ITER Peer Review on Methyl Mercury Meeting Summary

January 12, 1998
University of Cincinnati, College of Medicine
Cincinnati, Ohio
USA

A site-specific reference dose (RfD) for methylmercury in fish was reviewed by a panel of risk assessment experts on January 12, 1998. This meeting was convened by Toxicology Excellence for Risk Assessment (TERA), a non-profit organization dedicated to the best use of toxicity data in risk assessment. Expert peer reviewers donated their time and talents to provide an independent review of the assessment. Reviewers were requested to provide pre-meeting comments if able.

The peer review meeting began with a discussion of conflict of interest. Prior to the meeting each reviewer certified that he or she did not have a conflict (real or apparent) with the chemical under review or sponsor. Reviewers represent their own personal scientific opinions, and not those of their employers. Possible conflicts were discussed with the reviewer to determine if measures were needed to manage the conflict (or appearance). Options include excluding the reviewer from that chemical's discussion and consensus, or allowing the reviewer to participate in the discussion, but not be polled for consensus. The peer review panel discussed and agreed upon how to manage any potential conflicts. This is documented in Attachment A.

These reviews follow a standard format, beginning with a close examination of the supporting documentation and important references several weeks prior to the meeting. At the meeting, a discussion of conflict of interest and decision by the panel occurs, followed by a briefing by the authors of the assessment. The panel then systematically discusses the assessment, starting with a determination of whether adequate data exist to base a risk value, followed by a discussion of the appropriate critical endpoint and study. The quantitative aspects of the assessment are then discussed. Full discussion and participation are encouraged and agreement is reached by consensus. Consensus for the purpose of these meetings is defined as "an opinion held by all or most or general agreement."

The meeting was open to the public and individuals from the U.S. Environmental Protection Agency (EPA), Ohio Department of Health and various environmental consulting firms were in the audience. The meeting concluded with a presentation by Paul Price of the ChemRisk Division of McLaren/Hart on the use of the dose response approach to the issue of fish consumption and the evaluation of hazard indices above 1.0.

Derivation of a Site-Specific Reference Dose for the Ingestion of Methylmercury in Fish

Sponsor:
KS Crump Group, Inc. of ICF Kaiser International
The Aluminum Company of America (Alcoa)

Presentation Team:
Mr. Kirk Gribben, Alcoa
Mr. Harvey Clewell, ICF Kaiser International
Dr. Kenny Crump, ICF Kaiser International
Ms. Robinan Gentry, ICF Kaiser International
Dr. Annette Shipp, ICF Kaiser International

Chair:
Dr. Michael Dourson, TERA

Review Panel:

Dr. Robert Bornschein, University of Cincinnati
Dr. John Christopher, California EPA
Dr. Gary Diamond, Syracuse Research Corporation
Dr. Linda Erdreich, Bailey Research Associates, Inc.
Dr. Marvin Friedman, Cytec Industries, Inc.
Dr. Kenneth Poirier, The Procter & Gamble Company
Mr. Paul Price, ChemRisk Division of McLaren/Hart
Ms. Ruthann Rudel, Silent Spring Institute
Dr. Alan Stern,* New Jersey Department of Environmental Protection
Dr. William Stiteler,* Syracuse Research Corporation
Dr. Christopher Weis, U.S. Environmental Protection Agency

* These reviewers were not able to attend, but provided written comments which were discussed by the panel.

The methylmercury assessment was developed by the KS Crump Group, Inc., a subsidiary of ICF Kaiser International (ICF), for Alcoa. Alcoa is conducting a baseline risk assessment, in cooperation with the Texas Natural Resource Conservation Commission and U.S. EPA Region VI, for their Point Comfort Operations and the adjacent Lavaca Bay in Texas. The site-specific reference dose (RfD) is being developed to specifically address the potential human health effects associated with the ingestion of contaminated finfish and shellfish from Lavaca Bay.

Mr. Harvey Clewell, Ms. Robinan Gentry, Dr. Annette Shipp and Dr. Kenny Crump from ICF developed and presented the RfD, while Mr. Kirk Gribben of Alcoa provided background on the site and fish consumption rates around Lavaca Bay. ICF and Alcoa also arranged for Dr. Philip Davidson of the University of Rochester, one of the principal investigators for the Seychelles study, to attend and answer the panel's questions.

PRESENTATIONS & CLARIFYING QUESTIONS

Mr. Kirk Gribben of Alcoa presented a short overview of the Lavaca Bay site and results of surveys at the site. Alcoa is conducting a baseline risk assessment, in cooperation with the Texas Natural Resource Conservation Commission and U.S. EPA Region VI, for their Point Comfort Operations and the adjacent Lavaca Bay in Texas. Alcoa operated a chloro-alkali plant (CAPA) at this site which in the past discharged mercury-containing wastewater directly and indirectly into the bay. These elemental and ionic mercury discharges have biomagnified in the fish. In 1970, part of Lavaca Bay was closed to oystering and Alcoa was ordered to stop discharge of CAPA plant wastewater to the bay. While the bay was reopened to oystering in 1971, in 1988 the Texas Department of Health closed a portion of the bay to limit consumption of finfish and crabs (catch and release is allowed). Shrimping is allowed in the bay, as shrimp have not shown elevated mercury levels.

A consumption survey (Texas Saltwater Fishing Survey) was conducted of 2000 anglers living around the site. Sampling was stratified to target 50% of the fishing population of the nearest county (Calhoun). Results of the consumption survey suggest women of child-bearing age averaged 2-3 meals of locally caught fish per month, with the upper 95% at 5-6 meals/month. As expected, young children have the highest intake of fish per body weight. Red drum and sea trout are the preferred species, with red drum showing some of the highest average mercury concentrations. The Closure Area has been effective at reducing, but not eliminating, consumption from the higher contaminated area. There are no subsidence fishers fishing the Bay. Although there is a Vietnamese-American population located nearby that engage in shrimping along the Gulf Coast, interviews made in this community indicate that they do not fish in Lavaca Bay.

Finfish and shellfish in the area have been tested for levels of mercury. Mr. Gribben presented the average concentrations by species. Red drum taken from the Closure Area had the highest average (1.2 ppm methylmercury). The weighted average concentrations in fish from the Closure Area was approximately 0.8 ppm; from the Open Areas of Lavaca Bay was 0.3 ppm and from reference bays along the Gulf Coast was 0.15 ppm. In response to a reviewer, Mr. Gribben indicated that the percent methylmercury for finfish and blue crabs is approximately 100%; for shellfish from 30-70%.

Mr. Harvey Clewell of ICF summarized the approach and results of the derivation of the site-specific reference dose for methylmercury in fish. The basic methodology used was the same as that used by the U.S. EPA in deriving their RfD (U.S. EPA 1988; Dourson 1994; Barnes et al.

1995). The assessment included a critical review of the available literature, with the results from the Seychelles Islands (Davidson et al. 1995) selected as the most appropriate to derive an RfD due to its large size, its homogeneous population, its detailed neurological evaluation of children at various ages using an extensive battery of

widely used standardized tests, its careful determination of mothers' mercury hair levels and the absence of substantial exposure to other known neurotoxins, such as PCBs. The exposure to methylmercury in this population results from chronic, multigenerational ingestion of contaminated fish. Neurodevelopmental effects from prenatal exposure to methylmercury were not detected in offspring tested through 29 months of age. A dose-response analysis was developed using the Benchmark Dose method to represent an estimate of the traditional No Observed Adverse Effect Level (NOAEL). The lower bound on the Benchmark Dose (BMD) was converted to an expected distribution of daily ingestion rates across a population using Monte Carlo analysis, with a physiologically based pharmacokinetic (PBPK) model, to evaluate the impact of interindividual variability.

Mr. Clewell's presentation clarified a number of points related to the analysis and modeling raised by peer reviewers in their pre-meeting comments. The BMD was defined as the 95% statistical lower bound on maternal mercury hair concentration associated with an increase of 0.1 in the probability of an adverse effect (or, equivalently with this model, an adverse change in the mean response equal to 0.61 times the standard deviation of the response). Using the results of several child development tests and the k-power and Weibull models resulted in BMDs ranging from 19 to 26 ppm maternal hair concentration.

ICF found the BMD value preferable to the approach traditionally used with negative epidemiological findings (i.e.. the mean exposure designated as the NOAEL). The median is what was used by the Agency for Toxic Substances and Disease Registry (ATSDR) in their draft Toxicological Profile (ATSDR, 1997). ICF believes that there is much useful information in a generally negative study, the dose-response slope is just shallower than that from a study with positive results. The panel later discussed issues related to use of negative study results in this way (see below). Figure 4-2 of the supporting document (scatterplots of digitized data for visual attention at 6 months in Seychellois children from Myers et al., 1995, Figure 2b) illustrates how scores decrease slightly at higher exposures as compared to the mean of approximately 6 ppm. Benchmark dose modeling provides an objective way to quantify what one can see in the scatterplot. It finds that the best estimate of the slope is non-zero, but just slightly. The lower bound exceeds 10% at about 20 ppm and this point was identified as the BMD.

A physiologically based pharmacokinetic (PBPK) model was used to describe the relationship between ingestion rate and hair concentration in mothers. The average concentrations of mercury in maternal hair during pregnancy were used as a surrogate for fetal exposure. Data on the hair:blood partitioning of methylmercury were used to estimate the concentration in maternal blood corresponding to a given concentration in the hair. The distributions for pharmacokinetic parameters in U.S. women of child-bearing age were estimated from the published literature. Monte Carlo simulation was then used to estimate distributions of ingestion rates associated with the maternal hair concentration at the NOAEL (BMD) in the Seychelles study.

Both analytical (independent) sensitivity analysis and correlation analysis (Kendall,

Pearson, Spearman) yielded similar results. The model predictions are sensitive primarily to hair:blood partition, hair excretion rate constant, hematocrit, and, to a lesser extent, body weight and muscle mass. None of these parameters would be expected to be highly correlated.

The Monte Carlo simulation included 1000 iterations and tested for stability of the first and 99th percentiles. Physiological parameter constraints were incorporated in the PBPK model and apart from these constraints, the parameters are assumed to be independent. The predicted output variability was validated against data on variation in half-life excretion from four studies. The predicted half-life was 59 +/- 21 days, while the observed was 53 +/- 13 days. The central tendency of the distribution for this model output is consistent with observations, while the Monte Carlo analysis tends to somewhat overestimate the observed variability.

One reviewer clarified that what ICF is doing with the benchmark dose modeling is trying to estimate the first non-zero point from a negative study. Because there is no detectable response, they are seeking to find where the first non-zero response might occur. Mr. Clewell agreed in general with this explanation and indicated that the level of exposure associated with no harmful effects is based on the power of the study. Less variation and a greater number of people will provide higher confidence.

Another reviewer asked what would happen if one treated the Seychelles data as one dose group and calculated the error for x and y. ICF was not able to respond directly to this question, but explained that the Benchmark approach was an accepted method for statistical dose-response evaluation.

Another reviewer asked whether this data set could have picked up other neurological disorders and would this analysis have picked up polio or some other disease in the same way? ICF responded that the tests represented by the data were specifically chosen to evaluate the endpoint considered to be the critical effect for methylmercury exposure: developmental neurotoxicity.

In response to other questions, ICF indicated that the study results were continuous response data. An effect was defined to occur if a test score was lower than the predicted fifth percentile of scores in an "unexposed population." The fifth percentile was selected in analogy with the convention that the "normal range" in a clinical test is assumed to encompass test results of 95% of the population. The "unexposed population" results were predicted from the model because there was no control group in the study.

One reviewer asked whether deposition of mercury in hair varies across ethnic groups and questioned the use of a non-representational hair:blood ratio in the PBPK model. A definitive answer was not known on ethnic variability. Because ICF was trying to get to the blood level for the study population, they used the reported Seychelles value of 415 ug Hg/g hair /mg Hg/l blood for the hair:blood partition coefficient. This value is higher than the value of 250 commonly used. The study from Peru (Turner et al. 1980,) had a value of 190. When ICF ran the model with the full range of reported values, it did not

significantly change the distributions. The Monte Carlo analysis was surprisingly insensitive to the hair:blood partition coefficient for mercury.

A reviewer asked whether the model solved for the steady state rate between ratio between blood and hair levels. Mr. Clewell confirmed that the hair to blood ratio varies over time due to changes during pregnancy and that peak concentrations were used.

One reviewer asked for an explanation of the differences in the predictions of inter-individual variability between Stern (1997) and ICF's analysis. Mr. Clewell presented slides comparing the parameters used and results from several methylmercury analyses (U.S. EPA's IRIS, U.S. EPA Monte Carlo [U.S. EPA's Report to Congress, Appendix D], ATSDR 1997, Stern 1997). A slide comparing the parameters used in the one-compartment models was presented. Most of the difference in ingestion rates between the ICF analysis and the one-compartment model of Stern (1997) was due to the selection of "preferred values." The parameter values chosen by Stern (1997) predict a lower ingestion rate than any of the other analyses, with Stern (1997) predicting up to one--third to one-half what EPA predicts. The actual predictions of interindividual variability, as measured by the ratios of the 5th and 50th percentiles of the distributions were very similar for all three analyses (Stern, EPA and ICF).

A reviewer asked what the mercury consumption was in the Seychelles population and how it compares to the model predictions. Dr. Philip Davidson of the University of Rochester stated that there are two sources of information on fish consumption for the Seychelles population. The first was a study where mothers were asked how many fish meals they ate each week. The average was 11 meals, with a range of 7-15. The second, was a publication in the Seychelles by Bovet et al. (1997) describing a heart survey which included data on consumption of foods and determined that 85% of the Seychellois eat at least one fish meal per day. Dr. Davidson indicated that one cannot estimate the dose of methylmercury, however, because there is no information on the exact fish species eaten and mercury content varies by species.

Mr. Clewell summarized that the Seychelles Islands study provides more reliable and relevant information on the effects of methylmercury from chronic fish ingestion than the Iraqi data (Marsh et al. 1980, 1981, 1987). Benchmark Dose modeling over the wide range of neurological endpoints yielded a BMD of 20 ppm in hair. An uncertainty factor of 3 is proposed to account for equivocal results from the New Zealand (Kjellstrom et al. 1986, 1989 and Faroe Islands studies (Grandjean et al. 1992, 1994, 1995, 1997) in the vicinity of 10 ppm in maternal hair. Additional uncertainty factors are not needed because the study cohort represents the most sensitive subpopulation and Monte Carlo analysis takes pharmacokinetic variation into explicit consideration. With a distribution of daily ingestion rates associated with the BMD ranging from 0.9 to 3.0 ug/kg/day (median 1.6 ug/kg/day), this results in a range of RfDs from 0.3 to 1.0 ug/kg/day (median 0.54 ug/kg/day). ICF proposes that risk managers consider the distribution of RfDs derived from the Seychelles Islands study. By analogy with U.S. EPA guidelines for the use of percentiles in applications of distributions in exposure assessments (U.S. EPA 1992), that is, the 90th percentile is considered highly exposed, the 10th percentile of the

methylmercury intake provides a reasonably conservative measure. Therefore, a site-specific RfD of 0.4 ug/kg/day is suggested.

PANEL DISCUSSION
Hazard Identification

Because of the complexity of this assessment, the Chair began the discussion by offering a number of presumptions for the panel to consider, and if they were all in agreement, the discussion could proceed beyond these. After discussion, the following presumptions were agreed to:

1. There are enough data upon which to base an RfD. The panel unanimously agreed.

2. The critical effect is neurological development in offspring and potential delayed sequelae. The panel unanimously agreed.

3. Exposure rate may effect outcome and the mechanism of toxicity is important with different routes of exposure. One reviewer pointed out that one should not overlook the possibility of a mechanism being related to a different medium and dose rate. This is an important issue given the site specificity of what is proposed and the desire to avoid inappropriate use of the resulting RfD. The panel unanimously agreed.

4. Data from humans consuming fish are preferred over data from the animal studies. The panel unanimously agreed.

5. Choice of study for critical effect should be one in a fish eating population rather than the Iraqi grain study. The reviewers present unanimously agreed that use of data from a fish eating population was most appropriate for this site-specific RfD for humans eating fish, with some supporting its use as a general RfD because fish is the most common route of exposure to methylmercury. Several reviewers, however, could conceive of situations with a matrix (fish vs. grain) and or a dose rate (e.g., higher and shorter exposures) where the Iraqi data might be more appropriately applied. Other reviewers, however, had serious reservations about the quality of the Iraqi study and the ability of its investigators to obtain quality information. One reviewer asked whether the Iraqi study would be considered if the study on the population in the Seychelles had been performed first. An additional advantage to the fish studies are that the cohorts are at relatively low risk for other factors that could influence child development, thereby making it easier to detect adverse effects from methylmercury.

One reviewer pointed out that data on mechanism of action is lacking in the text. These data could be used to inform questions of variability in response among individuals and exposure routes. Related to mechanism, is the issue of bioavailability of methylmercury in fish. Methylmercury interacts with other minerals in fish tissue (e.g., selenium), which may make the methylmercury less bioavailable, and thereby give some protection.

The panel unanimously agreed that this assessment needs to be carefully qualified so that

people understand that the assessment is specifically for exposure to methylmercury by fish ingestion. One reviewer noted, and Mr. Clewell concurred, that the assessment should explicitly state that this RfD is intended as a remedial action value and not as a basis for permitting additional releases of mercury to the environment.

One reviewer, in written pre-meeting comments, raised a number of issues regarding choice of study, including interpreting the Iraqi data in light of the current information. He states that the Seychelles and Faroes studies with lower exposures fail to see the clinical endpoints identified from the higher exposure Iraqi study. This would indicate that the benchmark dose derived from the Iraqi data (purporting to predict the LCL on the 10% occurrence of these endpoints at 11 ppm in maternal hair) is almost certainly not correct. However, this extrapolation from the Iraqi data would not be unreasonable for the generalizable estimation of the occurrence of sub-clinical effects. Identifying a Lowest Observed Adverse Effect Level (LOAEL) and using standard uncertainty factors might avoid the issues relating to uncertainty in model extrapolation into the low exposure range. While acknowledging the possible weakness of poor maternal recall in the Iraqi study, he thought that the dose response models for the clinical neurologic endpoints, which were not influenced by maternal recall, were nearly identical to those for the attainment of the developmental milestones. ICF indicated that EPA combined all six endpoints, with three of them being unreliable given the way the data were collected. Based on the neurological score alone, the BMD would be 35 ppm in maternal hair. This reviewer thought that despite its shortcomings, and even in light of more recent data, the Iraqi data set of Marsh et al. is not entirely inappropriate as a basis for an RfD.

The panel members considered these comments seriously, but unanimously agreed that studies from fish-eating populations are a better basis for the proposed RfD than the Iraq study, because the population of concern at the Alcoa site is potentially exposed to methylmercury chronically by eating fish.

The Chair then asked the panel, which of the three fish studies it thinks is strongest. Discussion centered around a number of issues concerning the three main studies in fish eating populations.

The Faroe Islands study was actively discussed, but the panel agreed with the ICF position not to use this study as the basis of a site-specific RfD, primarily because of the unavailability of raw data to evaluate dose-response, and the consumption of marine mammals, which resulted in co-exposure to PCBs. This study, therefore, was considered not appropriate, given the site-specific nature of the proposed RfD, where only the consumption of contaminated fish is of concern. The published papers on the Faroes (Grandjean, et. al. 1992, 1995 and 1997) will not support quantitative inferences, although the necessary data are expected to be made available sometime in the future.

One reviewer disagreed with the conclusion that the Faroes data could not be used for dose-response modeling due to confounding from co-exposure to PCBs. While it appears that there is some indication of confounding of the effect of mercury exposure by PCB exposure for three specific test outcomes, there is no indication that such confounding

can be generalized to the influence of mercury on many (>5) other test outcomes. He also commented that the strong suggestion from the Faroes study that maternal exposure to methylmercury at doses corresponding to hair levels less than 10 ppm is associated with reduced performance in neurophysiological tests should preclude the adoption of a revised RfD based on the Seychelles study showing no effects in the same dose range. In response, at least one reviewer commented that the suggested positive results in the Faroes may not be inconsistent with the generally negative results in the Seychelles; in fact a BMD based on the Faroes data---when they become available---may indeed be close to those estimated for the Seychelles data, because the BMDs are estimated from an upper limit on the 10% response.

Dr. Philip Davidson pointed out some differences between the Seychelles and Faroe Islands studies. The published data used in this analysis from the Seychelles were through 29 months, while the Faroes is at six years. However, a paper currently in review on Seychelles children at 66 months shows no effects prenatal or postnatal on child development in this cohort (this paper should be available by spring). The one "positive" effect, a negative correlation between methylmercury maternal hair levels and reduced activity level in boys at 29 months, was based on an examiner rating after one hour of observation in a hospital. Dr. Davidson is unwilling to interpret this finding as it may be spurious, and thought comparing this one result to the Faroes results would be a mistake.

The Seychelles investigators calculated the in utero exposure averaged over nine months of pregnancy from maternal hair samples, while the Faroes study used umbilical cord blood samples at term. At a given intake, maternal blood mercury concentrations, and consequently fetal cord blood concentrations, will decrease over the course of pregnancy as blood volume increases. There are implications, therefore, for using the average or peak concentrations in the Seychelles study versus cord blood samples at term in the Faroes study. Answers to these complicated questions about mechanism and when the effects occur during development, however, are not known.

The New Zealand study was also considered, but it was smaller in size. The panel members present unanimously agreed with the ICF analysis using the results from the Seychelles as the basis of the site specific RfD. They also agreed with using both the Faroes and New Zealand studies to corroborate the results from the Seychelles. Several reviewers cited this checking and balancing among studies in the analysis as a strength of the ICF assessment.

The "clean" nature of the Seychelles data, in that mothers had low exposure to alcohol, raised the question of what effect modest alcohol consumption (more typical of U.S. populations) might have on mercury toxicity, and whether this should be a concern. ICF pointed out that in the Faroes study, alcohol consumption by about 25% of the cohort did not affect outcome. One reviewer pointed out that from a regulatory perspective, one does not consider concurrent exposures, these would be considered on a site-specific basis.

One reviewer questioned the statistical strength of the regression analyses used by ICF to

determine the influence of mercury on the test outcomes. ICF indicated that the variance in the New Zealand study was comparable to the Seychelles. Other reviewers did not see the variance as unusually statistically weak, citing other developmental assessments are around 20%. Dr. Davidson mentioned that Bendersky and Lewis (1994, 1995) indicate that reaching 25% to account for variance would be doing very well.

One reviewer questioned whether there was any seasonal differences in incorporation of methylmercury in hair. Dr. Davidson indicated that there are seasonal differences, but in the availability of different fish species at different time of the year. They looked at seasonality, as well as region of islands where fish were caught and Health Districts where children lived, but saw no effect from any of these factors on child development. When asked whether there were seasonal differences seen in hair, Dr. Davidson indicated that they had looked at hair concentration by trimester and compared hair concentrations for each trimester to an average hair concentration for the duration of pregnancy and found the hair concentrations comparable.

Dr. Davidson indicated that the paper in review on results at 66 months contains the results of the analysis of blood samples from a subset of the cohort that was analyzed for the presence of PCBs and lead. While they found some exposure to PCBs in the Seychelles, the overall exposure was very low (comparable to the lower end of normal for a person with no known PCB exposure).

The reviewers present at the meeting unanimously preferred the Seychelles study as a basis for the site specific RfD for humans eating fish for a number of reasons, including the following:

1. The study was particularly strong in design and numbers.

2. It is the largest cohort with a healthy population and good prenatal and antenatal care.

3. There were limited confounders which were identified a priori and controlled for in the analyses of the results.

4. The developmental tests used are sensitive and some have predictive abilities. The results are available from four time points (with additional 66-month results to be published in the next several months).

5. The population's exposure was limited to fish. They did not consume marine mammals (contaminated with PCBs) as the Faroes Island population.

The panel agreed that the Seychelles study was the best choice for derivation of a site-specific RfD for humans eating fish, with the Faroes and New Zealand results useful for corroboration and support. A benchmark dose analysis of Faroes data might not be inconsistent with that found in the Seychelles, and should perhaps be conducted when the data are available.

A reviewer asked whether PCBs are in Lavaca Bay. Mr. Gribben responded that PCBs have been measured in the ppb range in sediments, but are not a chemical of concern at the site. No sampling of fish for PCBs has been done for that reason.

Dose/Response

Choice of Critical Effect and BMD Modeling. To begin the dose/response discussion, the Chair asked the panel for opinions on the best choice of critical effect to model.

The use of a negative study for dose/response modeling was an issue that generated a significant amount of discussion. Reviewers questioned whether it is appropriate to estimate a dose at 10% response when there is no dose/response relationship between exposure and outcomes in the Seychelles study population. Without this relationship, the choice of endpoint appears arbitrary. Since there is no statistical basis for comparing hair Hg levels with any outcome observed, what is the rationale for using the data to estimate the dose associated with a 5% additional risk (or lower bound on the estimate)?

ICF responded that the traditional risk assessment approach would be to use the mean or median of the Seychelles exposures to serve as a NOAEL. This is what ATSDR has done in their Draft Toxicological Profile (ATSDR 1997). While in the past, these "negative" epidemiological data have been generally ignored, ICF sought to use the data, quantifying what dose-response relationship could have been missed, or answering the question "How steep can the slope of the dose-response function be and still be compatible with the data?" Or, as a reviewer put it "since there is no response, where might the first non-zero response occur?" The New Zealand and Faroes data support the assumption that a dose/response relationship would be seen if higher doses were present in the Seychelles data. The BMD modeling provides a way to use the data and to identify a point where one no longer has confidence that individuals with higher exposures are the same as (not different from) others.

A reviewer clarified that the Seychelles study is considered negative because not enough people were exposed at high enough exposure levels to see effects. Another reviewer thought that while it would be inappropriate to use benchmark dose analysis of the Seychelles data for hazard identification, because there are other studies that associated exposure to methylmercury and neurodevelopmental effects, these data could be used to characterize the potential dose-response.

ICF indicated that in comparing results from the three fish studies, the New Zealand exposures are comparable to the Seychelles (except for the one individual at 87 ppm), but because the cohort is smaller, the BMD would be expected to be lower, all other things equal. The Faroes raw data are not available, therefore the necessary analyses for that study cannot be done.

ICF calculated BMDs from 19 to 26 ppm mercury in hair, using published scatterplots of test scores (test scores adjusted for potential confounding variables) versus maternal hair

mercury levels (Davidson et al., 1995). ICF chose the lowest value of 19 ppm mercury in maternal hair to be conservative (health protective), and rounded it to one significant digit, resulting in 20 ppm. This value corresponds to a 95% lower bound on the exposure corresponding to an increased risk of 10%.

Several reviewers seemed troubled by labeling the 20 ppm as a benchmark dose or the 10% response rate because of the negative nature of the study. They suggested identifying this level as a point of departure, to capture where the effect might be expected to start. They asked for more explanation of this in the text. One reviewer asked whether the BMD reflects the fact that there are few individuals at 20 ppm or higher in the study. Another reviewer asked if the predicted dose-response relationship was independent of the measured outcome; that is, if you took the Seychelles data and made up responses, would you get the same outcome? ICF responded that you might, which is why they label 20 ppm as conservative. However, the use of the benchmark in the case of this study is justified by the identification of an association between methylmercury and similar neurological endpoints in other studies.

The Chair asked for alternatives to use of the BMD or use of the mean of the distribution as a NOAEL level. One reviewer suggested looking at the distribution of hair levels and see where the BMDs fall in the distribution (in this case they are at 99%). The mean was around 6 ppm; 20 ppm is about three standard deviations above the mean. But another reviewer pointed out that this would be like making up the rules after seeing the results. He did, however, think that the approach used here by ICF is analogous to determining what level of a metal in soil is no different than background; in which case 99% would be very acceptable.

Another reviewer suggested calculating a benchmark dose based on activity scores in boys at 29 months. Others (including Dr. Davidson), thought this one data point cannot be interpreted, and that the decreased activity level in boys, if real, is likely to be a beneficial result of fish consumption rather than an adverse effect of mercury. Dr. Davidson also indicated that at 66 months no effects were seen.

Several reviewers questioned why a simpler approach was not used, perhaps pooling the data? What are the statistical and public health advantages of the BMD versus pooling the data and treating it in bulk? Perhaps use more simple tools such as the mean and standard error. Another suggested taking the scatterplot and dissecting it into two or three groups. ICF responded that breaking the cohort up into groups decreases the power of the study.

After additional discussion, the Chair polled the panel on the use of the proposed BMD. Most of the reviewers agreed that use of the BMD was appropriate in this assessment, but it was not a unanimous consensus. Several reviewers were still not comfortable with using the BMD with negative results. The panel agreed that the document needs more explanation in order for the methodology and rationale for the BMD approach to be understood. Figure 4-2 needs clarification that where the dashed line is at 20 ppm, the corresponding point on the vertical axis is the score where 10% of the population would be expected to have a significant decrease in performance. Note that the decrement in

mean response is 0.61 times the standard deviation. Some of the figures (e.g., Figure 4-2) need to be reexamined as the dashed lines cross the solid lines which appears to be a graphic illustration problem. ICF should also indicate that these results are covariate adjusted and the model has biological constraints as explained in Crump (1995).

Calculation of Daily Ingestion Rates

The assessment used a PBPK model and Monte Carlo techniques to derive daily ingestion rates from hair concentrations.

The reviewers had a number of comments and questions on the PBPK model and Monte Carlo analysis. In general, they were positive on the use of these techniques for this assessment, but they wanted more documentation in order to fully evaluate the model and results.

Some of the reviewers comments and issues included:

* Greater description is necessary when the inputs to the PBPK model are probability distributions rather than single point estimates. One reviewer thought that the one-compartment model may be a less realistic representation of the processes underlying the dose reconstruction of methylmercury from hair data, but it is nonetheless considerably more intuitive and transparent. He acknowledged that the PBPK model might be more useful in predicting the approach to steady state, but could not say whether it had clear predictive advantages for populations who are already at steady state (such as the New Zealand, Seychelles and Faroes cohorts).

* Distributional inputs for the Monte Carlo analysis need to be better described with a discussion of specific references used and the data included. Discussion of the shape of the chosen distributions is needed.

* PBPK model parameters need better justification, and an explanation is needed for why different parameter values are used than previous analyses by U.S. EPA (1996a) and Stern (1997).

* The assumption of independence of PBPK parameters needs to be reassessed, or more fully explained.

* Uncertainty and variability need to be better described or distinguished. The sensitivity analysis needs more discussion and one should be able to identify critical parameters. The panel would like to see identified those parameters which are most sensitive and how certain/uncertain one is of these values. While the impact may be small, the question should not be left unanswered. ICF indicated that data are sparse and it is problematic to assess this carefully. OSHA's methylene chloride analysis provides the best example to date, but it did not change the results. These models have more parameters than are needed to describe a single data set, but the parameters are necessary to describe kinetics

for different exposure scenarios (acute versus chronic, etc.). It was suggested that perhaps ICF limit the Monte Carlo analysis to parameters that are important, such as the hair:blood partition and excretion rate constant.

* A reviewer pointed out that the variability between maternal blood and hair is being double counted and therefore overestimated, resulting in a lower RfD. Varying thehair:blood ratio may not have had a big effect, but it should be discussed in the report.

* A better description of how the Monte Carlo approach was implemented (computationally) is needed.

* Some reviewers questioned whether the PBPK model and Monte Carlo analyses may be overly complex. While one reviewer thought that the model was overparameterized and overly complex, another pointed out that it is better to use a well-established model with additional parameters that do not effect it, than to reinvent a new model each time. It was suggested that perhaps ICF would not need to use distributions for the less sensitive parameters, rather in these cases just use deterministic values. While ICF found this appealing, they thought it might raise criticisms of ignoring information. It was suggested that as an alternative for values with no empirical data or two data points, they might use a flat distribution since these parameters are likely insensitive, it will not make a difference.

* Hair:blood distributions from Seychelles versus pooled (global) data need to be presented in the report and discussed.

* How the PBPK model handled pregnancy was questioned and the difficulty in modeling this due to the changes in model inputs over the time-course of the pregnancy was noted. Even within a given trimester there is considerable temporal variability in the relevant pharmacokinetic inputs. ICF indicated that pregnancy is modeled explicitly. It was suggested that this be further explained.

In summary, the panel needed more information on the issues outlined above before they can concur with, or further comment on, this part of the dose-response assessment.

UNCERTAINTY FACTORS

ICF proposed an uncertainty factor of 3 be applied to the distribution of intake values to derive a corresponding distribution of RfDs. This factor is recommended to consider uncertainties regarding equivocal results from the New Zealand and Faroe Islands studies in the vicinity of 10 ppm in maternal hair.

The panel discussed the individual uncertainty factors used in the derivation of RfDs.

Intraspecies Uncertainty Factor: An uncertainty factor of 1 was proposed by ICF for intraspecies variability. This factor is generally considered to be composed of two components---one for dynamic and one for kinetic differences. Because the study cohort (children exposed in utero) represents the most sensitive subpopulation, a one-fold factor was suggested for the dynamics component. The consensus of the reviewers was that this one-fold factor was appropriate. A one-fold factor was also suggested for kinetic variability, because the use of PBPK modeling with distributions for each parameter in the model, resulted in a distribution of intake values. The corresponding lower confidence limits on the distributions could be used in lieu of a default factor. Rather than use a fixed uncertainty factor, ICF proposed letting the risk manager choose the selection of the intake value to use, because this RfD is proposed for site-specific use. The reviewers unanimously agreed with the use of this one-fold factor as well, if a lower limit on the distribution was used as a basis of the RfD.

One reviewer raised a concern that the study population had little exposure to alcohol, drugs, or other chemicals, yet the population at risk in the U.S. will be exposed to other substances that affect the central nervous system. He asked whether the intraspecies uncertainty factor should account for this. Other reviewers indicated that the RfD methodology does not consider other exposures when calculating RfDs because there is no way to predict how the RfD will be used, rather these should be considered on a site-specific basis, looking at the site population and what else they might be exposed to.

The reviewers present unanimously agreed that an overall intraspecies uncertainty factor of 1 is appropriate for this RfD, due to the number and sizes of the methylmercury studies which have identified neurodevelopmental effects on children exposed in utero as the critical effect, and to the distribution of intake values based on the PBPK model.

Animal to Human Uncertainty Factor: This factor was not needed since human data form the basis of the RfD.

Subchronic to Chronic Uncertainty Factor: This uncertainty was discussed below in the database uncertainty factor.

LOAEL to NOAEL Uncertainty Factor: This factor was not needed because a BMD was proposed as the basis of the RfD. In addition, a LOAEL was not identified in the Seychelles Island study.

Database Uncertainty Factor: An uncertainty factor of one was proposed for database uncertainty. The U.S. EPA in their RfD had applied an uncertainty factor of 3 to account for lack of data on long term sequelae of developmental effects and lack of a two-generation reproductive study in animals.

The ICF document noted that data from several stable fish-eating populations exposed for multiple generations, and some of which tested adults for adverse neurological effects, suggest that chronic sequelae are not of concern in populations exposed to low-levels of exposure from fish ingestion. Several reviewers were not convinced that such data

accounted for the possible sequelae later in life and thought that this assumption (and its associated uncertainty factor) should remain until there is clearly described evidence to the contrary. It was noted that the level of adverse effect which are potentially driving the RfD is not clinical effects, but subtle decrements in performance.

ICF also indicated that an uncertainty factor for the lack of a two-generation reproductive study, as indicated by the EPA Reproductive Guidelines (U.S. EPA 1996b), is to detect effects caused by prenatal and postnatal exposure, as well as effects on germ cells, that could be transmitted to, and expressed in, the next generation. Little work has been done on mechanism of action for methylmercury in recent years; however, based on the mechanism of action proposed for the most sensitive endpoint (Choi et al. 1978), generational effects would not be expected to be transmitted. Based on what is known about the mechanism of action of methylmercury, the neurodevelopmental effects observed are not expected to be heritable; therefore, a two-generation reproductive study would not be necessary. The reviewers asked that this be better explained in the document. Several reviewers also noted that reproductive effects were not specifically evaluated in the Peruvian and Seychelles populations and that the ICF discussion in this regard was not entirely convincing.

One reviewer indicated that the status of information on other endpoints was not well documented in the report (e.g., chromosome studies). ICF had not considered this necessary as both EPA and ATSDR had very recently reviewed all the data and reached the conclusion that reproductive/developmental effects were the critical endpoint.

Several reviewers questioned the significance of the visual field tests in the Amazon study (Lebel et al. 1996). ICF explained that this study included 29 subjects who were not randomly selected. The results do not make sense in that some individuals could not see at 180 and 120 degrees, yet they could see at 150 and 90 degrees. This was a one-time adult test, so it does not necessarily demonstrate chronic sequelae. The Peruvian study (Lebel 1996) included multigeneration exposures up to 40 ppm and no effects on vision were seen in adults.

Some reviewers thought a database uncertainty factor might be appropriate; others did not think this area needed an uncertainty factor.

Modifying Factor for Fish Eating Population

ICF proposed a modifying factor of 3 be applied to the distribution of intake values to derive a corresponding distribution of RfDs. This factor is recommended to consider uncertainties regarding equivocal results from the New Zealand and Faroe Islands studies in the vicinity of 10 ppm in maternal hair. In addition, it also could be considered to cover the potential for other concerns, such as chronic sequelae. The factor of three seems to be a comfort level for adjusting the BMD.

Peer reviewers did not necessarily comment on the use of this modifying factor as being

different than the data base uncertainty factor, but several agreed with the concerns expressed by ICF.

When the individual panel members were polled on choice of uncertainty factors, their preferences ranged from 1 to 10, with the majority choosing 3, primarily for uncertainties in the data base. Individuals cited the need for more information on chronic sequelae and the possibility that as many as four different studies (Iraq, Faroes, New Zealand, Amazon) can be interpreted as showing effects at maternal hair mercury levels below 20 ppm. Other issues not necessarily related to uncertainty factors were uncertainty in the use of modeling to identify the dose, use of CNS substances by individuals in target populations (but not in study population) and lack of documentation on other endpoints (which were discussed and merely need documenting). Some thought the document needs better justification for why a database factor of one is sufficient. One reviewer thought the assessment should say that when the Faroe Island data are made available, this could result in a different RfD.

OTHER ISSUES

Use of Distribution to Communicate RfD vs. a Point Estimate

The reviewers discussed this issue briefly, but did not reach agreement. Some favored the use of distributions so that the site manager could decide what to use. Some questioned what this particular distribution means and/or are still concerned about the dose extrapolation methods used and need more explanation of those issues before deciding.

Derivation of a Site-Specific RfD

Throughout the discussions, reviewers had questions and concerns about what a site-specific RfD means, how it would be used and how to prevent its misuse. These issues will require further discussion.

NEXT STEPS

The panel generally agreed that they are close to coming to closure on the assessment; however, there are issues related to the dose-response model, the PBPK model and the Monte Carlo analysis that they want further explained and documented by ICF.

The panel would like to review a revised document and meet (probably in conference call) to discuss and reach closure on the following issues:

Selection of Study, Critical Effect and Dose Level

* More discussion on mechanism of action is suggested. Such information may inform questions of variability in response among individuals and exposure routes.

* More explanation is needed to communicate to readers how the BMD was derived and what a BMD based on generally negative data means. Some of the figures in Chapter 4 need clarification and perhaps correction.

PBPK and Monte Carlo Analyses

* More documentation on the PBPK model and Monte Carlo analysis is needed. For example, the inputs to the PBPK model (particularly the probability distributions) need better description and justification; the assumption of independence of PBPK parameters needs to be reassessed, or more fully explained; how the PBPK model handles pregnancy needs further explanation, and a better description of the diagram for the PBPK model might be helpful. Some attempt should be made to simplify the model, perhaps consider deterministic values instead of distributions for insensitive parameters. The distributional inputs for the Monte Carlo analysis also need to be better described, with a discussion of specific references used and the shape of the chosen distributions.

* An explanation is needed for why the parameter values used by ICF are different from those used by U.S. EPA (1996a) and Stern (1997).

* Uncertainty and variability need to be better described or distinguished and the sensitivity analysis needs more discussion.

* Enhance the discussion of why varying the hair:blood ratio did not have a big effect, as well as the discussion of hair:blood distributions from Seychelles versus pooled (global) data.

Uncertainty and Modifying Factors

Some reviewers thought the document needed to better justify why a database factor of 1 is sufficient. The panel will discuss further the uncertainty factor for database and the use of the modifying factor proposed by ICF.

Other Issues

The panel will need to discuss further the issue related to use of a distribution to communicate the RfD, versus a single value. In addition, they want to discuss how to best communicate a site specific RfD to prevent its misuse.

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Method Discussion: The Use of the Dose Response Approach to the Issue of Fish Consumption and the Evaluation of Hazard Indices Above 1.0

Paul Price, Principal Health Scientist with the ChemRisk Division of McLaren Hart, Inc. made a presentation on the use of the dose response approach to the issue of fish consumption and the evaluation of hazard indices above 1.0. This presentation was based in part on a recent publication (Price et al. 1997) in Risk Analysis, and is the result of a four-year project between ChemRisk and the U.S. EPA, National Center for Environmental Assessment.

Mr. Price began his presentation by stating that the RfD (reference dose) approach and measures of hazard such as the Margin of Safety (MOS) and Hazard Index (HI) are useful to determine unsafe doses or aid in the evaluation of mixtures and comparison of chemicals, however, these approaches provide no guidance on risk. There is a need for guidance on doses above the RfD to help make decisions regarding costs, risk/risk tradeoffs and to determine how likely it is that adverse effects will occur with a HI greater than 1. Fish consumption leads to doses above the RfD for many compounds, but unlike soil consumption at a Superfund site, a simple fence does not stop the exposure. Fishing bans are unpopular and have economic impacts. In addition recreational fishing is a voluntary act that is not risk free and fish consumption can have beneficial effects.

There are difficulties in noncancer dose-response modeling; unlike carcinogenicity there is no single toxicological paradigm for dose-response modeling. The concept of thresholds suggests that the dose-response curve in humans is influenced by the distribution of concurrent stressors and other types of heterogeneity in humans and is not related to the dose-response in test animals. In addition, risk managers may wish to evaluate sub-populations at high risk separately.

Despite these limitations, Mr. Price concluded that it is possible to characterize noncancer dose and presented a specific numeric approach. The approach builds on the existing RfD framework, requires little additional toxicological data, and quantitatively deals with uncertainty in the response estimator.

The approach is based on three concepts:

* Use the RfD as a model of a zero (or minimal) risk (ED0) in humans.

* Use the current system of uncertainty factors to predict the dose that causes an effect in a typical human (ED50).

* Use a linear model as an upper bound to the actual dose response for doses between the

ED50 and ED0.

To model the ED0, one can use the definition of the RfD where ED0 is equal to the NOAEL or Benchmark Dose divided by the uncertainty factors for intra- and interspecies extrapolation. These two uncertainty factors are defined as distributions.

The concept of estimating the dose that causes an effect in a "typical individual" is not usually considered in noncancer risk assessment, but is conceptually similar to a chronic ED50. To calculate the ED50 for humans, the ED50 in animals is divided by the uncertainty factor for interspecies extrapolation (UFA). In this case the intraspecies uncertainty factor is not applied. This UFA is traditionally viewed as representing interspecies differences in the NOAEL, not the ED50's, use of the UFA to account for interspecies is therefore conservative. The ED50a should be based on all adverse effects in the test animals, not just the critical effect.

The third concept -- use of a linear model -- assumes that the fraction of the population that responds at doses between ED0h and ED50h is a linear function of dose in excess of the ED0h. This assumption will be conservative for compounds with sublinear dose-response curves.

In this model, the uncertainties in UFA and UFH are expressed as distributions. The model predicts the dose response by randomly selecting values for UFA and UFH and calculating a response to the dose. The process is repeated several thousand times and a range of response values is produced for each dose. There is a limitation to this approach in that the assumption that a linear response is conservative only holds for doses below the ED50. The proposed model cannot be used, therefore, to predict the dose that causes responses greater than 50 percent. The approach was demonstrated with several example compounds which are described in Price et al (1997), which also describes the dose-response model in detail.

How does one interpret what the predicted response means? First, since one or more effects are possible above the threshold for the critical effect, and due to the lack of concordance between animals and humans, the effect in humans would not necessarily be assumed to be the same. As a result, the response is best viewed as one or more adverse effects. The linear response will result in an overestimate of risk; therefore, the predicted response should be viewed as a conservative estimate of the probability of one or more adverse effects occurring in an exposed individual. This approach has several strengths: it can produce quantitative estimates of risk; the analysis is independent of the actual dose-response curve, and the analysis is conservative (linear model assumption).

The approach is not recommended for estimates of low risk doses. Because of the uncertainty in the level of risk at the RfD, this model should not be used to estimate doses associated with low risk. An estimate of a dose causing a 5% response (ED05), however, would not be expected to change. The assumptions upon which this approach is based are not without controversy. Many toxicologists and risk assessors are not comfortable with the assumption that the RfD is a measure of the ED0, while others believe that the RfD is

a subthreshold dose. For certain uses, this model is insensitive to whether the RfD compares to zero risk or merely very low risk (ED0.0001).

In conclusion, estimation of risk from doses above the RfD is feasible, but Hazard Indices are not consistent predictors of risk. This proposed method produces a constant measure of risk, is consistent with the RfD, and differentiates between uncertainty and variability.

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Attachment A

Managing Potential Conflicts of Interest

TERA peer reviewers donate their time and talents to this effort. They are selected based upon their expertise and qualifications and are employed by many types of organizations. TERA strives to create a balance of expertise and affiliations. However, individual peer reviewers are representing their own expertise and views, not those of their employer.

TERA has requested that each peer reviewer identify potential conflicts of interest related to the review of health risk assessments of methylmercury. Each reviewer has signed a statement indicating that he or she does not have a conflict of interest concerning these chemicals; with the following considerations noted below. These were discussed at the beginning of the January 12, 1998 meeting and agreed to by all.

Dr. Robert Bornschein is on the faculty of the University of Cincinnati College of Medicine. He has been involved as an expert reviewer for the Seychelles study, protocols and review of the data, but has had no contact with the study for the past two years. The panel agreed that Dr. Bornschein may participate fully in the discussions and consensus.

John P. Christopher - Dr. Christopher works for the California Environmental Protection Agency (Cal EPA). Cal EPA regulates various aspects of production, use, sale or disposal of virtually all chemicals; but he is not currently involved in any assignment or controversy regarding the toxicity of methylmercury. He worked for ICF Kaiser for one year, but not on methylmercury. The panel agreed that Dr. Christopher may participate fully in the discussions and consensus.

Gary L. Diamond -- Dr. Diamond works for Syracuse Research Corporation. He does not have any conflicts. The panel agreed that Dr. Diamond may participate fully in the discussions and consensus.

Michael L. Dourson - Dr. Dourson works for Toxicology Excellence for Risk Assessment (TERA). As an employee of EPA Dr. Dourson participated in the development and

review of the current U.S. EPA reference dose in the early 1990's. TERA and Dr. Dourson do not think this will prevent him from facilitating the meeting in an objective and unbiased manner. The panel agreed that Dr. Dourson may participate fully in the discussions and consensus.

Linda S. Erdreich - Dr. Erdreich works for Bailey Research, Inc. She does not have any conflicts. The panel agreed that Dr. Erdreich may participate fully in the discussions and consensus.

Marvin A. Friedman -- Dr. Friedman works for Cytec Industries. He did work on mercury approximately 20 years ago and published on the chemical. This work does not create a conflict. The panel agreed that Dr. Friedman may participate fully in the discussions and consensus.

Kenneth A. Poirier -- Dr. Poirier works for The Procter & Gamble Company. He does not have any conflicts. The panel agreed that Dr. Poirier may participate fully in the discussions and consensus.

Paul J. Price - Mr. Price works for the ChemRisk Division of McLaren/Hart. Mr. Price is not currently part of the regular TERA peer review pool, but has been asked by TERA to participate as an ad hoc reviewer because of his Monte Carlo expertise. McLaren/Hart has been employed by hundreds of companies, including on occasion, Alcoa. At one time, several McLaren/Hart personnel made a presentation to Alcoa on the topic of fish consumption issues; however, Mr. Price was not involved in this presentation, nor any other projects for Alcoa. TERA and Mr. Price do not think his objectivity would in any way be influenced by this. The panel agreed that Mr. Price may participate fully in the discussions and consensus.

Ruthann Rudel - Ms. Rudel is employed by the Silent Spring Institute. She does not have any conflicts. The panel agreed that Ms. Rudel may participate fully in the discussions and consensus.

Christopher P. Weis - Dr. Weis works for the U.S. Environmental Protection Agency, Region 8. He does not have any conflicts. The panel agreed that Dr. Weis may participate fully in the discussions and consensus.

The following individuals were not able to attend the meeting, but were asked to provide written comments.

Alan H. Stern - Dr. Stern is employed by the State of New Jersey, Department of Environmental Protection. He has published several papers dealing with methylmercury risk assessment, including a 1993 paper which derived a suggested reference dose and a 1997 paper which addressed appropriate uncertainty factor adjustments for a methylmercury RfD. He has not published papers dealing the toxicology and epidemiology studies subsequent to 1993 and is open to evaluating the new data and re-

evaluating the older data. New Jersey has methylmercury fish consumption advisories which are based, in part, on Dr. Stern's publications. TERA and Dr. Stern do not believe his prior work on methylmercury will prevent him from providing an objective review of the proposed value, without regard to the policy or opinions of the State of New Jersey. One member of the peer review panel, however, questioned whether Dr. Stern has a potential conflict given he is still working for the State of New Jersey, and making recommendations to the State regarding chemicals such as methylmercury is one of his responsibilities. The panel discussed this point and decided to fully consider Dr. Stern's written comments in their discussions. However, the issue of Dr. Stern's being polled for consensus was tabled until a later time, since he was not at the meeting. The panel also suggested that TERA consider this generic issue for the future.

William M. Stiteler. Dr. Stiteler works for Syracuse Research Corporation. He does not have any conflicts and should participate fully in the review. Dr. Stiteler will not be attending the meeting, but has provided written comments. The panel agreed to fully consider his comments.