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METHYLMERCURY RISK ASSESSMENT ISSUES

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ABSTRACT

This paper reviews the general background of health risks associated with mercury (Hg), primarily methylmercury (MeHg), with a view towards application to advanced technologies that could reduce any contributions from coal combustion. The need for accurate assessment of such risks is discussed, since Hg is now widely dispersed in the environment and cannot easily be eliminated. The primary pathway of MeHg intake is through eating contaminated fish. The issues of concern include identification of critical health outcomes (various neurological indices) and their confounding factors, accurate assessment of MeHg intake rates, and appropriate use of dose-response functions. Ultimately, such information will be used to evaluate alternative coal combustion systems.

INTRODUCTION

Mercury (Hg) has been identified as one of the trace elements found in fossil fuels leading to concerns about health risks. The Hg content of coal varies from about 0.02 to about 0.25 ppm and electric utility coal has been singled out as a major U.S. source of Hg emissions. The Clean Coal Technology Program of the U.S. Department of Energy is engaged in demonstration of various advanced coal combustion and emission reduction technologies, whose commercialization could depend in part on their ability to reduce Hg emissions in response to possible future regulations and concerns about health risks.

At current ambient conditions, these concerns are mainly limited to organic Hg, i.e., methylmercury (MeHg), and stem from previous poisoning incidents and the fact that Hg and MeHg now appear to be nearly ubiquitous in the environment. The primary pathway is through eating fish that have been contaminated with MeHg that has worked its way up the aquatic food chain. As a result, many states and foreign countries have issued warnings advising consumers to limit their consumption of selected fish species. Consumption by pregnant females is often singled out for special attention, since the developing fetus may be more sensitive to potential neurological damage from MeHg than adults.

Since the health risks cannot easily be entirely eliminated, there is a need for public health officials and environmental

agencies to try to assess their magnitudes. The problem is especially critical for those sub-populations for whom fish is a major component of their diet. Since there appear to be important health benefits to the general public from eating fish, it is important to not overstate any risks that might be entailed from the small residues of MeHg that are inevitably present. (A similar balance is appropriate when other contaminants in fish are considered, such as PCBs, for example.) In any event, the public wants assurances that its food supply is safe.

The general population in the United States is characterized by relatively infrequent consumption of fish, of the order of once per week, which is confirmed both by dietary surveys and the concentrations of Hg found in blood and hair. It may safely be assumed that the mean population is not at risk to neurological damage from MeHg; any such risks will be limited to the extremes of the distribution. Thus, careful attention must be given to proper characterization of the tails of the various distributions that may be used in MeHg risk assessments. Fortunately, a great deal of toxicological and physiological information is available for use in this task, perhaps in more detail than what exists for any other air pollutant.

MeHg was identified as the causal agent in "Minamata disease" in the 1960s, after an intensive research effort to find the source of severe neurological effects in people who consumed fish from a bay that was directly contaminated with industrial Hg discharges. Since then, steps have been taken to curtail aquatic Hg discharges, chiefly from chlor-alkali plants, and the main environmental pathway for Hg is now from airborne emissions. Because of the long lifetime of Hg vapor in the atmosphere, these emissions are often dispersed over large distances, which has resulted in the existing global background of Hg.

RISK ASSESSMENT FRAMEWORKS

A basic understanding of the nature of MeHg poisoning is required before risks can be assessed (see WHO, 1990, for example). Mercury attacks brain cells, and the organic forms (MeHg) can pass the blood brain barrier and the placenta. MeHg is almost completely absorbed from food and distributed to all parts of the body by the bloodstream. It is removed

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through excretion as a first-order decay process and has a half-life of about 60 days. This means that neither acute intake levels (such as a peak from eating a meal of especially contaminated fish) or chronic ingestion (such as a lifetime of eating fish) are particularly important. Since cellular repair mechanisms appear to allow a certain amount of Hg to be tolerated and since the ingested Hg passes through the body as a quasi-steady flow process, we assume that the equilibrium body burden is the best indicator of exposure.

However, for congenital effects, there may be a particular time during pregnancy that is most critical with respect to the developing fetal brain. It has been shown that the Hg deposited in hair provides a temporally-resolved record of exposure for each individual (absent use of hair preparations containing Hg). However, the relationships between dietary intake and hair concentration and between maternal hair and infant brain concentrations vary among individuals, which leads to statistical uncertainties in the epidemiology. In addition, the most critical timing for maternal MeHg exposure has not been determined.

A number of attempts have been made to assess the risks that might be entailed in more normal situations, not involving direct aquatic contamination. Many of these involved sampling hair and blood levels in fish-eating populations, some involving very large number of subjects, but none has found clear linkages with frank cases of mercury poisoning. The problems involved have been typical of many environmental epidemiology studies: end points that can be affected by many other factors, heterogeneous responses among individuals, and uncertain doses. Under these circumstances, large populations are required to even approach statistical significance, and the weak associations that have been found or perhaps only suspected do not support precise determination of the shape of a dose-response function (DRF) or the finding of a "safe" level or threshold (Kjellstrom *et al.*, 1986,1989; Myers *et al.*, 1995a,b,c; Davidson *et al.*, 1995).

The data sets that have been used most often in assessing neurological risks from MeHg ingestion are those that were developed from an acute incident in rural Iraq in 1971-2, during which many people consumed bread made from seed grain that had been treated with fungicides containing MeHg (Bakir *et al.*, 1973; Clarkson *et al.*, 1994). Various curve-fitting exercise have been performed with these data to postulate DRFs, which have then been used to estimate risks involved in eating fish containing MeHg.

In using the data from this unfortunate incident, the risk assessment process involves selecting a health endpoint of interest and the accompanying dose metric and then estimating the corresponding dose(s) in the population of interest. For adult endpoints, such as paresthesia (tingling of the extremities), for example, the dose metric is usually expressed as the overall body burden of MeHg, which is analogous to a weighted average concentration (mg/kg) of Hg in the body. For congenital effects, the dose metric used has been the average or peak concentration of Hg in the mother's hair during pregnancy. The risk assessment then involves estimating the distributions of these dose-metrics for the populations and conditions of interest and then the corresponding health risks, for which various approaches have been used.

THE EXTANT RISK ASSESSMENTS

Several risk assessments have been performed for MeHg, and their bases differ substantially. Below we outline some of their salient features.

The U.S. Environmental Protection Agency (EPA)

EPA's approach to risk assessment for toxic substances (EPA, 1995) revolves around the concept of the "reference dose" (RfD), which is the amount that could be ingested daily for a lifetime without adverse effects, with an adequate margin of safety. The RfD is given in terms of an average daily intake rate (ug/kg/d) and does not take into account the frequency of consumption or the rate of elimination. Until recently, the RfD for MeHg had been set at 0.3 ug/kg/d, which is equivalent to eating a 200 g portion of fish containing 0.2 ppm of MeHg every other day. EPA recently suggested that the RfD be reduced to 0.1 ug/kg/d, which would then suggest reducing the frequency of consumption to about one such portion per week. Fish containing around 1 ppm of Hg (shark or swordfish) could only be eaten once per month, according to this RfD.

A Baseline Risk Assessment for New Jersey

Stern (1993) postulated probability distributions for fish consumption and for the MeHg content of fish and combined them to estimate the distribution of doses to New Jersey residents. He also reviewed the epidemiological literature and recommended a lower RfD (0.07 ug/kg/d) to protect against congenital effects. Using his distribution of doses, he estimated that 3% of the fish-eating population would exceed the RfD for adult effects and 23% would exceed the lower limit for congenital effects. However, Stern's probabilistic approach pertains only to individual fish meals and not to long-term averages or to the equilibrium body burden. The aspect of the problem that was not modeled is that high rates of intake of MeHg can only be obtained by eating fish more often, and that the resulting increased number of independent samples will tend towards the (fish) population average over time. This will reduce the doses at the extremes of the distribution and thus the percentages of the population that might be at risk.

The BNL Assessment of MeHg Risks from Coal Combustion

Lipfert *et al.* (1994) attempted to address the question of long-term dose averaging by developing a closed-form representation based on the log-normal properties of the distribution of the Hg content in fish. An alternative method used by Carrington *et al.* (1996) involves a nested Monte Carlo analysis, in which each person in the population at risk samples the fish population according to his dietary habits, from which his equilibrium body burden may be estimated. The population distribution of body burdens is then estimated by sampling from these individuals. Lipfert *et al.*'s analysis consisted of a baseline case derived from the extant distributions of Hg in fish and an "impact" case in which that distribution was incremented by Hg deposited from a hypothetical nearby coal-fired power plant. The baseline distribution of Hg in hair was found to compare well with a distribution obtained from a survey of 1427 females of childbearing age (Smith *et al.*, 1985). Given these distributions of equilibrium body burdens, the probabilities of health effects were estimated from the Iraqi data and found to be trivial for adults but somewhat larger for congenital effects.

RISK ASSESSMENT ISSUES

Selection of Health Endpoint

MeHg poisoning can have many different manifestations, which are usually considered separately for adults and for congenital effects on children. Since risk assessment usually has as its goal the determination of the most critical responses (i.e., the lowest exposure levels that might lead to adverse consequences), there is more interest in the most subtle effects. According to Bakir et al. (1973), for adults, this endpoint is paresthesia. The onset of paresthesia was found to be at a body burden of about 1 mg/kg, which is about 200-300 times the mean U.S. population baseline body burden (Lipfert et al., 1994). It is thus extremely unlikely that anyone in the U.S. could routinely eat enough contaminated fish to reach this level of equilibrium body burden (a diet completely consisting of swordfish or shark would be required!).

Congenital effects have been more difficult to assess. At very high maternal exposure levels, such as in the poisoning episodes of the past, effects on children include severe retardation and may be obvious at birth. However, at lower maternal exposure levels consistent with the current environment, the expected outcome may be the loss of a few points in IQ or its equivalent, which becomes very difficult to detect (the standard deviation of IQ is 15 points). For the Iraqi children, endpoints of interest included "late" walking and/or talking, but such determinations were problematic in the rural societies involved because of uncertainties as to the actual birth dates. Other neurological endpoints that have been employed in various studies include detailed neurological examinations, in which the metric becomes the percentage of children deemed "abnormal" or "questionable." In one recent study (Myers et al., 1995a,c), statistical significance was only obtained when these two categories were combined, and then in only one of two cohorts.

Questions have also been raised about the ages of children at which congenital effects might be expected to appear. There seem to be differences in results based on behavioral end points (such as developmental delays) and in bona fide symptoms of the central nervous system as determined from detailed neurological examination. It seems only logical that a child whose mother was a heavy consumer of fish may also be exposed to dietary fish after birth, raising questions as to whether any observed neurological effects were congenital or the result of childhood exposures.

Estimating Doses

Various *ad hoc* methods have been used to estimate population doses of MeHg. The minimum requirements are data on fish Hg content and fish consumption patterns. However, these are not necessarily independent; the highest rates of consumption are often found among indigenous peoples with ready access to fish supplies; the most abundant species may not be especially high in Hg. For example, the staple fish in parts of the Arctic is often salmon, which is lower in Hg content than large predatory species such as tuna, swordfish, or shark. Fish consumption habits of Indian tribes in the more temperate zones may be similar to those of the general public (Peterson et al., 1994).

The question of interpreting the reference dose concept is more difficult. It appears to have been conceived as a means of converting animal toxicity data for human use by incorporating factors of safety to deal with the uncertainties of differences among species. This is undoubtedly a regulatory convenience for toxic substances about which relatively little is known, but there appear to be much more dependable ways of estimating the risks from methylmercury, based on the epidemiology, for example. It would appear to be preferable to try to estimate the actual risks as well as possible and then to apply the safety factor to the risks rather than to the dose. Lipfert et al. (1996) showed that a dose safety factor of 10 may correspond to a risk safety factor of four orders of magnitude for MeHg.

The use of hair concentrations as an indicator of congenital health effects has its own special problems arising from the heterogeneity of the population in terms of ratios between the mercury level in maternal hair compared to that in the infant's brain. Data from autopsies show brain-hair correlations of the order of 0.7, which means that the true slope of the dose-response function may be twice as high as suggested by the use of hair data as the exposure metric.

Dose-Response Function Shapes and Thresholds

Because of the general compactness of the distributions of doses and of adverse health effects, estimating risks often involves the intersecting tails of two distributions, which is inherently a very uncertain situation. The particular mathematical function that has been selected to represent the data can be very important. Only a small fraction of the U.S. population has MeHg doses high enough to even approach levels of concern, and very few instances of bona fide adverse health effects have been demonstrated at these doses.

Figure 1 shows several alternative curve fits to the Iraqi paresthesia data, for example. Since there is physiological support (such as cellular repair) for the "hockey-stick" function, and since its slope tends to be robustly defined by data at doses high enough to be sure of the outcomes, this simple approach may well be the one of choice. The question of uncertainty (in this case, heterogeneity rather than measurement error per se) in the dose measure used (such as maternal hair Hg concentration) raises some difficult issues. Not only do such uncertainties bias the slope towards the null, they also bias the apparent threshold toward lower doses. Thus, a DRF that appears to be linear (i.e., no threshold) may actually have an appreciable threshold, depending on the nature of the exposure uncertainties. Figure 2 shows how the logistic function reported by Myers et al. (1995) from the Seychelles Islands study would change after correction for measurement error. The corrected (steeper) curve is more consistent with the higher probabilities of adverse effects that would be expected at hair concentrations over about 100 ppm.

When fundamentally noisy endpoints such as IQ are used, it is difficult to distinguish alternative models from one another on statistical grounds, since they all tend to fit equally poorly. Figure 3 shows such data from Kjellstrom et al. (1989). In this data set, there were also issues of confounding and of the methods used to select "cases" and "controls" (Lipfert et al., 1996).

CONCLUDING DISCUSSION

In spite of all the uncertainties that have been raised here on the details of MeHg risk assessment, there is probably more known (or at least as much) about the effects of this pollutant as about any environmental contaminant. For example, the target organ is known as are some of the mechanisms of damage, and there is widespread agreement about the additional sensitivity of the developing fetus. Many of the technical problems of risk assessment may come from trying to extract more information than the available data can provide, including the estimation of risks of less than a few percent or so. The incremental risks due to the local effects of coal combustion were found to be much less than this (Lipfert et al., 1996).

A more stable procedure might involve comparing whole populations, so that the problems of individual variability are "averaged out". Figure 4 shows a plot of average hair concentration vs. estimated average MeHg intake (Lipfert, 1996). The data obtained from various fish consuming populations all fall along the same characteristic line. All of the populations with hair Hg below about 10 ppm were considered "healthy" (including the Seychelle Islands; a complete account of the Faroe Islands study has yet to appear). Given the mean intake level and an estimate of its standard deviation, one could readily estimate the percentage of individuals exceeding any selected threshold level. Such an approach would likely be more robust than trying to fit complicated functions to inherently uncertain individual data.

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Figure 1. Alternative curve-fits to the Iraqi data on prevalence of paresthesia due to consuming poisoned grain. Data from Bakir et al., 1973.

Figure 2. Alternative dose-response functions for developmental test results in Seychellois children, based on the results of Myers et al., 1995a.

Figure 3. IQ data from New Zealand children as a function of maternal hair Hg concentration. Data from Kjellstrom et al. (1989).

Figure 4. Average concentrations of mercury in hair plotted against average MeHg intake for various populations.