Mercury Neurotoxicity Workshop Notes

Overview

The Mercury Neurotoxicity Workshop was convened by EPA's Office of Air Quality Planning and Standards in coordination with the Office of Research and Development to support the development of a benefits methodology for methylmercury regulatory and policy options. The workshop was intended as a working session for an in-depth discussion of the available literature, and was not established as a formal Federal Advisory Committee Action (FACA) process. The workshop product was intended as one input into EPA's process of developing a benefits methodology. The report presents the views of the workshop attendees and has not been subject to further review. It will be considered along with other available information as the Agency explores alternative methodologies.

The workshop was organized by Abt Associates and took place in Washington, D.C., November 4th 2002 at EPA Headquarters. Dr. Bryan Hubbell was the EPA project manager at Office of Air Quality Planning and Standards (OAQPS) and Deborah Rice from the Office of Research and Development (ORD) served as the technical advisor. They were assisted through a contract with Abt Associates, Inc.

The workshop convened experts from different disciplines and backgrounds to develop and evaluate dose-response functions for developmental neurological health effects associated with exposure to methylmercury for use in evaluating the public health benefits of reductions in fish-tissue concentrations of methylmercury. Such benefits assessments are required as part of the regulatory activities associated with promulgation of rules to reduce atmospheric emissions of methylmercury. The regulatory analysis process will ultimately include the monetization of the health benefits associated with reduction of exposure to methylmercury throughout the food supply.

EPA was seeking a wide spectrum of views at the workshop and was not seeking a consensus recommendation from workshop participants. Participants were selected based on their expertise in the fields of neurotoxicology, epidemiology, and risk assessment. Workshop participants included: Dr. Louise Ryan (Harvard School of Public Health, and NAS Committee on the Toxicological Effects of Methylmercury), Dr. David Bellinger (Harvard Medical School, and NAS Committee on the Toxicological Effect of Methylmercury), Alan Stern (New Jersey Department of Environmental Protection, and NAS Committee on the Toxicological Effects of Methylmercury), Andy Smith (Maine DEQ), Rey de Castro (Harvard University), Joseph Jacobson (Wayne University), Dr. Paul Stewart (State University of New York, OSWEGO), Jeff Swartout (U.S. Environmental Protection Agency), and Glenn Rice (U.S. Environmental Protection Agency). In addition, a number of technical experts in the EPA attended and contributed to the discussion, including: Kate Mahaffey, Rita Schoeny, Carl Mazza, Debora Martin, Ellen Brown, Herman Gibb, Marilyn Engle, Stan Durkee, and Tamara Saltman.

Participants were informed that expected outcomes from the workshop include a report documenting: (1) proposed sources of dose-response information from the epidemiological literature for use in developing dose-response functions for mercury related neurological health effects, (2) proposed methods for generating dose-response functions for mercury-related health effects, (3) proposed methods for developing appropriate estimates of dose for use as inputs to dose-response functions, (4) expert discussants' views on developing a methodology for central tendencies and distributions in risk assessments for mercury for use in benefits analyses; and (5) how best to identify limitations and uncertainties in the risk assessment methods.

Purpose

EPA is interested in assessing the economic benefits associated with health improvements from reductions in mercury emissions**.** The ability to assess these benefits rests on the development of methods for translating reductions in methylmercury concentrations in fish tissues into changes in the incidence of adverse health effects in the human population. EPA conducted this workshop as part of its development process to generate a proposed methodology to calculate estimates of the quantified and monetized benefits of reductions in exposure to methylmercury. This workshop will focus on developing 1) appropriate methods for converting methylmercury intake to methylmercury body burden and 2) best estimates of dose-response functions that relate changes in body burden to changes in developmental neuropsychological function, keeping in mind the need to translate these changes in incidence into economic benefits through application of appropriate monetary valuation functions.

The overall goal of this activity was to identify methods for the Agency to consider using in estimating population level health impacts that can be combined with valuation functions to estimate monetized benefits from a decrement in intake of methylmercury.

Essentially, economists need (a) well-defined adverse health effects; (b) dose-response functions from epidemiological and toxicological studies which support estimates of risk reductions in terms amenable to economic valuation; (c) reliable estimates of changes in population exposure to methylmercury (i.e. fish consumption); and (d) reliable estimates of the relationship between fish consumption and methylmercury body burdens. Uncertainties related to the health benefits of reduction of exposure to air pollutants have generally been represented by standard confidence intervals based on measures of within and between study variation in the estimated health effects. For the range of potential effects on the developing nervous system from exposure to methylmercury, there are major information gaps related to these issues. The focus of this workshop was to develop an understanding of the data available to support the development of estimates of central tendencies, population variance**,** and uncertainty associated with dose response functions for developmental neuropsychological deficits as a result of in utero exposure to methylmercury.

EPA's current reference dose (RfD) for methylmercury is based on benchmark dose (BMD) analysis of a number of neuropsychological endpoints from three epidemiological studies of in utero exposure to methylmercury. Endpoints include standard measures of IQ, the effects of which have been monetized by EPA and others with respect to lead. The endpoints modeled for methylmercury also include other effects, such as deficits in attention, memory, language

processing, and visuospacial functioning. Monetization of these effects is less straightforward. In its current RfD derivation, EPA used a one-compartment model to convert from cord blood to maternal intake. Other models have also been published. In addition, EPA assumed that the ratio of cord to maternal blood was 1:1; however, there are data from a number of studies that document a ratio greater than 1:1. This ratio bears directly on the conversion from cord blood levels to intake of methylmercury by the mother. These issues and previous analyses provided a starting point for discussions by the members of the workgroup.

To facilitate discussions, prior to the workshop participants were provided with the following documentation, along with the charge questions to be discussed.

- Clewell HJ, Gearhart JM, Gentry PR, Covington TR, VanLandingham CB, Crump KS, Shipp AM. "Evaluation of the uncertainty in an oral reference dose for methylmercury due to interindividual variability in pharmacokinetics." Risk Analysis; 1999 Aug; 19(4):547-58.

- Grandjean P. "Effects of methylmercury exposure on neurodevelopment." JAMA. 1999 Mar 10; 281(10):896; discussion 897.

- National Academy of Sciences/National Research Council. Toxicological Effects of Methylmercury. 2000.

- Stern, A.H.; "Estimation of the Interindividual Variability in the One-Compartment Pharmacokinetic Model for Methylmercury: Implications for the Derivation of a Reference Dose." Regulatory Toxicology and Pharmacology; 1997 Jan; pp. 277-288.

- U.S. Environmental Protection Agency. Integrated Risk Information System. Compound: Methylmercury; available at http://www.epa.gov/iris/subst/0073.htm.

- U.S. Environmental Protection Agency. *Mercury Study Report to Congress Volumes I to VII*. Washington, DC: U.S. Environmental Protection Agency Office of Air Quality Planning and Standards. EPA-452-R-96-001b. 1996. **http://www.epa.gov/oar/mercury.html**.

The following section provides each charge question and the discussion of views from workshop participants. EPA recorded the workshop and reviewed the tapes to prepare the Notes provided below. All participants were requested to review the Notes and provided comments prior to finalizing the document.

Workshop Charge Questions and Participant Responses

1. *Which study or studies should be considered in generating dose-response functions for the developmental neurotoxicity of environmental exposure to methylmercury?*

The NAS considered that the most appropriate study was the Faroe Islands study. EPA calculated "sample" RfDs for a number of endpoints from both the Faroe Islands and New Zealand studies in its RfD derivation. Should more than one study be considered, and if so, which studies?

Summary of Expert Response: It is best to consider the results of all of the studies. An integrative analysis is possible with a structural model to bring together information relevant to IQ (for example) for each of the studies. Another possibility is to estimate separate slopes for IQ for each of the different studies (after estimating IQ for the Faroe Islands) and then use the range.

Details of Response:
There is no evidence that there is a threshold for the dose-response functions in the available data. We note that the possibility of a threshold is not excluded (Swartout). One can argue that both the dose effect and body burden effect functions are linear. An assumption of linearity is reasonable for all neurological endpoints (Bellinger).

There was agreement among participants that there is no evidence to assume a threshold at this point in time, though there will be arguments about a non-threshold claim. However, the data do not support a zero response intercept except at zero dose. Using a linear extrapolation with the data currently available, the intercept for dose - response is not 0. However, we do not have data in the very low dose range.

The NAS chose to rely on a single study (the Faroe Islands study) because EPA usually selects one study to derive an RfD. The Faroe Islands study was not chosen because the committee thought it was optimal to use that study alone. It is preferable to synthesize across studies and the NAS committee conducted a cross study analysis. However, the committee felt that the approach was too unconventional. Important note: one reason the Faroe Islands study was chosen as the basis for the RfD was that the number from the Faroe Islands is very similar to the outcome of the synthesized analysis. (Bellinger)

Some workshop participants would not rely on the New Zealand study alone. In addition, some experts indicated that the design and analysis were not as robust as they would like.

An approach would be to utilize a linear dose-response and obtain a linear best estimate. This makes it possible to estimate uncertainty bounds. One could either combine all studies and report uncertainty bounds or use the array of the three study results to represent high, low, and

mid-range estimates of effects. This option was especially favored by Ryan.

Regarding weighting the studies for a multi-study approach to generating a dose-response function (or functions): This is going to take some consideration due to the many questions such an action raises: Do we really think that these populations are different? What about the size of the populations studied and how well they represent the populations to which the results will be extrapolated? What is the importance of the fact that the positive slope from the Seychelles is not significant? Does it provide more balance to use the Seychelles results incorporating the insignificant slope?

Linear structural equation models attempt to describe "true" exposure and "true effects" and there is a dose-response relationship between the two. Fish, hair and cord blood reflect true effects. Study results that could be considered include Boston Naming, California Verbal, factor analysis, variables analysis, and recent papers by the Faroe Islands authors. One approach is to assume they all have a similar importance weighted by the study size of the cohort. Inter- study consistency lends itself to this framework. Weighting according to the variability is another option that can be used to find generalizable effect.

2. *Which endpoint or endpoints should be considered in the monetization of the potential benefits of reduction of environmental mercury levels?*

The NAS chose the Boston Naming test as the most appropriate for derivation of the RfD, whereas EPA considered all endpoints negatively correlated *in utero* methylmercury exposure in its RfD derivation. In generating dose-effect functions for monetization, which endpoints should be considered?

Summary of Expert Response: Do not rely solely on the Boston Naming Test, look at other neurological tests that might lead to changes in IQ or other developmental impacts. They noted the problem that other neurological impacts must be related to IQ if they are not monetizable independently in order to use them in benefits assessments.

Details of Response:

IQ Derivation

It is possible to impute IQ from the Faroe Islands study (Bellinger). Text by Sattler has tables based on the standardization sample of the WISC. The text suggests the best sets of two, three and four sub-tests that are valid for IQ calculation. Bellinger talked to Philipe Grandjean about doing this. Grandjean is reluctant to do this because the test was not standardized to the Faroe Islands population. Bellinger feels that while the test has not been standardized to Faroe Islands, the goal is to find info about where kids fall in the distribution in relation to methylmercury. He

stated that it is well accepted to predict IQ from the WISC subsets, but there is considerably less certainty when other tests are relied on to predict IQ. Bellinger stated that using other methods than sub-tests to predict IQ has not been done, so it is probably not a good idea in this analysis.

Paul Stewart thinks that sub-scales and performance on digit span, block design BNT and CVLT have a good ability to predict IQ. His study (the Oswego Newborn Project) has evaluated many of these endpoints and the upcoming report will link them to IQ. His data may answer questions regarding how some sub-scores to predict IQ can be aggregated. However, the results will not be published for over a year. Prediction of IQ from these tests is not as fully grounded as full scale IQ tests.

When NAS calculated the BMD they found consistency within the endpoints of a given study (Ryan). She sees an advantage to putting in all data into our model (not just IQ) and suggests that we predict IQ empirically from a suite of scores within a study. For example, it might be appropriate to use a Bayesian hierarchical model in order to employ all the data. It would be possible to set up a model to estimate IQ as a latent variable. There is some debate about whether the endpoints need to have a known relationship with IQ or not. Bellinger feels that most of the neurological test manuals document their relationship with IQ in the validity chapter. This information could be used as an informative prior.

Although some questioned whether the Faroe Islands team chose not to test IQ because they thought they wouldn't get significant results, Bellinger stated that IQ was not measured because it was not translated and standardized for that population. IQ is probably not well suited to being a sensitive measure of methylmercury neurotoxicity. The test doesn't account for the idea that methylmercury damages different parts of the brain differently.

Can we use the New Zealand IQ results? The New Zealand results can be used to see how the other tests in the battery work (Bellinger). If a relationship between tests administered in New Zealand is derived, then the relationship can be used with the Faroe Islands data to estimate IQ impacts. The study population in New Zealand is heterogeneous; minority groups scored low on the IQ test, possibly due to cultural differences (Mahaffey).

The McCarthy test can be interpreted as IQ, because it is similar to IQ tests. If this is true, McCarthy can be used to get IQ in Faroe Islands (Bellinger). Then the upper bound measure of IQ can be represented by New Zealand and the lower bound estimate can be the Seychelles. The Faroe Islands and New Zealand BMD and results cluster within the different studies but this is more true for Faroe Islands and Seychelles Islands.

If you also had IQ from Faroe Islands, you would have three widely dispersed data points and three different slopes. Smith asked if one option is to get three different measures of IQ and the other is to include all the subtests that are related to IQ. Ryan would rather synthesize with more endpoints that would give more confidence than the IQ alone.

In the case of criteria pollutants it is standard to pool studies using inverse variance weights and to assume that a large sample size provides a more accurate estimate. You can also weight the studies for other measures, like giving the New Zealand study more (or less) weight for being

more heterogeneous (Hubbell).

There is a fair bit that can be done with summary statistics from the three studies (Ryan). One could do both analyses and then see what the difference in results is between the two approaches.

Stern stated the following questions: Are the tests specific enough that we know we are not looking at multiplicative effects? Are we looking at a cascade of effects that lead to something like a decrease in IQ?

Other Neurological endpoints

Do any of these neuromuscular tests have meaning? The experts said no.

The Faroe Islands endpoints are important, but most are not clearly or easily monetizable. The Faroe Islands researchers used domain-specific neurological assessments. If you look at the nests of neurological tests in the study results you see that kids that have ADHD (for example) tend to do poorly on the tests, but that doesn't mean that kids that perform poorly on the test have ADHD. One concern about the use of the Faroe Islands study endpoints is that there is no real relationship with specific health effects or monetizable endpoints. In the near future there may be a definition of learning disability from the scores on the tests (Stewart and Bellinger).

Grandjean reported mercury dose in relation to developmental delay (in months) in the Faroe Islands (Stern). It would be possible to do a willingness to pay (WTP) study for some endpoints that are not linked to income or direct medical costs. The key is to put the endpoints in terms that people can value (Hubbell).

What can we communicate to people in terms of health effects (developmental delays, etc.) that they can value with WTP? Special education is preferable to developmental delay because it is more easily monetized and more objective. Getting to developmental delay is empirical. Information about special education is coming from the Faroe Islands, but we currently don't have the relationship. Developmental delay can be analyzed in the mean time. Lead analysis has used assumptions to go from IQ to special education. The analysis for methylmercury will be similar to lead and can use those techniques. It is important to keep in mind that learning disabilities will be undercounted, because kids with learning disabilities and a high IQ are going to have higher compensatory skills (Bellinger). Can we find a way to include them? Does NHANES ask about ADHD? There is literature about developmental delays and longer term effects and it would be worth looking for prospective data. IQ will be the endpoint that is easiest to sell, but other endpoints should be kept in mind.

3. *What is the appropriate model for generation of dose-response functions, and how should these be chosen? How should variability and uncertainty be assessed?*

The NAS panel recommended that a K power model be used, and determined that K = 1 provided the best fit to the Faroe Island data; however, no information was provided regarding goodness of fit. The Faroe investigators determined that other models allowing supra-linearity at low exposures were a better fit to the data than K = 1. The NAS provided no information regarding the best model(s) for the New Zealand data.

What approaches should be considered in modeling the dose-response function? What issues need to be considered in identifying sources of variability and uncertainty, and what further information does EPA require?

Summary of Expert Response: It is valid to assume that the dose-response function is linear as the best alternative. Use the uncertainty around the mean response *and don't worry too much about the variability in the population because it is a linear function.*

Details of Response:
The K power model restricts K to 1 or greater (so linear or sublinear, not supralinear). Faroe Islands researchers found results that are supralinear (K less than one). NAS asked Faroe Islands researchers to replot the data so that their results would fit the model. The best fit was K= 0.4 Faroe Islands argued for a log or square root function, but that approach was ultimately rejected by the NAS because these models dictated a response which was non-linear in a manner which was not biologically possible. The New Zealand data was modeled by Crump using the K power model (i.e., also restricting K to 1 or greater).

All of the analyses gave a slightly better fit for log transformation which is the limiting case of K going to zero. The log transformed dose-response function is so steep at the beginning that it pushes the dose response function to yield a very low BMD. The logarithmic fit is better because of a few points in the far right hand side. There are no unexposed individuals, so extrapolation is necessary in the zero dose region. None of the models fit optimally because there is so much scatter in the data.

No threshold identification was attempted. If each individual had a threshold and there was a distribution around that threshold then you would expect to see a sublinear function, but the data do not show that (Stern). One could also have a supralinear model with a threshold (Swartout). There is conceptual evidence for a threshold, but you can't measure one (Swartout and Stern).

From the intake of mercury we want to get to blood mercury and from there want to get to health effects (Smith).

Can we do anything with the half-life of elimination? Can you map in people with long mercury body burden half-lives? If you only use the central tendency then you are just protecting the average individual (Rice). One should include information about people with long half-lives as

part of the uncertainty distribution (Swartout).

Reducing the exposure by the same amount will result in the same IQ readjustment no matter how the IQ distribution starts out in the first place. Is the relationship between intake and blood linear? If not, there is some fear that we are losing both the variability and the uncertainty around that. The one compartment model is a linear model. It gives a reasonably good fit across the range of exposures to which it has been applied. There is no reason to suspect that the relationship between intake and blood methylmercury concentration is not linear. However, because blood concentration declines exponentially with time, linearity will be found only when comparing the blood concentrations at the same time after a dose (Stern). The error term is log normal because the relationship is linear in log space. For blood concentrations, the distribution of doses that could have produced that concentration is log normal and the best fit is linear. If one reduces intake by one half, then you reduce blood levels by one half. However, the distribution around that is not normal. For a given individual or two individuals differing in intake, the mean prediction is that the blood levels are reduced by a factor of two.

4. ***What factors need to be considered in choosing a potential model (or models) for estimation of methymercury intake from maternal body burden (hair or blood mercury)?***

EPA used a one-compartment model to derive intake of methylmercury from body burden (maternal blood mercury levels). What are the sources of variability and uncertainty associated with EPA's choice of parameters? Can these sources of variability and uncertainty be quantified, and if so, how? Are there data available that suggest another model should be considered? If so, what are the sources of variability and uncertainty? Can these be quantified?

Summary of Expert Response: The one-compartment model is the better model for dose and concentration calculations. Physiologically-based pharmacokinetic models (PBPK) may in fact, be more accurate (especially for estimating the concentration in a tissue under non-steady state conditions, but the one-compartment models is a much more accessible model, and requires fewer assumptions for estimating population variability.

Details of Response:
The PBPK model is unwieldy and requires lots of inputs. The model makes it difficult to look at interindividual variability and requires lots of hand waving and more assumptions than the one-compartment model. The downfall of the one-compartment model is that it has parameters that are not the parameters that actually drive the outcome in reality. Instead they are loose surrogates of those parameters. It is best to stay with the one-compartment model because we know what we are doing and can paramatize the distributional information with some degree of certainty. However, in choosing it, it's limitations should be realized.

Data development - PBPK model has lots of data development. Clewell, et al., and Crump did an analysis (Clewell HJ Gearhart JM, Gentry PR et al. Risk Anal. 19:547-58 (1999)). There is not a lot to show that the PBPK model is a whole lot better than the one-compartment (Stern). PBPK does let you look at the short term vs. steady state and the changes in concentration. However, if you are asking for dose in a given compartment or attempting to determine for a certain compartment concentration what the intake dose is, there is not a huge difference between the models. Analysis was done on the two models and leaving aside central estimates, the normalized distributional outputs are very close. This implies that if a central tendency can be agreed upon, both models would end up at the same place (Stern).

Are there any new data to better define parameters of the model? No, the models stem from the time when people were dosed with radioactive mercury but that can not be done now.

Sporadic fish consumers can have a time offset between levels of mercury in hair and blood this can be very erratic. In regular fish consumers (Faroe Islands and Seychelles Islands), the relationship is more stable. Why can't this be studied easily with dietary history and regular blood draw (Bellinger)? This is a reasonable approach, but few studies (including the Faroes, Seychelles and New Zealand studies) have collected dietary data which is of sufficient quality and detail to allow calculation of exposure based on dietary intake alone (Stern).

Why do we need hair to blood ratios? Dr. Hubbell stated that it must match input to dose-response relationship. We can only predict one piece of the puzzle from the PBPK model and we can derive the other from the relationship. It is ideal to have a hair to blood ratio so that you can covert back and forth between the two. NHANES data might help with the uncertainty in the hair to blood ratio. If you have blood and hair levels and fish consumption data, can we work with these and forget the model? With empirical data do we need to go to a model (Smith)?

NHANES has 24 hour recall data and an idea of the fish consumed in the last 30 days. However, there is some concern about the degree of variability associated with a 24 hour recall (Ryan, Stern). Optimally we want to derive for a given dose-response function what is the corresponding intake for a point on the curve. How much fish needs to be eaten to get to a given dose? To answer this, we need information about the relationship between hair and blood levels for the population under study. This will allow you to estimate responses for a given exposure (Swartout). We then need hair to blood ratios to apply to the target population. If you have the concentration in a body compartment, then you can say at 10 ppm in hair ALL HUMANS would have same effects and predict what intake that corresponds to (Stern). NHANES is probably the best human study; however it contains only women and children. OAQPS needs to consider other people of concern (Schoeny). Keep men in, especially with cardiovascular risks associated with mercury (Mahaffey).

Are there special issues with women that are pregnant? General agreement that we do need to address these. (No elaboration on this point.)

5. *What are the sources of variability and uncertainty in the pharmacokinetics of methylmercury distribution and elimination?*

The NAS discussed three studies that estimated the distribution of elimination half-life from maternal blood, and these analyses were used by EPA in its consideration of the uncertainty factor for pharmacokinetics. Additional pharmacokinetic issues that need to be considered include the ratio of maternal to fetal blood mercury concentrations, and transfer of methylmercury to and from fetal compartments, particularly fetal brain. What factors need to be considered in determining the best estimates for central tendency? What are the potential sources of variability and uncertainty, and can these be quantified?

Summary of Expert Response: There is uncertainty in the parameter estimates.

Details of Response:
Body weight is not random like a lot of the other measures of uncertainty. Body weight is correlated to blood volume and so if you have the same intake then you essentially get a lower dose with a higher body weight. Mothers who weigh more would also have a lower dose to the fetus. The competing factor is that people who are larger tend to eat more (Stern).

We should start with fish contamination levels at a point in space and determine who will eat fish (Hubbell). Translate that to body burden and then to individual information from the Census. If there is variability across the population that is systematic, then we can account for that.

6. *How can appropriate endpoints be used for monetization?*

IQ has been monetized by a number of investigators, particularly for lead (e.g. Schwartz). The New Zealand study measured IQ, as well as other endpoints, whereas the Faroe Islands study used domain-specific tests that did not include IQ. Can other measures be compared to IQ, or monetized in some other way? What approaches should be considered in monetizing effects on other endpoints? What are the sources of uncertainty?

Summary of Expert Response: IQ should be used because of its monetizability. To get IQ from other studies, one can link tests and can get good values. Also keep track of learning disabilities and developmental delays if they can be monetized. (Discussed previously - see question #2 above.)

7. *Based on what is known about the effects of methylmercury, is there sufficient information to generate dose-response functions for more severe effects?*

These effects might include for example the need for special education; clinical syndromes such as autism, ADHD, an increased need for medical services as a result of low birth weight, etc. Are there other effects in addition or instead of these that should be considered? Are there studies that can be used to identify doses or body burdens at which such effects may be observed? What are the potential sources of uncertainty related to higher-dose neuropsychological effects? uncertainty related to higher-dose neuropsychological effects?

Summary of Expert Response: There is not sufficient information available at this time.

Details of Response:
Hair levels don't get to steady state in the Gerhart and Sherlock papers. Lower hair levels per unit dose never did level off. We just don't know a lot about the relationship with more severe effects. The best shot is the Faroe Islands study (Bellinger). No epidemiological study can look at autism and we can't rely on Minamata because there is no dose information.

High doses can be acute, but also can be considered chronic in terms of pregnancy outcomes (Swartout). There have been findings of increased prevalence of low birth weight with increases in dose (Rice). Stern says that there are small studies that look at birth weight. Minor neurological signs tend to occur among kids with other problems.

The Amazon study results found seasonal differences in neurological effects.

Final Comments

Smith:
1) Look at the relationship between intake and maternal blood. One needs to go from maternal to fetal blood levels, and there is not a 1:1 relationship. It looks more like the relationship is 1:1.7 or 1:1.8, so this issue needs to be dealt with.

2) Also, if you work with the Faroe Islands data, then you need to decide if you have to adjust for PCBs in the Faroe Islands population. NAS said this was not necessary, but the SAB that established the IRIS RfD said it was. Some studies indicate that there is no significant interaction. They found no significant interaction in the Faroe Islands between mercury and PCBs. Bellinger said that they see a PCB effect in the highest mercury tertile, but the mercury slope is the same across the PCB tertiles.

Ryan:
We do not see strong arguments to model in ways other than linear, though linearity is probably not entirely accurate. There is uncertainty about the correct dose-response function and she is

very concerned about log transformations. If we are not sure about the dose-response model then we should use a linear function. We should absolutely not assume a threshold.

The group agreed that there is no threshold indicated.

Bellinger:
Do not focus so much on the Boston Naming Test. There are other measures of IQ that are better. NAS chose it because they had to choose one endpoint but did not imbue it with any greater significance. He suggests going with IQ.

Smith:
He has had discussions about the significance of these tests. The neurological person on the SAB panel had feelings about the relative tests showing effects on kids. You should have this discussion with a panel if you are doing a test thing, but not if there is some integrative analysis.

Stern: There is no hard evidence, but there is a suggestion that dose-response functions for large populations are masking dose-response functions for the most sensitive populations. There are inferences from Iraq that even at the highest exposures, there were children that were ostensibly normal. The slope is probably significantly greater for the sensitive population. The "sensitive population" dose-response functions are being modulated by the response of less sensitive populations. Though, we have no idea what fraction of the population is really sensitive. This is true for both the pharmacokinetic portion and the pharmacodynamic portion.

Final question: Is there a way to use the lead data to document that the lower SES folks are more vulnerable (Rice)?

Some of the SES data goes the other way with a greater impact in the higher socioeconomic group (Bellinger).

Chronic effects in adults may become the more important endpoint. Chronic effects usually win out over developmental effects in RfDs and are easier to value. However, lower IQ is a lifetime effect (Swartout).