

PERSPECTIVE

Mercury and Health

Mercury, particularly methylmercury, is an established worldwide environmental pollutant with known toxicity in humans. The toxic effects of methylmercury in fish were first brought to light after several episodes of poisoning in Japan that involved a spectrum of adverse clinical outcomes. These ranged from paresthesias and blurred vision to more specific signs of methylmercury intoxication, such as concentric vision and deafness, and to coma and death in some cases. Pronounced deficits in neurologic development were also noted. These outcomes were associated with the ingestion of fish that contained methylmercury at levels of 10 ppm or higher — levels clearly linked to pronounced environmental contamination and well above those normally found in fish (average level, 0.12 ppm).

More recent data suggest that fetal exposure to methylmercury at high enough levels results in subtle decrements in several measures of neurologic development. On the basis of this concern, the National Academy of Sciences–National Research Council published a congressionally mandated report on the developmental risks of methylmercury, which led to several modifications of federal policy. The Environmental Protection Agency revised its definition of a safe level of exposure, specifying a lower level that was consistent with the report. At the same time, the Food and Drug Administration (FDA) issued a new consumer advisory on methylmercury and fish consumption.

The most recent advisory was prompted not only by the National Academy of Sciences–National Re-

Species	Methylmercury Concentration (ppm)	
	MEAN	RANGE
Tilefish	1.45	0.65–3.73
Swordfish	1.00	0.65–3.73
King mackerel	1.00	0.10–1.67
Shark	0.96	0.05–4.54
Tuna (fresh and frozen)	0.32	ND–1.3
Pollack	0.20	ND–0.78
Tuna (canned)	0.17	ND–0.75
Catfish	0.07	ND–0.31
Salmon (fresh and canned)	ND	ND–0.18
Shrimp	ND	ND

Methylmercury Levels in Selected Commercial Fish Species.

ND denotes not detectable. The mean for salmon is presented as not detectable because most of the samples did not have a detectable value and therefore the true mean is below the level of detection.

search Council report but also by a body of evidence from large-scale prospective studies linking methylmercury exposure to neurologic toxicity in humans, along with estimates of methylmercury exposure from consumption of fish. The potential risks of methylmercury ingestion were weighed against the presumed health benefits of fish consumption.

The current advisory recommends that pregnant women and women who may become pregnant avoid fish species with the highest average amounts of methylmercury: king mackerel, tilefish, shark, and swordfish. Particularly high methylmercury levels are found in these species because methylmercury concentrates in species that are long-lived and are at the top of the food chain. The Table lists methylmercury levels in these and other key commercial species consumed in the United States. (A more comprehensive list is available from the

FDA at <http://www.cfsan.fda.gov/~frf/sea-mehg.html>.)

The advice to avoid the four species with the highest methylmercury levels was extended to women who are breast-feeding and to young children. Although there is no direct evidence of a link between the consumption of contaminated fish and adverse effects in these two groups, they were included in the advisory as a matter of caution, on the basis of the susceptibility of the developing nervous system to mercury exposure.

What about other commercial fish? The range of methylmercury in other commercial species is fairly narrow, from trace levels to about 0.4 ppm. It is these low-methylmercury fish that are most commonly consumed in the United States. Accordingly, the FDA advisory recommends a “balanced” diet of seafood consumption that will keep methylmercury levels low. The recommendations reflect not only

the methylmercury levels in individual fish species but also the amount of fish consumed over time and the frequency of consumption. Even among women who are pregnant or are likely to become pregnant, consumption of 12 oz (340 g) per week of a variety of cooked fish (excluding the four species with the highest mercury levels) is considered to be safe. If this advice is followed, resulting exposures will be well below that reported to be associated with subtle deficits in development. In addition, this level of fish consumption is consistent with the recommendations of the American Heart Association and the Public Health Service, which are based on the presumed cardiovascular benefit.

Although the current recommendations provide useful guidance, some questions remain. For example, how much canned tuna is safe to eat? What level of fish consumption is safe for children? To begin to address these questions, the FDA sought the advice of its Food Advisory Committee, which provided several recommendations. These include conducting a detailed assessment of the level of canned-tuna

consumption and the associated level of methylmercury exposure, defining what is meant by “a variety of fish,” relating dietary recommendations to the age or size of a child, working with other federal and state agencies to include commercial and recreational fish under the same umbrella advisory, and expanding the monitoring of methylmercury levels to include measurement of levels in humans (in blood, hair, or both).

The current estimate is that 8 percent of women who become pregnant exceed the most conservative definition of a safe level of methylmercury exposure. An ultimate goal is to reduce methylmercury exposure in all such women to safe levels.

Although the current advisory on methylmercury focuses on a subgroup of women of reproductive age, a large case-control study reported in this issue of the *Journal* (pages 1747–1754) suggests that methylmercury exposure may have a negative effect on cardiovascular health in adult men. Guallar et al. found a significant association between toenail mercury levels and the risk of myocardial infarction, af-

ter adjustment for levels of beneficial n-3 fatty acids. However, the findings of another study reported in this issue of the *Journal* underscore the controversy; Yoshizawa et al. (pages 1755–1760) found no association between methylmercury exposure and coronary heart disease in a large cohort of male health professionals.

The notion that methylmercury contributes to cardiovascular disease is certainly a testable hypothesis and one that warrants further testing. Robust prospective studies are needed in populations in which fish constitutes a major staple in the diet. Data from such studies are essential if major changes in dietary recommendations for the U.S. and other populations are to be made.

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BEHIND THE RESEARCH

An Oral Drug for Leishmaniasis

Encouraging results are reported in this issue of the *Journal* for an oral drug for use in the battle against visceral leishmaniasis in India (pages 1739–1746). Given the hurdles that typically stymie the development of drugs for diseases endemic primarily to impoverished regions, the story of miltefosine may offer a model for future successes.

In Bihar, in northeastern India, with 83 million residents who are among the poorest and least educated people in the country, as many as 200,000 deaths from visceral leishmaniasis occur each year. Nearly everyone in this region of India has watched a neighbor or family member waste away and die from complications of this infectious disease, which is transmitted by the bite of a sandfly. For decades, treatment with injected pentavalent antimony was effective, but the parasite in Bihar has developed resistance, rendering this approach nearly useless there. The second-line medication, conventional amphotericin B, can require a month of intravenous infusions and carries a risk of renal toxicity. Short-course treatment with lipid formulations of amphotericin B are highly effective but are financially out of reach in Bihar.

In the mid-1990s, miltefosine was shown to have activity against leishmania in vitro and in animal models. Researchers in Bihar began working with a company that had developed miltefosine as an anticancer drug. But no one was certain whether adequate support would be available to develop this drug

for use almost exclusively in impoverished populations. In 1995, Tropical Disease Research (TDR), a program sponsored by the World Health Organization and other international groups, and the company now known as Asta Medica-Zentaris entered into an agreement to develop miltefosine for visceral leishmaniasis in India.

“We’re dealing with a drug that would not make a lot of money,” said Juntra Karbwang, M.D., clinical coordinator for product research and development at TDR. “Convincing people to contribute to this kind of development is hard.” TDR officials wanted to ensure that research was of adequate quality that the drug, if effective and well tolerated, could be registered quickly in India and elsewhere. Adherence to the Guidelines for Good Clinical Practice (GCP), as defined by the World Medical Assembly in the 1989 Declaration of Helsinki, would be crucial — although such a goal was daunting in a region of poverty and limited medical resources.

TDR assembled a task force that included not only scientists from the drug company and three clinical investigators from India, but also an American physician and a British physician with experience in drug development and with the disease. “We went to Bihar to convince investigators there that we wanted not just a paper in a journal, but an end product that could be used,” Karbwang said. “Some scientists don’t think that far ahead. They would have to comply with Good Clinical Practice.”

The Bihar investigators were on board immediately, which was crucial to the success of the study. “When one is initially introduced to GCP, it seems irritating and a lot of unnecessary paperwork,” said Shyam Sundar, M.D., one of the Indian investigators. “The greatest challenge is to get used to the idea

that someone will verify every word or finding that you wrote or the lab report, and you will be questioned umpteen times. There is huge amount of paperwork. It is absolutely different from what you did earlier. But once you know [how to do it], it flows like a silk.”

As part of the effort to comply with the guidelines, TDR introduced clinical monitors into the study. These physicians and scientists provided oversight and direction for the study, from the writing of the protocol to the verification of the data. Two clinical monitors from India, one from Thailand, and one from Vietnam visited the study site monthly. Investigators typically are not eager to see monitors, said Karbwang, but “in this case, they asked ‘When will the monitors come?’ This [cooperation] contributed greatly to the success” of the study.

In the phase 3 trial reported in this issue of the *Journal*, patients were randomly assigned to receive either oral miltefosine for 28 days or intravenously administered conventional amphotericin B every other day for a total of 15 infusions. All patients were hospitalized so that the oral therapy could be observed and patients could be monitored. Recruitment was not a problem, even though many patients were not yet so sick that they would have been hospitalized otherwise. Most patients in the study were illiterate. If no literate family member was present, a social worker read an information sheet to the patient in the local Hindi dialect, and consent was given orally.

The patients, noted Sundar, “have seen someone next door suffering and dying from visceral leishmaniasis, and they are dead scared. In 90 percent of cases, patients agreed to be admitted without difficulty. Some, however, chose not to take this treatment. Unfortunately, in Bihar, the only drug for them is

amphotericin B, which needs to be infused in the hospital, so [the study conditions were] not much different.”

The results with miltefosine, at each stage of research, surprised even the investigators. At the doses that are needed to be effective against visceral leishmaniasis, oral miltefosine had less general toxicity than it did when used in patients with cancer and did not have the toxic effects on the eyes and the male reproductive system that have been seen in studies in animals. The reasons for this lower toxicity are not clear, but they may be related to the specific population of patients involved in the study.

Planning is under way for a phase 4 trial, supported by the Indian government, to learn more about outpatient use of miltefosine, which is now registered for use in India. The price for the drug in India has not yet been set.

However, the involvement of the Indian government early in the development of the drug suggests that it may reach patients more quickly than many new drugs do.

In practice, with an outpatient drug, compliance with the full four-week regimen is likely to be the biggest challenge. Given the rapid clinical improvement induced by miltefosine, there will be a great temptation to discontinue treatment prematurely. Underdosing will be common, predicts Sundar, which will result in a risk of increased tolerance and, ultimately, failure. “There is a great need to educate the physicians [who will be] using this drug, and in turn, patients need to be warned and educated,” he said. Staff training has begun in 20 centers in Bihar and Nepal.

Meanwhile, other countries have asked to use the drug, even though its effectiveness against other variants of visceral leishmaniasis is un-

certain. Miltefosine is imperfect: it cannot be used in pregnant women. And the sickest patients were excluded from the current study. Yet its success to date has been cause for great hope. “The story of miltefosine is extraordinary on three fronts,” says Barbara Herwaldt, M.D., M.P.H., of the Division of Parasitic Diseases at the Centers for Disease Control and Prevention. “It’s extraordinary that it is an oral drug, that it went through the development phases specifically for leishmaniasis, and that it cleared so many toxicity, efficacy, and logistic hurdles. This drug has the potential to revolutionize treatment of visceral and perhaps other leishmanial syndromes, especially in the impoverished regions where leishmaniasis typically occurs.”

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