Ecosystem approaches to mercury and human health: A way toward the future

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Ambio is well-known for its interdisciplinary approach to environmental issues and interest in cross-disciplinary research that advances both scientific knowledge and policy-making. For the organizers of the 8th Conference on Mercury as a Global Pollutant, held in 2006, *Ambio* was the ideal journal to present the principal findings and consensus conclusions of four expert panels, who examined key policy-relevant questions concerning atmospheric sources of mercury, methylmercury exposure and its effects on humans and wildlife, socioeconomic consequences of mercury pollution, and recovery of mercury-contaminated fisheries. The Madison Declaration on Mercury Pollution, published in volume 36 (2007), included consensus statements from the panels. As first author of the article, written by the panel on health risks and toxic effects of methylmercury, entitled: *Methylmercury Exposure and Health Effects in Humans: A Worldwide Concern* (Mergler et al. 2007), I examine, here, our work with respect to *Ambio's* mission.

The importance of *Ambio's* appeal to a wide range of disciplines and its contribution to cross-disciplinary research and policy is well-illustrated in the following statistical comparison. According to the Web of Science, which covers a very wide range of scientific journals, this article on the health effects of mercury in humans has been cited 736 times,¹ almost five times more than the number of citations ($n = 154$) recorded, at the same date, in Pubmed², which is limited to articles in the biomedical literature. *Ambio* indeed provided this work on mercury exposure and human health, a platform to provide input to a wide number of disciplines and approaches.

EXPOSURE TO METHYLMERCURY

Methylmercury is a highly toxic compound that biomagnifies through the aquatic food web, placing at risk humans who consume significant quantities of predatory fish from upper trophic levels or who rely heavily on fish as a food source. Elevated methylmercury exposure in humans is not restricted to isolated populations, because of worldwide export and availability of commercially caught fish. Rather, human exposure to methylmercury at levels exceeding those considered clearly safe and without risk of adverse effect has been observed across geographic, social, economic, and cultural boundaries.

When the article in *Ambio* was published, fish consumption and fish-eating birds and mammals were the main known source for MeHg exposure; the authors mention that there were a few reports about rice *Oryza sativa*. Since then, a number of studies from Asian countries have identified rice as an important vehicle for exposure. Rothenberg et al. (2014) reviewed 51 studies reporting rice total mercury (Hg) and/or MeHg concentrations, based on rice cultivated or purchased in 15 countries. Although concentrations were significantly higher in polluted sites compared to non-polluted sites, the percentage of MeHg did not differ statistically, suggesting comparable mercury methylation rates in paddy soil across these sites and/or similar accumulation of mercury species. A review by Zhao et al. (2020), describes Hg cycling in the rice paddy ecosystem and an article in *Ambio* by Hsu-Kim et al. (2018) discusses the need to balance management

¹ Web of Science, <https://clarivate.com/webofsciencegroup/solutions/web-of-science/> accessed July 31, 2020.

² Pubmed, <https://pubmed.ncbi.nlm.nih.gov/>. accessed July 31, 2020.

strategies to reduce MeHg in rice with the need to maximize crop production.

TRENDS IN METHYLMERCURY EXPOSURE AND HUMAN HEALTH

Present exposures throughout the world are lower than those that produced the historic epidemics of methylmercury poisoning in Japan and Iraq. In many populations, however, there is growing evidence that current exposures are sufficient to alter normal function of several physiological and developmental systems, indicating that methylmercury exposure still constitutes an important public health problem. Long-lasting effects of fetal methylmercury exposure have been described in children throughout the world.

Since that time, an impressive body of research has confirmed these findings, even at very low Hg concentrations (Karagas et al. 2012; Ha et al. 2017). Today, there are many longitudinal birth cohort studies, which focus on or include Hg, as one of the multiple contaminants to which populations across the world are exposed. Since the 2007 publication, high Hg exposures among coastal and inland northern Indigenous communities have come to the fore; the former from consumption of marine fish and/or fish-eating mammals, the latter from freshwater fish. For many Indigenous communities, this adds to the stress due to climate change (Dudley et al. 2015). A recent article published in *Ambio* (Callaghan et al. 2020), discusses the importance of improving the dialog between Indigenous communities, researchers, local and decision-makers to address climate change. The need for this type of collaboration is likewise true for Hg exposure since the vehicle for exposure is often subsistence foods that can likewise contain important concentrations of beneficial nutrients. The Nasivvik Research Chair in Ecosystem Approaches to Northern Health³ provides a good example of a multi-sectorial approach to these complex issues.

BIOMARKERS OF METHYLMERCURY EXPOSURE IN HUMANS

Concentrations of mercury in hair and blood (including umbilical cord blood) are both valid biomarkers of methylmercury exposure. Each measure conveys somewhat different information on exposure, and the most useful picture of exposure is obtained by data from both

biomarkers, along with dietary information on the fish species consumed and other dietary data. Total fish consumption—without differentiating the fish species consumed—is not necessarily a dependable metric for estimating methylmercury exposure.

Indeed, Hg concentrations in umbilical cord blood, blood and hair are extensively used as exposure biomarkers in populational studies; some studies have used breastmilk, meconium, fingernail and/or toenail Hg. In general, hair is 250 to 300 times more concentrated in mercury than is blood. This ratio is in common use in research, governmental documents and the World Health Organization (Legrand et al. 2010). However, a review of Hg research, carried out by a plenary panel at the 12th International Conference on Mercury as a Global Pollutant (Ha et al. 2017), held in 2016, question the use of this metric, citing studies that show large variations in hair-to-blood ratio. Indeed, each biomarker reflects different time periods of exposure and the kinetics with respect to Hg intake are different. Unfortunately, despite a growing interest, little is still known about the factors that may modulate Hg absorption in humans, and research is needed to better understand this complex issue.

The amount of MeHg taken up in animals or plants depends upon the degree of pollution of their external environment and for fish, its feeding habits and size. Today, in many countries, consumption guidelines for MeHg exposure include fish species, and fishing guidelines refer, as well, to the size of the fish. For fish consumption, there is growing recognition that not only is the external ecosystem important to the understanding of the health effects of MeHg exposure, but so is the “internal ecosystem” or co-occurrence of beneficial nutrients. Omega-3 fatty acids and/or selenium, have been shown to counteract some of the harmful effects of MeHg (Fillion et al. 2013; Jacobson et al. 2015). To maximize nutritional benefit and minimize toxic risk, some guidelines for fish consumption include both Hg and fatty acid concentrations for different fish species.

RISK ASSESSMENT

Methylmercury is a developmental neurotoxin, and its developmental neurotoxicity to the fetus constitutes the current basis for risk assessments and public health policies. Uncertainties remain in the risk assessment for the neurodevelopmental effects of methylmercury. Yet there is sufficient evidence to warrant the prudent selection of fish species in the diet, particularly for pregnant women and children.

Engleson and Herner (1952) from the University Hospital Lund, Sweden described the first cases of severe

³ <http://en.nasivvik.chaire.ulaval.ca/>. accessed July 31, 2020.

organic Hg poisoning in two infants from the same family. The mother was asymptomatic, and both children appeared normal at birth. The authors surmised that Hg intoxication, perhaps during early fetal life, may be a possible cause. In 1958, Professor Kitamura discovered that many infants from Minamata, born after 1955, displayed symptoms resembling cerebral palsy and wrote: “It is possible that the substance causing the poisoning was transferred to the infants through the placenta or mother’s milk, producing symptoms similar to those of Minamata disease” (cited in Harada 1978). Subsequent epidemiological and pathological studies identified in 1962, methylmercury poisoning via the placenta (Harada 1978). Since that time, we have learned that not only does methylmercury cross the placenta, but it is actively transported; cord blood Hg concentration is, approximately, 1.7 times that of maternal blood (Mergler et al. 2007).

Because the developing fetal brain is so highly sensitive to Hg poisoning, it is considered the most adequate endpoint for risk assessment by governmental and international agencies. Today, throughout the globe, birth cohort studies are examining the relation between prenatal mercury exposure and childhood neurodevelopment; most report dose-related neurocognitive deficits, even at low concentrations. (Ha et al. 2017). While most studies have focused on fish-eating populations, a recent study from China showed intellectual deficits in children exposed to methylmercury through contaminated rice (Feng et al. 2020). Loss of intellectual abilities has important social and economic consequences (Trasande et al. 2006, 2016).

In 2007, the panel noted that uncertainties remain in the risk assessment for the neurodevelopmental effects of methylmercury and that is still true today. Despite a large number of studies on the possible role of genetics, many essential nutrients, gut microbiota and the co-occurrence of other contaminants, there are still uncertainties probably due to the wide variety of external ecosystems in which methylmercury is incorporated into the animals and/or plants and the human situations in which methylmercury exposure and effects occur.

A recently published analysis of Hg concentrations in blood and urine samples of pregnant women and children, collected between 1999 and 2016 as part of the United States National Health and Nutrition Examination Survey, showed an increase in organic Hg and a decrease in inorganic Hg (So et al. 2020); the increase in organic Hg parallels the reported increase in seafood consumption. These findings stress the importance of continuing to examine and update risk assessment within a more global dietary context.

METHYLMERCURY AND OMEGA-3 FATTY ACIDS

Fish can contain both methylmercury and beneficial omega-3 fatty acids. Methylmercury exerts toxicity and can also diminish the beneficial health effects of omega-3 fatty acids. As with mercury, there are large variations in the level of omega-3 fatty acids in fish. Selection of fish species for consumption should maximize the intake of beneficial fatty acids, whereas limiting the exposure to methylmercury.

The large majority of epidemiologic studies on health effects of Hg, including those used to establish reference values, were carried out on marine fish consumers. The findings have been applied to all fish-eaters, including those whose diet contain primarily or solely freshwater fish. Freshwater fish, which likewise vehicle methylmercury, have lower concentrations of omega-3 fatty acids, the ratio of total n-3 to n-6 fatty acids is much higher compared to freshwater fish than for marine fish (Seabert et al. 2014).

There is a very extensive literature on the beneficial effects of omega-3 fatty acids from seafood consumption, but few studies have examined the effects freshwater fish consumers. According to international sources, freshwater capture fisheries account for only 7% of reported global fish harvests, concentrated in low-income countries and in Indigenous communities in some industrialized countries.

Since 1976, *Ambio* has published many articles concerning freshwater fish, several of which addressed Hg contamination in different areas of the globe: Thailand, the Amazon, the Arctic and Sweden. In a study of Hg and omega-3 fatty acids in the Canadian Northwest Territories (Laird et al. 2018), negative associations were observed between Hg and N-3 PUFAs in several freshwater fish, and like Hg, differences were observed in fatty acid and Hg profiles across lakes, underscoring the importance of considering both species- and lake-specific findings for risks and benefits.

CARDIOVASCULAR EFFECTS OF METHYLMERCURY

Current studies suggest that exposure to methylmercury could increase the risk of adverse cardiovascular effects in a significant fraction of the human population. Reported effects include cardiovascular disease (coronary heart disease, myocardial infarction, ischemic heart disease), increased blood pressure and hypertension, and altered heart rate. The strongest cause–effect evidence is for cardiovascular disease, particularly myocardial infarction in adult men.

When the panel wrote the article in 2007, there was some evidence of a link between methylmercury exposure and cardiovascular disorders, but the findings were inconsistent (for review see: Chan and Egeland 2004; Stern 2005). As research continued, in 2011, the U.S. Environmental Protection Agency convened a workshop to review the evidence with a view to possible regulation; the participants concluded that a dose–response function relating methylmercury and myocardial infarction and should be established for regulatory purposes. (Roman et al. 2011). More recently, Hu et al. (2018), published a systemic review and meta-analysis of 29 studies that examined blood pressure and hypertension in relation to biomarkers of mercury exposure; the authors observed no or weak associations from studies of populations with low-to-moderate mercury exposure and positive association among populations with high mercury exposures. Again, beneficial nutrients, present in marine fish and seafood, may counteract, to differing extents, the harmful effects of mercury exposure.

CONCLUSIONS

On this 50th anniversary, we salute *Ambio*'s role in promoting cross-disciplinary research, relevant for decision and policy-making. The health effects of mercury, like other environmental pollutants, need to be considered in the context of an ecosystem approach to health, as described by Webb et al. (2010), which seek to shift the research paradigm to one that embraces transdisciplinarity, social justice, gender equity, multi-stakeholder participation and sustainability. In this context, interventions can be based on understanding the why's and where's of this pollutant, how it circulates in the global environment and the local ecosystems, how it affects people's health, and how, in turn poor health affects social and economic development.

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