

Fish Mercury: Some Inconvenient Truths

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The current government standard allows consumption of reasonable levels of fish — provided the species are selected carefully. However, as described below, the standard may not adequately protect health, particularly for individuals with genetic susceptibilities, preexisting toxicities, or other sources of mercury exposure such as dental amalgams. Nonetheless, consumption of reasonable levels of very-low-mercury fish yields an average mercury ingestion that is well below the standard and thus appears to be safe.

Fish contains methylmercury, a type of organic (carbon-containing) mercury. The toxicity of methylmercury is similar to that of elemental mercury vapor — both are lipophilic, thus travel easily throughout the body and readily cross cell membranes including the blood-brain barrier.¹ Both oxidize into inorganic mercury (Hg^{2+}), which is lipophobic and thus becomes trapped inside the cells.²

Fish mercury is found primarily in the muscle, bound to protein.³ Due to bioaccumulation up the food chain, the concentration of mercury in fish is one thousand to ten thousand times the mercury concentration in other food sources.⁴

Mercury toxicity versus natural defenses

In humans, mercury toxicity depends on genetics, epigenetics, micronutrient status, and the burdens of other stressors. At the molecular level, mercury binds to sulfhydryl — a common functional group within proteins such as enzymes, which drive fundamental biochemical processes. Mercury also binds to the sulfhydryl in glutathione, the body's most important antioxidant.

Regarding genetics, in the past decade twelve common genetic variants that convey increased susceptibility to mercury toxicity have been documented in human population studies,⁵ and many more are likely.⁶ These

genetic susceptibilities were not recognized at the time that the regulatory safety standard for methylmercury ingestion was set.

Selenium status and other endogenous natural defenses can mitigate or delay the toxic effects of chronic mercury exposure as follows. Mercury binds irreversibly to selenium, but intracellular selenium availability is limited by kidney processes and by mineral transport mechanisms. The glutathione system facilitates excretion of mercury, at least until the enzymes that recycle glutathione become impaired by mercury. The metallothionein metal storage proteins can sequester mercury (instead of storing zinc) until they become full. Other natural defenses include the cellular replacement of certain tissues, the protein repair mechanisms, and the levels of non-critical sulfhydryl targets in the body. But these defenses are limited. When mercury toxicity eventually affects the body's detoxification and repair systems, a vicious cycle of escalating toxicity may be inevitable, and some toxic effects may be permanent.

Regulatory safety standards

The US Environmental Protection Agency sets a regulatory standard for methylmercury ingestion, called the Reference Dose; and the US Food and Drug Administration sets a standard for mercury contamination in commercial fish, called the Action Level (although no action is mandated).

The EPA's Reference Dose for chronic methylmercury ingestion (set in 2001) is 0.1 microgram per kilogram-body-weight per day.⁷ This standard rests on many assumptions, most of which are optimistic, and it appears to be too lenient by at least a factor of two. (See the sidebar.)

Under the current standard, a 60-kg (130-pound) adult can consume up to 6 micrograms per day of fish mercury. Incidentally, this level is roughly equivalent to the dose that the US EPA set in 1995 for tolerable chronic *inhalation* exposure to *elemental mercury vapor*⁸ (which is toxicologically similar to methylmercury). However, a similar mercury inhalation standard set by the California

¹ Berlin M, Zalups RK, Fowler BA. Mercury. In: Nordberg G, editor. Handbook on the toxicology of metals. Amsterdam; Boston: Academic Press; 2007.

² *Ibid.*

³ EPA Fact Sheet: Mercury Update: Impact on Fish Advisories. June 2001. Available from: http://water.epa.gov/scitech/swguidance/fishshellfish/outreach/upload/2001_05_31_fish_advice_mercupd.pdf

⁴ *Ibid.*

⁵ Woods JS, Heyer NJ, Russo JE, Martin MD, Farin FM. Genetic polymorphisms affecting susceptibility to mercury neurotoxicity in children: Summary findings from the Casa Pia Children's Amalgam Clinical Trial. *Neurotoxicology*. 2014 Sep;44:288-302. PMID: 25109824.

⁶ Many more mercury-susceptibility genes are likely because mercury blocks sulfhydryl groups, which are common within proteins — and proteins are coded by genes that vary among individuals Berlin, *op cit.*

⁷ US EPA, Integrated Risk Information System. Methylmercury [Internet]. 2001 [cited 2013 Mar 23]. Available from: <http://www.epa.gov/iris/subst/0073.htm>

⁸ The EPA Reference Concentration for chronic inhalation of elemental mercury vapor is 0.3 micrograms per m^3 — which equates to 4.8 micrograms per day (assuming 20 m^3 per day and 80% absorption) as a tolerable daily dose of elemental mercury. (US EPA, Integrated Risk Information System. Mercury, elemental [Internet]. 1995 [cited 2014 Oct 11]. Available from: <http://www.epa.gov/iris/subst/0370.htm>).

EPA in 2008⁹ is ten times stricter. This range suggests large uncertainties in mercury standard-setting and suggests that the EPA standard may be too lenient by as much as ten-fold.

The FDA's Action Level for methylmercury contamination in commercial fish is 1 part per million (ppm).¹⁰ Typical concentrations of mercury in fish range from less than 0.1 ppm for low-mercury fish to more than 1.0 ppm for high-mercury fish,¹¹ but even within species, levels may vary widely depending on local environments.

Choosing high-mercury fish, at 1.0 ppm, would allow a 60-kg (130-pound) adult to consume only 6 grams of fish per day — equivalent to only about 6 ounces per month — without exceeding the EPA health standard. In other words, many commercial fish that are legally marketed with no point-of-sale warnings are nonetheless contaminated to the degree that consumption must be carefully limited to avoid exceeding a health standard that is probably too lenient to protect health.

Choosing very-low-mercury fish is key. For example, choosing salmon, with a mercury level of 0.02 ppm, would allow the same 60-kg person to consume 300 grams (over 10 ounces) of fish per day without exceeding the EPA health standard. A risk-averse person could safely consume each week up to 8 ounces (227 g) of salmon (0.02 ppm), thus ingesting an average of 0.6 micrograms of mercury per day — ten-fold lower than the EPA standard. Choosing sardines, assuming a mercury level of 0.01 ppm, would allow twice as much consumption.

On the other hand, the risk-averse person may wish to avoid tuna altogether. Even canned light tuna at 0.13 ppm, which some call low-mercury since it is well below the FDA Action Level, has ten times the mercury of very-low-mercury fish.

⁹ The CalEPA Mercury Chronic Reference Exposure Level for chronic inhalation of elemental mercury vapor is 0.03 micrograms per m³ — which equates to 0.48 micrograms per day (assuming 20 m³ per day and 80% absorption) as a tolerable daily dose of elemental mercury. (California Office of Environmental Health Hazards Assessment [2008]. Chronic toxicity summary: Mercury, inorganic).

¹⁰ US FDA. Action Levels for Poisonous or Deleterious Substances in Human Food and Animal Feed: Mercury [Internet]. 2000 [cited 2013 Mar 26]. Available from: <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ChemicalContaminantsMetalsNaturalToxinsPesticides/ucm077969.htm#merc>

¹¹ US FDA. Mercury Levels in Commercial Fish and Shellfish (1990-2010) [Internet]. 2013 [cited 2014 Oct 5]. Available from: <http://www.fda.gov/food/foodborneillnesscontaminants/metals/ucm115644.htm>

EPA Reference Dose for Methylmercury Ingestion

The EPA Reference Dose was based primarily on a study of about 1000 mother-infant pairs from a fish-eating population in the Faroe Islands. At age 7, the children were tested for neurobehavioral deficits, and an association was found with their cord-blood mercury levels measured at birth. A “Benchmark Dose Lower Limit” (a tolerable dose, with 95% statistical confidence) for cord blood mercury was identified. Then, using several crucial assumptions, this level was converted to maternal blood mercury and then to maternal mercury ingestion. Finally, an Uncertainty Factor of 10 was applied to account for these assumptions and unknowns, yielding the regulatory standard — the Reference Dose.

Reasons why the standard may be too strict:

- The fish diet included pilot whales with very high mercury levels and relatively low selenium levels.

Reasons why the standard may be too lax:

- Adverse effects were measured via clinical neuropsychological test results, yet clinical tests may fail to detect significant subjective symptoms, e.g., reduced stamina and a need for more down-time.
- Early effects of mercury toxicity include induction of stress hormones and activation of certain brain enzymes, both of which may cause improved test scores, thus muddying the search for adverse effects at low levels.
- The agency used a “Benchmark Dose” method in which the results of the lowest 5th percentile of children were presumed to be abnormal and were ignored. In addition, 7 children with overt neurological disorders (out of roughly 1000 in the cohort) were excluded from the study.
- The standard assumes that mercury toxicity is linear, when in fact it is unpredictable in early stages and may become exponential in later stages.
- Instead of choosing the most critical neuropsychological test (i.e., the test at which the adverse effects were observed at the lowest mercury level) as is typical in regulatory standard setting, the agency based its Benchmark Dose on a combination of several tests. (Table 2 of US EPA 2001 *op cit.*)
- The imputed maternal blood mercury levels were assumed to be equal to cord-blood levels (which were measured), although the best evidence suggests that the fetus concentrates mercury by two to three fold. This means that the actual maternal mercury blood levels were probably lower than the researchers assumed (i.e., the researchers assumed that the fetus did not concentrate mercury).
- The imputed maternal ingestion of mercury assumed a partitioning of the ingested mercury into the blood that was based on limited data. This should require the use of a larger Uncertainty Factor.
- The imputed maternal ingestion of mercury assumed an average elimination rate even though this parameter has wide individual variation.
- The island-dwelling population was probably relatively genetically resistant to mercury-toxicity compared to the general US population. The standard does not address genetically susceptible subgroups.
- The EPA standard incorporates an Uncertainty Factor of 10, which is lower than is typical in regulatory standard-setting, given the number of optimistic assumptions and unknowns. For example, the CalEPA inhalation standard for elemental mercury vapor uses an Uncertainty Factor of 300 (three hundred). For toxicants like methylmercury, in which a No Observable Adverse Effects Level is not identified, an Uncertainty Factor of ten is typically used to cover this single concern, and other Uncertainty Factors are included to cover such things as interindividual variability.

See also:

Rice DC. The US EPA reference dose for methylmercury: sources of uncertainty. *Environ Res.* 2004 Jul;95(3):406-13. PMID: 15220074. (This EPA scientist lists the many uncertainties behind the EPA Reference Dose, she implies that the Uncertainty Factor should be higher, and she notes that the very concept of a Reference Dose for methylmercury may be inappropriate since available data suggest no safe threshold.)

Stern AH. A revised probabilistic estimate of the maternal methyl mercury intake dose corresponding to a measured cord blood mercury concentration. *Environ Health Perspect.* 2005 Feb;113(2):155-63. PMID: 15687052. (A more refined analysis suggests that the EPA's estimate of the implied maternal fish intake based on cord-blood mercury levels is twice as high as it should be. The choice of Uncertainty Factor is not addressed.)

Budtz-Jørgensen E, Grandjean P, Weihe P. Separation of risks and benefits of seafood intake. *Environ Health Perspect.* 2007 Mar;115(3):323-7. (Studies of the toxic effects of mercury in dietary fish are confounded by the beneficial nutrients in fish and are thus likely to underestimate mercury toxicity by perhaps 2-fold.)