Workshop on Mercury Exposure and Public Health

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Introduction

Mercury is a metal that is widely distributed in the environment. It is mobilized by natural processes such as volcanic activity and by man through diverse industrial, mining, and fuel-burning activities. Roughly one third of mercury in the environment is estimated to derive from natural sources and two thirds from human activity (Seigneur et al. 2003) and (Mason and Sheu 2002). Mercury is released into the air from burning coal and from chloralkali plants as well as volatility from non-point sources and is distributed globally via atmospheric winds and deposition.

There is considerable evidence that humans acquire mercury primarily through seafood (National Research Council (U.S.). Committee on the Toxicological Effects of Methylmercury. 2000). Therefore, there has been interest in understanding the fate and transport of mercury once it enters aquatic (freshwater and marine) environments. Mercury can enter aquatic ecosystems through dry and wet deposition, and riverine input into estuaries. In low oxygen regions such as in some sediments, sulfate-reducing bacteria, and probably other bacterial forms, can methylate inorganic mercury to monomethylmercury. Both inorganic and methylmercury are highly reactive for particulate matter, including living particles such as phytoplankton that lie at the base of most aquatic food chains; these particles are commonly enriched $>10^4$ times relative to ambient water. Living cells therefore represent especially enriched sources of mercury for herbivores, but it is only methylmercury that penetrates appreciably into phytoplankton cytoplasm (Mason et al. 1996; Pickhardt and Fisher 2006). Herbivores that ingest these cells assimilate methylmercury appreciably (Mason et al. 1996) (Karimi et al. 2007; Mathews and Fisher 2008) and are, in turn, enriched sources of methylmercury for predators that feed on them. By contrast, herbivores assimilate significantly less of the inorganic mercury they ingest, and that which is assimilated is lost rapidly (Pickhardt and Fisher 2006). Thus fish are exposed primarily to methylmercury in their diet, which accounts for nearly their entire body burden of this metal. Fish also retain methylmercury very effectively, with loss rates typically 1-2% per day (Pickhardt and Fisher 2006; Mathews and Fisher 2008). As larger fish eat smaller fish methylmercury gets increasingly concentrated, and methylmercury is almost unique among the metals in that it characteristically displays clear evidence of food chain biomagnifications (that is, tissue concentrations increase with each trophic step in the food chain). Consequently, larger and longer lived fish contain very high levels of methylmercury since their input over long periods of time exceeds their loss rates.

Methylmercury at elevated concentrations is known to be toxic to humans and other mammals that consume seafood, and acts primarily as a nerve poison. While numerous studies have documented the effects of methylmercury, particularly on developing fetuses that acquire this contaminant in utero, there remain many uncertainties regarding the long-term health effects of moderate consumption of methylmercury in adults. Further, the public is often confused by seemingly contradictory information regarding seafood. On the one hand, it is told that seafood consumption is advisable because it provides a rich source of protein, minerals, and essential fatty acids. On the other hand there are health advisories warning against the consumption of too much seafood because of

contamination by methylmercury and other bioaccumulative organic toxic chemicals such as chlorinated hydrocarbon contaminants that are largely lipophilic. Compounding the advice by government organizations such as the Environmental Protection Agency (EPA), the Federal Drug Administration (FDA), and state departments of health are the numerous notices on the internet by diverse nongovernmental organizations. Meanwhile there are still regular news stories and articles published about populations at risk that continue to be affected by mercury contamination in seafood.

Analysis of the 1999-2004 National Health & Nutrition Examination Survey (NHANES) data indicates higher levels of mercury in people correlate with fish consumption, with concentrations typically higher for those who live on islands and the coastal areas of the U.S. Specific groups with high exposures are high income women and Asian women (Mahaffey et al. 2009; McKelvey et al. 2007). There are, as well, numerous reports of deleterious health effects presented by consumers of diets dominated by seafood, particularly items such as tuna that are especially enriched in methylmercury (Hightower and Moore ; Groth 2008).

A new program, The Gelfond Fund for Mercury Related Research & Outreach, was recently established at Stony Brook University in New York to focus on improving understanding and awareness of the health effects of methylmercury. As a first step to assess what is known and to recommend activities to address the uncertainties in this field, a workshop of experts was convened in New York City in May of 2009 to summarize the status of current knowledge of the health effects of methylmercury and to provide guidance as to where research and outreach efforts should be focused. This report describes those recommendations. This effort should be regarded in conjunction with a report (Chen et al. 2008) that describes the outcome of a workshop in New Hampshire in which detailed recommendations for further research were made relating sources of methylmercury in marine systems to concentrations in seafood.

Report of New York Workshop: Consensus of what is known and what is not known about mercury and public health

Human Exposure to Methylmercury

1. Fish and other seafood consumption is the primary route of methylmercury exposure for almost all humans. Some subpopulations are more highly exposed, such as those that eat a lot of fish, or tend to eat fish types higher in mercury. Data from NHANES (1999-2004) indicate that people living in coastal areas and the northeast USA have higher blood Hg than people living in other parts of the U.S. Specific demographic groups with more elevated blood Hg levels include Asians, Pacific Islanders, and Native Americans, and persons with higher incomes (e.g., > $75,000) primarily due to higher fish consumption, or a preference for predatory fish. Fish vary substantially in their mercury concentrations, ranging from < 0.1 ppm to >> 1.0 ppm.

2. The fate of mercury and methylmercury in the human body is poorly understood. Compartmentalization and speciation of mercury in different tissues and organs and rates of demethylation and ultimate loss from the body are not well characterized. Mechanism of methylmercury toxicity, and genetic susceptibility to mercury toxicity, are also not well understood. Until body distributions/speciation and mechanisms are better understood, no remedial action can be developed for people with elevated mercury levels in their blood. Need exists for appropriate biomarkers of exposure and especially effects. While there is potential for application of genomics in this work, little has been done to date.

History and Research

3. Acute poisonings in Minamata, Japan via industrially-contaminated seafood from the 1950s and 1960s, and in Iraq via contaminated grains from the 1970s, focused scientific attention on the health effects of methylmercury. These episodes suggested that the fetal brain is the most sensitive tissue for the toxic effects of methylmercury. More recently studies in New Zealand and the Seychelles and Faroe Islands addressed effects of mercury among offspring of mothers who habitually consumed marine seafood. Data from these chronic exposure studies are somewhat conflicting (e.g., impact on motor and cognitive function). Potential causes for this discrepancy include confounding by the presence of other contaminants (e.g., PCBs) and the beneficial effects of omega-3 polyunsaturated fatty acids, and further complicated by lack of a single approach in sample collection and data analysis. Other studies in the U.S., the Amazon, the south Pacific, and among Inuit people provide some additional information. There is no question that very elevated levels of methylmercury can be toxic to developing fetuses, young children, and adults. Major questions include: What levels of methylmercury cause detectable deleterious effects? Is there a threshold level below which no harmful effects are observed (if so, does this vary with age?) or is methylmercury toxic at any dose? It appears likely that levels even below the U.S. Environmental Protection Agency (EPA) reference dose may be

associated with detectable adverse effects. There is still no reliable dose-response curve describing methylmercury toxicity to humans, and curves likely differ for fetuses vs. adults, as well as among populations (not yet well characterized) with different sensitivities. Genetics almost certainly plays a role in influencing sensitivity to methylmercury, but we have not yet identified which genes are key. Differences in diet, such as intake of omega-3 fatty acids (see below) or other nutrients, may also explain apparent differences in the effects of methylmercury among different populations.

4. Recent studies of maternal fish intake and child development in the U.S., United Kingdom (U.K.), and Denmark suggested no overall harm from moderate prenatal intake of low mercury fish. However, these studies are limited by small sample size, or insufficient information on mercury exposure. Also more information is needed on the types of fish consumed in these populations. Re-analysis of data from the Faroe Island cohort and new data from the Seychelles suggest no overall harm with greater fish consumption, despite higher methylmercury exposure consumption. Future studies should be well-powered, and should include appropriate measure of diet, levels of nutrients and mercury, and sensitive outcome measures.

5. Large epidemiologic studies of mercury exposure and cardiovascular disease risk among adults have been performed. However, mercury exposure was relatively low in many of the studied populations. It is not yet clear what level of mercury exposure outweighs the benefits of omega 3 fatty acids on cardiovascular disease. Case studies suggest some evidence of adult neurologic effects of moderate methylmercury exposure, but a well-designed epidemiologic study to reveal dose-response curves at moderate exposure levels has yet to be performed. There is also some, still limited, evidence that neuro-opthalmologic and autoimmune effects may be associated with methylmercury exposure in adults.

Risks and Benefits

6. Risk/benefit messages from various sources based on total fish intake are inadequate and are often conflicting. The scientific and health risk story is complex and nuanced, but public health messages from individual sources are often over-simplified, e.g., “fish is bad,” or “fish is good” without describing these subtler but important details such as amount, type of fish, risk/benefit, potential individual differences in sensitivity, etc. There is still considerable confusion among clinicians and the public.

7. Essential omega-3 polyunsaturated fatty acids are beneficial for human health at all stages of life, as adequate exposure during fetal life is necessary for optimal neurologic development, and adequate intake in adulthood is protective against cardiovascular disease. Seafood can constitute a major source (but not the only source) of these compounds for people. Omega-3 fatty acid content can range from < 100 mg to > 2000 mg/100 g serving of fish.

8. The mercury and omega-3 PUFA content of fish vary independently, so that some fish types are relatively high in mercury and low in omega-3 PUFA, and vice versa. Therefore, the expected risk and benefit varies not only with the amount of fish consumed, but also the type.

9. Selenium has been hypothesized to have a protective effect against mercury toxicity, but this area needs further rigorous testing. The interaction between mercury and selenium and whether mercury inhibits the positive effects of selenium or selenium counters the adverse effects of mercury has not been resolved. Data on this topic remain preliminary, and thus the argument that selenium eliminates or even reduces mercury toxicity is not yet supported.

Mercury in the Marine Environment

10. Rates and sources of mercury input into the ocean, its methylation in the ocean, and factors influencing its trophic transfer in aquatic food chains and ultimately bioaccumulation in key fish and shellfish species are still under-studied. Thus, it is difficult to quantitatively evaluate the influence of anthropogenic activities, and changes in those activities, on mercury consumption by people.

Recommendations for future actions

1. Risk communication messaging: reach out to the public; reach out to the medical community For the public, the focus should be on advising which types of fish should be minimized and which fish can be consumed more frequently. There is a need to strike a balance for consumption of sufficient essential fatty acids and avoidance of elevated methylmercury (and PCB) consumption. Consideration should be given to developing seafood advisories that can be available at time consumers are making their decisions, such as via "smart" phones or with wallet-sized cards specifying which fish are most problematic and which are healthiest. Newspapers, magazines, and the internet may be a venue for communicating real-life stories about risks (e.g., mercury poisonings) and benefits (e.g., improved cardiovascular health) of consuming different types of fish. *Estimated cost: low to moderate*

   For physicians, patients with non-specific neurological symptoms and possibly cardiovascular symptoms should be questioned about their seafood consumption. Individuals who eat at least 2 seafood meals per week or who regularly eat high mercury fish such as swordfish, shark and tuna and who show symptoms or conditions that may be consistent with mercury toxicity should have their blood tested for mercury levels (inexpensive, especially in comparison with other diagnostic tests).

Communication to the commissioner of the FDA about messaging for the public in a user friendly format where fish is purchased is necessary for fish advice: health risks of methylmercury combined with nutrient benefits in some fish. *Estimated cost: low to moderate*

2. Improved training of medical students in environmental toxicology and nutrition
   Currently, students in U.S. medical schools typically receive very little training in the basics of nutrition, toxicology, or in how environmental contaminants can influence human health. To address this deficiency, a course and/or module could be developed (perhaps at Stony Brook's School of Medicine) to serve as a model for medical schools elsewhere. Given the recognized problems of environmental and occupational medicine, and the role of food as a vehicle for both contaminants and nutrients, such a curriculum would be a timely and valuable addition to medical training. In addition, accurate information for the practicing clinician, available in a just-in-time format (e.g., web resources for clinicians and their patients, webinar modules, web links, blogs, etc.) would assist the medical community at large and their patient population in finding and trusting information about mercury and fish. *Estimated cost for course development: low to moderate*

3. Studies of body distributions and toxicological mechanisms of mercury in mammals
   Basic studies are needed on methylmercury toxicity in rodents (and other mammals?), including assessments of internal distribution and mercury speciation in body compartments, biological half-lives in key compartments, and mechanisms of action in the brain. Better characterization of dose-response curves to methylmercury exposures (chronic and acute). Studies should emphasize effects of moderate to high mercury consumption (via diet) on adult animals. *Estimated cost: high*

4. Epidemiologic studies of adults
   Attempts should be made to statistically evaluate existing data bases (e.g., NHANES, NYCHANES) to determine if relationships exist between moderate to high Hg levels in blood with other biomarkers or known health problems in adults. *Estimated cost: moderate*

   Attempts should be made to measure mercury in blood of Framingham participants for those individuals with moderate to high seafood diets, or for those individuals with known cardiovascular problems. Blood analyses should be followed by statistical analyses looking for relationships of high Hg with symptoms or disease outcomes. *Estimated cost: high*

   Explore other available cohort studies with blood samples (e.g., near Lake Chapala, Mexico) that can be used for mercury analysis and relationships with known symptoms.

   Consider conducting a clinic-based study to examine risks from methylmercury consumption at the high exposure range in the US population. Possible health outcomes include adult neurologic, neuro-ophthalmologic, cardiovascular,

autoimmune, and sensory system deficits. Attention should be paid to confounding influences of omega-3 fatty acids and PCBs, specific types of fish regularly consumed, biomarkers of exposure, and timing of exposure-disease relationships. *Estimated cost: high*

5. Mercury cycling in the marine environment.
   Most of the mercury taken in by adults is via seafood consumption. While much is known about mercury methylation and cycling in freshwater systems, comparatively little has been done in ocean ecosystems. Improved knowledge of the sites (e.g., sediments versus water column), biogeochemical mechanisms, and rates of mercury methylation (and demethylation) in the oceans is essential. Moreover, the pathways, accumulation within marine food-webs, and rates of methylmercury acquisition by marine fish need to be better assessed to know how changes in anthropogenic mercury release into the environment are likely to be reflected in bioaccumulation of mercury in people. *Estimated cost: high*.

A number of these recommendations are consistent with the National Academy of Sciences report(National Research Council (U.S.). Committee on the Toxicological Effects of Methylmercury. 2000) that identified unfilled research gaps. Specifically noted are: further investigation of the impact of low-dose exposure to methylmercury on neurological development; assessment of factors that can potentially modify individual responses to methylmercury exposures including genetics and diet; and improvement of estimates of dietary methylmercury intakes through collection of species-specific information on fish consumption.

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