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Methylmercury in Fish: A Review of Residue Levels, Fish Consumption and Regulatory Action in the United States

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The dangers associated with the consumption of large amounts of methylmercury in fish are well recognized, and there is some evidence to suggest that methylmercury may be the cause of subtle neurological impairments when ingested at even low to moderate levels, particularly the prenatal and early childhood periods. This concern has prompted a continuing assessment of the risk of methylmercury toxicity among fish consumers in the United States as well as other countries. The toxicokinetics of methylmercury in humans are reviewed and used to estimate body burdens associated with toxic effects. To determine seafood consumption patterns among the continental U.S. population the Food and Drug Administration (FDA) has analyzed data from a diary study commissioned by the Tuna Research Foundation. Mercury residue levels in domestic fish sampled by the FDA were used to determine the level of exposure to methylmercury. Until evidence is presented that substantially lowers the known body burden of methylmercury which causes toxicity, calculations indicate that the current 1.0 ppm regulatory level provides adequate protection for the average fish consumer, for young children, and for a significant number of consumers exceeding the acceptable daily intake. However, additional studies are being carried out in a continuing process to ensure that safe levels of prenatal exposure to mercury residues in fish are maintained.

Introduction

Public health officials have long been concerned about the hazards associated with methylmercury ingestion that occur primarily from the consumption of several species of fish. The toxic effects of methylmercury are irreversible and severe enough that the potential risk to the United States population from consuming a variety of fish should be reviewed on a continuing basis. Methylmercury compounds pass easily through the blood–brain barrier and the placenta, causing damage both postnatally and prenatally. It has been suggested that methylmercury poisoning may be the cause of subtle neurological impairments, even at low to moderate levels. In particular, prenatal life and early childhood may be especially sensitive to low body burdens of methylmercury.

All forms of mercury entering the aquatic environment, either as a result of man's activities or from natural geologic sources, may be converted to methylmercury, which can be concentrated by fish and other aquatic species. Swedish investigators discovered that organisms present in aquatic sediments were able to methylate inorganic mercury (*1*).

Fish may concentrate methylmercury either directly through the water or through components of the food chain. Methylmercury has a very long half-life in fish, approximately 2 years (*2*); this is two to five times the half-life of inorganic mercury. The loss appears to occur in two stages: first, methylmercury is distributed throughout the tissues, primarily to muscle, over a period of a few weeks, and then it is discharged from the established binding sites very slowly. This extremely slow loss is one of the reasons why fish, in particular salt water fish, are a major source of mercury exposure for humans. Further, during this period the fish are continuously supplied with methylmercury from the water, providing a mechanism for the continuous increase of mercury residues. This steady increase of mercury results in large, older fish accumulating considerably more mercury than small, younger fish.

The hazardous nature of mercury residues in fish has been emphasized by the Minamata Bay (1953–1960) and Niigata (1965) poisoning episodes in Japan. A more recent poisoning episode occurred in the fall and winter of 1971–1972 in Iraq as a result of ingestion of homemade bread prepared from wheat seed treated with alkyl mercury fungicide and intended for planting. As a result of this episode, 6,530 cases were admitted to hospitals throughout the country, with 459 deaths (*3*).

Acute poisoning episodes of populations by methylmercury results in very dramatic effects. However, subclinical effects of methylmercury on some subgroups of

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the population may also be of public health importance and constitute a threat that is more difficult to evaluate. Concern that low levels of methylmercury may have subtle neurological effects is the stimulus for continuing research efforts. To help determine if a hazard exists among fish consumers in the United States, FDA has continued to review fish consumption and mercury residue data in fish in the United States and to provide research support for groups such as the one at the University of Rochester. The risk to special groups such as infants, prenatal life, and those consuming large quantities of fish has also been evaluated.

Toxicological Evaluation

The best indices of exposure to methylmercury are levels of mercury in hair and blood. Detailed studies of the patients of poisoning episodes, particularly those supplying information on mercury levels in blood, hair, and in some cases brain, has provided valuable information for estimating acceptable levels for exposure of humans to methylmercury. Additional information has also been provided by (a) studies in Scandinavia on the metabolism of trace amounts of ^{203}Hg-labeled methylmercury by humans, which allowed calculation of the half-life of mercury in humans (about 70 days) and also the relative concentration of mercury in the various parts of the body (*4*), and (b) the relationship between ingestion of methylmercury from contaminated fish and mercury levels in blood and hair.

A Swedish expert group evaluated data on human methylmercury toxicity derived from cases which occurred in Minamata and Niigata. The Swedish group determined (by extrapolation) that the lowest blood mercury level associated with toxic effects was 220 ppb and the lowest hair mercury level associated with toxic effects was 50 ppm (*5*).

The Iraqi outbreak of methylmercury poisoning has been extensively studied by many investigators. The blood level of mercury at which symptoms of toxicity were first detected in the Iraqi episode was approximately 240 ppb (*3*). This calculation was made on samples collected 65 days after the end of exposure, which is the approximate half-life of methylmercury in humans. Since the actual clearance times from the blood are not known, the level may lie between 240 and 480 ppb. These values are for adult exposures only.

Any chemical can be toxic to humans if enough is ingested. Therefore, most governments have tried to place a limit on the daily intake of a suspected toxic substance for the protection of the public health. The acceptable daily intake (ADI) is the amount of a food additive or residue that can be consumed daily over a long period of time without risk (*6*). It is usually expressed in terms of milligrams or micrograms of residue per kilogram of body weight of the consumer.

The concept of an ADI may not always be applicable to trace contaminants because, for the most part, the level in food is unpredictable and uncontrollable, and consequently the daily intake is highly variable. In addition, the susceptibilities of the fetus, infant, and child to many substances are presently unknown and subclinical effects have not been adequately described. Moreover, in the case of methylmercury and many other contaminants that are cumulative, the individual daily exposure may only make a small contribution to the body burden. Hence, it would be reasonable to specify an average limiting weekly or monthly intake rather than daily.

A Joint FAO/WHO Expert Committee on Food Additives (*7*) established a provisional tolerable weekly intake of 0.3 mg of total mercury per person, of which no more than 0.2 mg should be present as methylmercury. These amounts are equivalent to 5 and 3.3 μg, respectively, per kilogram of body weight. Using the value for methylmercury, this tolerable level would correspond to approximately 230 μg/week for a 70-kg person, or 33 μg/day.

The estimate of tolerable weekly or daily intakes of methylmercury was based on information developed primarily by Swedish studies of Japanese individuals poisoned in the episode of Niigata, which resulted from consumption of contaminated fish and shellfish. Data on mercury levels in blood and hair provided a basis for establishing methylmercury levels at which toxic effects were observed. The blood level at the time of onset of symptoms was estimated by extrapolation and it was concluded that the lowest blood level for the appearance of signs and symptoms of methylmercury poisoning was 200 ppb (0.2 ppm) (*5*). Biochemical studies in Finland and Sweden on the movement of methylmercury through the human system made it possible to relate blood levels to daily intake. By using trace amounts of radiolabeled methylmercury, it was shown that methylmercury is completely (more than 95%) absorbed from food and is distributed rapidly throughout the body, and that its estimated average biological half-life is about 70 days (*4*). This information was used to calculate the theoretical total body burden of mercury as a function of time when a constant dose of methylmercury is ingested. This calculated body burden becomes essentially steady after about a year. In this steady state, a conservative estimate of the total amount of methylmercury in the body is 100 times the daily intake. At steady state, the blood level expressed in ng/mL (ppb) is approximately equal to the daily intake expressed in μg/day for a 70-kg person (*8*).

These relationships have been found to hold true in a study of high fish consumers in Sweden. A linear relationship was found between daily ingested methylmercury and the level of methylmercury in blood, and the data indicated that a steady daily intake of approximately 300 μg Hg as methylmercury for a 70-kg person would result in a blood concentration of roughly 200 ppb at steady state (*9*). This is a somewhat lower body burden than that calculated by Clarkson's model (*8*), which is recognized to be conservative.

The more recent poisoning episode (1971–1972) in Iraq caused by the ingestion of contaminated bread prepared from wheat treated with alkyl mercury fungicide

and intended for planting has provided additional data relating exposure to toxic effects. The body burden of methylmercury in these patients was calculated, using the kinetic data developed in Scandinavia, and related to the frequency and signs and symptoms in the population. The results of this study indicate that the effects of methylmercury can be detected at a body burden of approximately 25 mg mercury for a 70-kg person (*10*).

Clarkson et al. (*11*) reviewed the Iraqi data and determined that the lowest toxic body burden of methylmercury was approximately 50 mg for a 70-kg person. This is the level at which an increase over the background frequency of paresthesia could be detected.

Based on the available data, a threshold value at which symptoms of toxicity associated with methylmercury are first noticeable has been estimated at 50 ppm in hair and 200 ppb in whole blood, which would be reached with a minimum daily intake of 300 μg mercury present as methylmercury in the diet. Dose-response relationships below this range of intake are not known. In addition, there is concern about the relative sensitivity of the developing fetus. The question of interaction of other chemical factors such as selenium on the toxicity of methylmercury has not been conclusively demonstrated at this time, but may be a factor to be considered when more information is developed. Because of these areas of uncertainty, a safety factor of ten has been used to provide a sufficient margin of safety. Thus a maximum tolerable level would be 30 μg methylmercury daily in the diet, resulting in 20 ppb of methylmercury in blood and 5 ppm in hair.

The following limitations to this approach were recognized: (1) it was not known to what extent particular individuals are more or less sensitive to mercury than others; (2) the estimates were based on the "lowest level that caused an effect" rather than the normal procedure of using a "no-effect dose level"; (3) paresthesia is usually the first symptom of methylmercury toxicity noted but is not sufficient to diagnose poisoning because it can be caused by many other factors (*12*); (4) questions about dose-response relationships in human fetuses and newborn infants were unanswered; and (5) there is a possibility of subclinical effects arising from exposure to very low levels of methylmercury.

Paresthesia continues to be the first detectable symptom ascribed to methylmercury poisoning, but this effect occurs relatively late in the progression of toxic changes. Therefore it would be desirable to find an earlier indicator of toxicity, or ideally, of pretoxicity. Woods and Fowler (*13*) found that rats chronically exposed to methylmercury hydroxide had increased levels of urinary uroporphyrin and coproporphyrin as a result of changes in the renal heme biosynthetic pathway enzyme activities. No discernible organ damage was found at the dosage levels used in their experiment, suggesting the clinical utility of urinary porphyrin levels as a sentinel of pretoxic exposure to methylmercury. In this regard it is noteworthy that Minamata patients were observed to have porphyrinuria (*14*).

In the Woods and Fowler experiment (*13*), rats were divided into four groups receiving drinking water with 0, 3, 5, or 10 ppm methylmercury hydroxide for 6 months. Changes in activities of renal heme biosynthetic pathway enzymes were accompanied by increases in urinary heme precursors. There was a 5- to 12.5-fold increase in urinary uroporphyrin and a 14- to 21-fold increase in urinary coproporphyrin. Initial porphyrinuria occurred between 1 and 2 weeks following commencement of exposure. Later, Woods et al. (*15*) found that rats acutely treated with inorganic mercury did not have significant increases in urinary uroporphyrin levels. The authors suggested that further studies are needed to fully explain the porphyrinogenic response induced by chronic mercury exposure.

Fish Consumption and Mercury Residues

Several populations exposed to methylmercury through high fish consumption have been studied epidemiologically. From Sweden there are reports of families consuming fish containing 0.3 to 7 mg Hg/kg or up to 5 μg Hg/kg body weight of the consumer, resulting in blood levels of Hg up to 60 ppb with no signs or symptoms of poisoning (*9*).

Turner et al. (*16*) described a Peruvian population that was chronically exposed to methylmercury because of its long-term and heavy consumption of ocean fish. Approximately 70% of this population's dietary protein came from fish. Although the mean blood methylmercury concentration was 82 ppb, no individual could be identified as having symptoms of methylmercury poisoning. There was a high prevalence of paresthesias in the population but the condition was no more frequent than in a neighboring control group with a mean blood methylmercury concentration of 9.9 ppb. Hair analyses for methylmercury indicated that the mercury levels were constant over long periods, confirming the suggestion that this population had been chronically exposed to methylmercury for many years.

A group of fishermen in American Samoa who were at sea for periods up to 22 months ate up to 9 ounces of fish per day. The average blood concentration of methylmercury of this group was 64 ppb. None of the fishermen showed any evidence of methylmercury poisoning (*17*).

In these studies, many normal individuals had blood levels of methylmercury higher than the lowest estimated blood level reported from Niigata that was associated with overt symptoms. However, no attempt was made to specifically search for the more subtle effects of methylmercury poisoning, such as behavioral problems and learning disabilities. It would also be helpful if these individuals could be checked for porphyrinuria as an indication of toxic changes due to mercury.

To determine the intake of fish and shellfish in the United States, a consumption study was conducted in 1973–74 by the National Purchase Diary Panel, Inc. (NPD). NPD is a marketing research and consulting

firm that specializes in the analysis of consumer purchasing behavior as recorded in monthly diaries by families over time. This study was commissioned by the Tuna Research Foundation (TRF) to provide a representative and projectable sample of seafood consumption patterns among the continental U.S. population. It is the most recent fish-specific national survey available. The objective of the survey was to provide data on seafood consumption patterns by species, by individuals within family, by young children (10 years or less), and by pregnant women.

NPD maintains two national panels of over 6,500 families in addition to panels in 35 local test markets. Members of one national panel plus 2,000 families from local market panels were asked to participate in this project. Panelists recorded their seafood consumption by family member in a diary for a 1-month period. Data from one-twelfth of the sample population were recorded each month for 1 year, from September 1973 to August 1974.

Total sample counts (returns) were: number of families, 7662; number of individuals, 25,165; number of young children, 4952; number of pregnant women, 10. Because of the small number of pregnant women, no data on them are presented in the report (*18*).

The NPD panel is balanced nationally with regard to a number of major demographic characteristics. However, because diary panels nearly always gain better cooperation among some groups than others, NPD projects its data to total U. S. households. Because of small geographic and demographic panel imbalances, each panel family is simultaneously weighted upward or downward from this average, depending on whether they are over-represented or under-represented in the panel. Demographics controlled upon in this stage are: census region, in/outside Standard Metropolitan Statistical Areas (SMSA), family size, age of housewife, and income.

Based on consumption data from the NPD survey and residue data provided by the National Marine Fisheries Service (NMFS) and assuming that sampling methods are valid and the diary recording reasonably accurate, it appears likely that the probability of a systematic exposure to substantial intakes of methylmercury in fish and shellfish by the average consumer is low. Some examples of the variables to be considered for a variety of the important species of fish and shellfish are presented in Table 1.

Approximately 93% of the individuals sampled consume seafood; tuna is the most usual seafood eaten, with 61.5% of all the individuals sampled eating tuna. The average consumption of total seafood per individual was 18.58 ounces per month. This corresponds closely to the report of Newberne and Stillings (*19*), who estimated the national average fish consumption in the United States during the past 50 years to be approximately 16 ounces per month.

NMFS attempted to determine if the persons eating more than 90 ounces of seafood per month (1.4% of the sample survey) continued to consume seafood at this rate over a long period. These individuals kept an additional diary for an extra month in November 1974. The average consumption recorded for the first diary month was 124.2 ounces per individual and the average consumption for the second diary month was 45 ounces. This is a net change in consumption of −64%. The highest mean consumption recorded in the two diaries was 197.5 ounces per month. Therefore, few if any persons in the United States maintain a steady total seafood consumption of more than 200 ounces per month.

FDA Data on Mercury Concentration in Fish on the U.S. Market

Table 2 contains data from the U.S. FDA showing the relationship of mercury levels that existed in samples of domestic fish during the fiscal year 1979 (*20*).

Table 3 contains data from Simpson et al. (*21*) on mercury levels in freshwater fish from the Great Lakes sampled by the FDA in 1970, showing that the average levels of methylmercury in most fish are well below the present 1.0 ppm guideline.

Discussion

Data from the TRF survey have indicated that the average consumption of all fish among the fish-eating population of the United States is 18.58 oz/month or approximately 18 g/day. Daily consumption of species containing relatively high levels of methylmercury such as tuna, swordfish, or halibut would be considerably less. For example, the mean daily consumption of halibut is 7.2 g with two standard deviations increasing the total to 16.6 g. This would include some 97.5% of all consumers of halibut. The consumption of 16.6 g of halibut with 0.179 ppm mercury would provide a daily mercury intake of approximately 2.9 μg.

The mean daily consumption of swordfish is 6.53 g with a standard deviation of 2.5 g. If 11.53 g of swordfish with a mercury level of 1.5 ppm were consumed each day, and this would include over 95% of all swordfish eaters, the daily mercury intake would be 17.3 μg, still below the ADI of 30 μg.

At the highest level of swordfish consumption shown by the NPD study, i.e., 511 g in a month or 17 g per day, with a mercury residue of 1.5 ppm the daily mercury intake would be 25.5 μg, still below the ADI of 30 μg. If in addition to the highest level of consumption of swordfish in the NMFS, i.e., 17 g per day with a mercury residue of 1.5 ppm, the same individual consumed the average daily amounts of tuna, halibut, and salmon at the present average residue levels of mercury for each of the three species, then the total daily intake of mercury from all four species would average 31.7 μg, only 1.7 μg above the ADI. Such consumption, which would realistically be on a periodic basis to derive daily exposure, seems very unlikely, particularly since the cost of swordfish, halibut, and salmon is prohibitively high.

Additional data developed on the biological half-life of methylmercury in humans, however, indicate a need

Table 1. Consumption patterns and methylmercury residues in seafood.[a]

Fish species	Projected no. persons consuming	Monthly consumption, g		Mercury level, ppm	
		Mean ± SD	Range	Mean ± SD	Range
Tuna	132,025,000	166.4 ± 125.8	24.4–3728.3		
Albacore				0.156 ± 0.057	0.04–0.25
Yellowfin				0.324 ± 0.252	0.04–0.87
Skypjack				0.199 ± 0.083	0.03–0.39
Lobster	13,240,000	232.6 ± 173.8	18.2–1605.2	0.175 ± 0.148	0.07–0.28
Salmon	19,834,000	206.3 ± 319.5	23.9–3479.9		
Pink				0.018 ± 0.015	0.01–0.04
Coho				0.056 ± 0.055	0.02–0.21
Sockeye				0.059 ± 0.085	0.10–0.21
Halibut	5,140,000	216.4 ± 142.0	25.0–766.8	0.179 ± 0.123	0.01–0.38
Shrimp	47,081,000	224.4 ± 177.8	25.6–1439.9	0.113 ± 0.179	0.10–0.56
Swordfish	409,000	196.0 ± 74.9	99.4–511.2	[b]	

[a] Consumption data from TRF (*18*); residue data provided by National Marine Fisheries Service.
[b] No data provided.

Table 2. Mean mercury levels in FDA fiscal year 1979 survey.[a]

Species	Hg level	
	Mean, ppm	Maximum ppm
Bass, fresh water	0.19	0.62
Bass, salt water	0.07	0.25
Bluefish	0.19	0.81
Carp	0.11	0.37
Catfish	0.10	0.74
Cod	0.15	0.83
Halibut	0.27	0.51
Perch, fresh water	0.13	0.30
Perch, salt water	0.17	0.44
Pike, walleye	0.26	0.75
Pollack	0.05	0.14
Swordfish	0.83	1.82
Trout, fresh water	0.13	1.01
Trout, sea	0.09	0.24
White fish	0.06	0.24

[a] Data from Food and Drug Administration (FDA) (*20*).

to take into account the problem of variations among individuals. In the Iraqi episode, 90% of the individuals studied had a biological half-life of methylmercury between 60 and 70 days, but 10% showed values of 110 to 120 days (*22*). Individuals having a long biological half-life would accumulate much higher steady-state levels than those having short biological half-lives and would thus be at greater risk from the same level of methylmercury intake.

Table 3. Mean mercury levels in selected Great Lakes fish FDA 1970 survey.[a]

Lake	Species	Mean ± Standard deviation, ppm
Lake Erie	Walleye	0.58 ± 0.26
	Perch	0.24 ± 0.14
	White bass	0.49 ± 0.31
	Smallmouth bass	0.51 ± 0.19
Lake St. Clair	Perch	0.88 ± 0.75
	All others	0.48 ± 0.32
Lake Michigan	All types	0.11 ± 0.11
Lake Ontario	All types	0.30 ± 0.30
Lake Huron	All types	0.19 ± 0.11
Lake Superior	All types	0.13 ± 0.11

[a] Data from Simpson et al. (*21*).

In addition, information has been developed on the so-called "late onset of symptoms" associated with methylmercury poisoning. Specifically, by 1973, in the Agano area of Niigata, Japan, new cases of methylmercury poisoning were reported years after the consumption of contaminated fish had ceased (*23*). This finding indicates that there may be some damage which is not diagnosed under current procedures, and it introduces further uncertainty into the determination of the "lowest effect level" used to estimate tolerable intakes. Further concern has been generated by the follow-up studies of Iraqi infants by Amin-Zaki et al. (*24*), in which the investigators found neurological and developmental dysfunctions in infants initially thought to be free of the toxic effects of methylmercury.

Prenatal life and infancy are the life stages most vulnerable to methylmercury because of the sensitivity of the developing nervous system. Methylmercury compounds are known to cross the human placenta (*25*). The mercury concentration in fetal red blood cells is 30% higher than in those of the mother; this may be due to the accumulation of methylmercury in cord erythrocytes (*26,27*). The mercury concentration of human breast milk varies but is approximately 5% of the serum mercury concentration of the mother (*28*).

The first reports of fetal methylmercury toxicity came from Minamata, where approximately 6% of the children born between 1955 and 1959 developed cerebral palsy (*25*). The mothers generally had no overt symptoms of methylmercury poisoning although some experienced mild paresthesia. Most of the infants were breast-fed, and abnormalities were not noticed until a few months after birth (*29*). In a study of infant–mother pairs exposed to methylmercury during pregnancy during the Iraqi outbreak in early 1972 (*30*), a few children of mothers with peak hair concentrations of mercury less than 25 ppm were found to have symptoms such as delayed speech, mental retardation, and microcephaly.

The data currently available for evaluating quantitatively the association of neurological symptoms of tox-

icity with exposure to methylmercury are sparse and inconsistent. Additional studies are being carried out on the prenatal effects of methylmercury to determine that this lifestage continues to be protected by the 1.0 ppm regulatory level for mercury in fish. However, even with the above-outlined uncertainties concerning the results of exposure in Japan and Iraq, where exposures were considerably higher than anything experienced in other countries, U.S. fish consumption data do not indicate any cause for concern of methylmercury poisoning for the average American. The majority of fish consumers in the United States could easily double their intake and still remain below the mercury ADI. The current 1.0 ppm regulatory level for marine species provides more than adequate protection at the current average fish consumption levels in the U.S. In addition, the enforced limit of 1.0 ppm mercury in marine fish provides a sufficient margin of safety for young children and for significant numbers of consumers exceeding the acceptable daily intake.

In summary, FDA will continue to monitor fish consumption and mercury residues in fish and support programs to study the potential prenatal neurotoxicity of methylmercury exposure in populations consuming large amounts of fish with mercury residues. Should more data indicate the need for a change in the 1.0 ppm level for mercury in fish, FDA is prepared to take action to continue the protection of the public health of consumers.

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