy and lactation) and young children, whose nervous systems are developing, benefit from keeping exposure to methylmercury, a known neurotoxicant, low. Public health agencies, especially state and local public health departments, serve a valuable function by providing state-specific fish advisory information, alerting both the general public and medical professionals to appropriate levels of fish consumption.

In the long term, controlling mercury releases into the environment will improve the health of fish, other wildlife, and humans, particularly those subsistence fishers who rely almost exclusively on local sources of fish. Consumers of large amounts of fish have the greatest potential to benefit because they are the most exposed. It is important to recognize that high levels of fish consumption occur among diverse ethnic and economic groups. Consequently, reduced mercury contamination of the food supply has the potential to benefit a broad spectrum of people as well as providing benefits to wildlife populations and the ecosystem.

The views expressed in this manuscript are the professional opinions of the author and should not be interpreted as policies of the US Environmental Protection Agency.

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