ITER Peer Review on Methyl Mercury Meeting Summary

February 26, 1998
Conference Call

A panel of risk assessment experts reviewed a site-specific reference dose (RfD) for methylmercury for fish-eating populations on January 12, 1998. At that meeting the panel raised a number of issues and concerns which it asked the authors (ICF Kaiser International) to address in a revised document. This same panel of reviewers discussed this revised document in a conference call on February 26, 1998. This conference call was organized 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. For a complex assessment such as this, each reviewer brought to the review his or her particular expertise, which when combined, provided a comprehensive overall review of the assessment document.

The peer review conference call began with a discussion of conflict of interest. Prior to the first meeting in January each reviewer certified that he or she did not have a conflict (real or apparent) with the chemical under review, or with the 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 the original certifications again, and agreed upon how to manage any potential conflicts. This discussion 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 on which 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 conference call was open to the public and individuals from the California Environmental Protection Agency (CalEPA) and Public Service Electric and Gas Company took part.

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Derivation of a Site-Specific Reference Dose for Methylmercury for Fish-Eating

Populations

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

Presentation Team:
Mr. Harvey Clewell, ICF Kaiser International
Dr. Kenny Crump, 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 participate in this conference call due to scheduling difficulties and therefore, their opinions are not reflected in this document. They were present at the first meeting.

The KS Crump Group, Inc., a subsidiary of ICF Kaiser International (ICF) developed the methylmercury assessment, for Alcoa. Alcoa is conducting a baseline risk assessment 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.

Dr. Michael Dourson, as Chair, began the meeting by suggesting a process for conducting the conference call which would facilitate an efficient discussion. The panel agreed to follow a process whereby each of the eight issues identified from the first meeting would be discussed in order. Dr. Dourson called upon a different individual peer reviewer to begin each issue's discussion with his or her opinion on whether or not ICF answered the question or issue as identified, and whether he or she agreed with the ICF position. The discussion was then opened to others, with an alphabetic roll call used to solicit each

reviewer's opinion. Opportunity for ICF to respond to the peer reviewers' comments was also provided. Observers were offered the opportunity to present technical comments.

ISSUES FROM THE JANUARY 12, 1998 MEETING

Because the panel generally agreed that it was close to coming to closure at the first meeting; discussion for this meeting was generally limited to those issues identified in the "Next Steps" portion of the January meeting summary (available at http://www.tera.org/peer). They are:

Selection of Study, Critical Effect and Dose Level

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

2. 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

3. 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.

4. 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).

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

6. 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

7. 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

8. 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.

PRESENTATION & CLARIFYING QUESTIONS

Mr. Harvey Clewell, Dr. Annette Shipp and Dr. Kenny Crump from ICF presented the revised assessment to the panel by highlighting the changes made to their document based upon the issues raised at the January 12 meeting.

Issue 1. Mechanism of action. Dr. Annette Shipp indicated that following the suggestion of the reviewers ICF revised and expanded the discussion on what is understood about mechanism of action to inform the selection of uncertainty factors.

Issue 2. Benchmark Dose (BMD) explanation. Dr. Kenny Crump indicated that significant discussion was added to explain the use of benchmark modeling with a negative study. In addition, the lower bound on the benchmark dose (BMDL) calculated for the test for visual attention at 6 months (Davidson et al., 1995) was corrected to 24 ppm maternal hair concentration for both models (in the previous draft they were 20 and 19 ppm, respectively). This correction was made after Dr. Davidson informed ICF that they had modeled that endpoint incorrectly, in that shorter focusing times are desirable.

A new Figure 4-1 was provided to illustrate a benchmark calculation from both a "positive" study and a "negative" study (where the terms "positive" and "negative" reflect the results of standard significance testing). Consistent with Crump (1995), for continuous data the BMD is defined as the exposure associated with a change in mean test score equal to 0.61 times the standard deviation (sigma) of test scores. The BMDL is the 95% statistical lower bound on the BMD.

In the figure for the positive study the solid line gives the estimated mean response at any exposure (the regression line is drawn to be linear, although it does not have to be). The dashed line above the solid line defines the lower bound on the BMD, the BMDL, or it can be viewed as an approximate upper confidence bound on the increase in the mean at a given dose. It is important to note that the lines defining the confidence bounds do not flare out at low exposures as some reviewers had suggested that they might. The confidence bounds necessarily approach the mean at zero exposure because the model represents the change in the response, not the response itself. In all of the modeling that ICF performed, the BMD was consistently defined as a change equal to 0.61 times the standard deviation of the test scores. The illustration for the "negative" study differs from that for the "positive" study, in that there is no dashed line below the BMD, representing the upper bound on the BMD, because that quantity is not defined in a "negative study."

The BMDL, the lower bound, is well defined and has the same meaning as when the study is "positive."

Figures 4-2 to 4-6 illustrate the digitized data for various tests. They have been relabeled from the previous report so they are easier to interpret. They have the same interpretation as Figure 4-1, in that the solid line is the mean response at a given dose. Moving a value of 0.61 times the standard deviation on the vertical axis from the value of zero one can draw a horizontal line across to where it intersects the dashed line (lower bound) then drop vertically down to the horizontal axis to obtain the BMDL.

Issues 3-6. PBPK and Monte Carlo Analyses. The most extensive revisions to the document were in the areas covering the physiologically based pharmacokinetic (PBPK) modeling and the Monte Carlo analysis. The documentation now contains a complete description of the model so that a competent modeler could reproduce it. The model structure has not changed -- just the parameterization -- and that has not changed significantly. ICF searched for additional sources for the parameter distributions in the literature, particularly for those parameters to which the model predicts are most sensitive.. The text of the revised document provides a more thorough description of all the compartments in the model and the various parameters.

Figure 4-8 shows maternal hair and blood concentrations during pregnancy predicted by the PBPK model for a daily methylmercury ingestion rate of 1 ug/kg/day. The left side of the x-axis starts at 1200 days because the model was run for several years in order to assure steady state for the given ingestion rate before initiating pregnancy. This Figure shows that on a small scale there is considerable variation in the hair and blood concentrations during the course of pregnancy, which is the reason for using the model to calculate the average hair concentration during pregnancy for this analysis.

The new Appendix G provides monkey parameters, and documents the changes in the model compartments during pregnancy. The ability of the model to reproduce data for the monkey during pregnancy is shown in Figure 4-9. In both the monkey and human, in addition to fetal growth, there is an increase in the breast, uterus, and fat tissues, distributed over the period of pregnancy. There is also a change in the maternal ingestion rate. All of these changes cause a fluctuation in the maternal and fetal blood concentrations.

One of the reviewers at the January meeting suggested focusing on the key parameters in the model and set the other parameters' variation to zero to see whether the key parameters account for most of the variability. Table E-1 shows that there is very little sensitivity to a number of the parameters in the model. The most important parameters were, body weight, hair:blood partition coefficient, hair excretion rate, and fecal excretion rate. These are important, both in terms of direct analytical sensitivity when one parameter is allowed to vary and in terms of the correlation coefficients obtained from the Monte Carlo analysis. Appendix E documented the parameters that account for essentially all the variation in the model. The others are necessary for physiological realism, but do not actually affect this particular output. The sensitivity of the model is

output dependent.

The parameters important to hair concentration were also significant for half-life. Therefore, looking at the half-life provided a useful output to test how the predictions of the model for variation compared with the real world. ICF considered this a very good test of the results of the Monte Carlo analysis.

ICF revised the table comparing parameters for the deterministic one-compartment model and the PBPK model inputs/outputs. They pointed out that there is more agreement than disagreement between these. A table comparing ingestion rate estimates using the deterministic and the Monte Carlo approaches was also presented. The U.S. EPA (1997a) and ATSDR (1997) one-compartment analyses are both consistent with the PBPK analysis in terms of central estimates of the dietary conversion factor, while the Stern (1997) estimates were lower. To determine why that might be so, ICF plotted the time course of methylmercury in whole blood of human subjects who had consumed methylmercury-contaminated halibut at four different dose levels. Lines were drawn representing one-compartment model simulation using parameters from the U.S. EPA (1997b) RfD, ATSDR (1997) and U.S. EPA (1997a) Monte Carlo analyses. A second figure showed the one-compartment model simulation using alternative parameter sets from the Stern (1997) analysis. It appears there are differences in dietary conversion factor predictions because the estimates of preferred values are different; in particular, the volume of blood is lower and the fraction of methylmercury in the blood is higher in Dr. Stern's analysis. These differences tend to work together to give lower ingestion levels for a given hair level. There is actually little difference in the variability predicted by EPA's (1997) Monte Carlo, Dr. Stern's (1997) analysis, and the ICF PBPK Monte Carlo analysis. For the lower end of the dietary intake distribution, which is of interest for risk management, they are all very similar. Based on their review of the literature and the agreement with the EPA and ATSDR results, ICF determined that their estimates of the central values of the parameters are appropriate. They also concluded that the ICF distribution for variability is consistent with previous analyses.

Issue 7. Better justification for a database factor of 1 and appropriate uncertainty and modifying factors. To address reviewers' concerns and comments, ICF performed a complete review of the literature, to look for evidence of latent effects of chronic sequelae in human populations. To address the issue of the possibility or likelihood of chronic sequelae occurring in populations exposed to fish ingestion at low levels, ICF considered the following points.

* Evidence for latent effects or chronic sequelae in human populations. In Iraq (Clarkson 1992 the latency was a matter of weeks, but in Minimata (Harada 1982, 1995) the latency may have been a matter of years. The doses for Minimata are not clear, however, these were exceptionally high doses for the most part.

* Animal evidence indicates that development of chronic sequelae is dose and dose-rate dependent. There are three longitudinal type studies in laboratory animals (the same test or a similar test was administered at an early age and then again at a later age), which

showed the progression of disease or endpoints. The Evans et al. (1977) study in monkeys showed that with increased dose, latency decreased and severity increased, although there was a level below which these effects were not seen. A similar conclusion can be drawn from the rodent study by Spyker et al. (1972). The latent effects of methylmercury exposure in primates has been characterized by Rice (1989) with an observation (at age 13 years, exposure from birth until age 7) where primates appeared clumsy; the equivalent human dose would be about 65 to 125 ppm in maternal hair.

* There is a lack of chronic effects in fish-eating population chronically exposed at low levels through fish ingestion. The population studied in Peru (Turner et al. 1980)) was exposed throughout a lifetime and according to the authors may have even been exposed in utero for generations. They were given complete neurological examinations, including sensory and visual tests, and no mercury-related effects were found in this population. Subclinical effects such as sensitive cognitive functions, have been measured in children, but not in adult human populations exposed chronically.

* There is a lack of evidence for delayed or persistent effects on cognitive function in non-human primates. Studies in primates exposed in utero, and administered cognitive function tests at several ages, have been conducted in two different laboratories. Early effects in two-week old and one-month old primates were detected on some cognitive function tests, but when tested again as adults, there were no differences in the cognitive function tests between the controls and the treated animals (Gunderson et al. 1988; Burbacher et al.1990a: Gilbert 1993). In the Rice (1989) study there were no differences on cognitive function tests between treated animals and controls, either at an early age or again when tested as juveniles. Human equivalent blood levels were quite a bit higher than levels of concern for this Superfund site.

* The possible mechanism of action provides a plausible rationale that chronic sequelae are unlikely in fish-eating populations exposed through maternal fish ingestion to low levels of methylmercury, such as those recommended for the site-specific RfD. While the mechanism of action is not known with certainty, it is likely that the mechanism of neurotoxicity in humans exposed as adults, in particular from poisoning episodes, is fundamentally different from that which happens in children. According to U.S. EPA (1997a), some of the basis for the latent toxicity in adults may be from the total production of free radical. Once cellular defense systems are overwhelmed, there is rapid progression of damage done by free radicals, whether that is effect on the axon or on synapses. With in utero exposures, the underlying damage is more diffuse. Currently the dominant theory is that there is an interruption of microtubule formation, spindle formation and migration of neurons in certain areas of the brain (Chou 1978). In each case, it appears that there is a threshold for these effects. The concern is what happens with aging.

* While the weight-of-evidence provides a compelling argument that chronic sequelae are highly unlikely at the recommended site-specific RfD, it cannot be proven with absolute certainty. The weight of evidence indicates that it is likely that when damage to the brain occurs during in utero development, once that damage is done it is manifested

only as those particular domains of the brain are called upon for age-specific functions. Studies in monkeys indicate that subtle alterations in sensory function may precede effects on cognitive function. If that is the case, one would expect to see cognitive function deficits if sensory function deficits are seen. However, if sensory function deficits are not seen it is questionable whether cognitive functional deficits will appear as the child ages. While there is a concern with regard to aging, evidence in the Peru study and cognitive function tests in adult primates indicate no lasting decrements. The overall weight of the evidence indicates that it is highly unlikely that one would see chronic sequelae or delayed effects in asymptomatic populations exposed to low levels of methylmercury in utero.

With regard to the need for a two-generation study, the weight of evidence from a mechanistic standpoint, these effects do not appear to be heritable, nor are there effects on germ cells. Therefore, at low levels, reproductive toxicity in the absence of other toxicity is highly unlikely.

Clarifying Questions on Presentation:

One of the reviewers asked why the slope in figure 4-1 is positive when this is a negative study. ICF indicated that it could be drawn with either a positive, zero, or negative slope, it just cannot be statistically significantly positive. It was drawn with a positive slope to make it readily comparable with the other graph of the positive study results.

In response to a reviewer's question, ICF indicated that for the Monte Carlo analysis they used PBPK_Sim, which is PBPK Monte Carlo analysis software developed by the K.S. Crump Group, Inc. for use with ACSL (Advanced Continuous Simulation Language). The software allows the user to input distributions for each parameter and performs Monte Carlo sampling to generate a command file that is suitable for running the model for each of the parameter vectors. The software can include correlations between parameters without disrupting the necessary physiological constraints; this is documented in Appendix E. In response to another question, ICF indicated that although PBPK_SIM allows for consideration of normal, log normal, uniform and triangular distributions, ICF only used normal and log normal for the analyses. They did not try to put in the empirical distributions, as they did not think it would make a difference.

One reviewer asked about the model's sensitivity to the hair:blood partition coefficient. In the first document the model's lack of sensitivity to this was a surprising finding, yet Table E-1 indicates it had the largest effect. Mr. Clewell clarified that it has the largest effect for half-life output, but not for ingestion to hair concentration. What was used in the Monte Carlo was the average concentration in maternal hair during pregnancy that had a sensitivity of only .22, which is not very high (normally in lower range of parameters of concern). This is a fairly stable model and such results are not uncommon for a physiological model. Sensitivity is dwarfed by the parallel excretion mechanisms that control the steady state concentrations. This partially explains why the resulting distribution of fish ingestion rates is so narrow.

PANEL DISCUSSION

Issue 1 - Mechanism of Action

Several reviewers agreed that the literature has not defined any given mechanism for adults or child, but also noted that the literature identifies other possible mechanisms, including oxidative stress or apoptosis, blockage of cell-surface recognition for migrating neurons. However, another reviewer indicated that oxidative stress covers a lot of these potential mechanisms. Two reviewers were not comfortable with the conclusion that the mechanism of action for adults and children are clearly different, although it is clear that in frank poisoning episodes, the mechanisms are different for adult and child. This question is relevant to the uncertainty factor discussion.

One reviewer pointed out that the animal data suggest that effects might be reversible for child exposure to low doses, although the human data at high doses do not support this.

One reviewer suggested that the document make clear that while the Faroes study was not used because the data were not available, that the results from the two studies (Faroes and Seychelles) are not necessarily inconsistent.

Another reviewer remarked that the concept of significance of methylmercury being in fish, and thereby providing some protective effect from chronic sequelae, as discussed by Clarkson (1995), is pertinent to the issue of this RfD being limited to fish consumption. Another reviewer, however, identified the paper by Kajiwara et al. (1997) which contradicts this hypothesis, although the authors do not venture a guess as to mechanism.

The panel reached consensus that the documentation on mechanism of action was informative and would add to the later discussions, particularly on uncertainty factors.

Issue 2 - Benchmark Dose (BMD) Explanation

One reviewer asked why the slope of the solid line was positive in Figure 4-1 for the negative study results. ICF indicated that they drew it this way for illustrative purposes, it could be positive or negative, but this would not change the interpretation about the lower bound, it is still the lowest dose one could get for the BMD that is consistent with the data. One reviewer suggested constructing the figure the same way as that in Figure 4-2 to show a slope that is near zero.

Another reviewer pointed out that this BMD may not be analogous in concept with other BMDs which are generally portrayed as an approximation of a NOEL; however he thought this a reasonable application nonetheless.

The reviewers reached consensus that the revised explanation and figures were quite helpful in understanding the concept of use of BMD with generally negative data.

Issue 3 - Documentation of PBPK Model and Monte Carlo Analysis

The reviewers asked a number of questions seeking greater understanding of the model and analysis. One reviewer asked whether ICF tested different inputs and determined that one sees the same degree of interindividual variation at different dose levels. ICF confirmed that they did, and that the model is mathematically linear as a function of dose.

In response to a question on parameter values on Table 4-3, ICF indicated that they had changed some values as a result of an additional literature search, but that these better values did not impact the analysis. Reviewers suggested that ICF could add a column to Table 4-3 to indicate the reference for the parameter values. It was also suggested that ICF could include plots of the distributions used in the model and the data on which they are based in Appendix E to justify use of the parametric forms in the model.

One reviewer expressed surprise at the small differences in Pearson correlation coefficients for average hair concentration vs. peak hair concentration in Table E-1, and asked whether it was due to random sampling variability or some small amount of non-linearity. ICF answered that the peak hair and average hair are different because they occur at different times and the sensitivity coefficients are time dependent, that is the dependence of a model output on a model input is not constant over time.

The clarity of the Monte Carlo analysis was a concern to several reviewers, with one person indicating that it might not conform to EPA's guidance for a validated Monte Carlo analysis; however he did not have concerns over the conclusions of the analysis and noted that the predicted magnitude of variability across the population is similar for the EPA, Stern and ICF analyses. He was uncomfortable that the analysis was limited to normal, log normal and uniform distributions, and also noted that using small reference data sets to determine the shapes of the distributions made him a little uneasy.

The question of over-parameterization, identified at the January meeting, was again raised. Reviewers indicated that they now understood why all the parameters are included, but one reviewer asked whether the over-parameterization might result in an understatement of uncertainty, which might affect the shape of the output. ICF responded that this is why they did the test with half-life and determined that the model over predicted the variability observed. ICF believes that this was a good test of the model prediction of variability. They pointed out that the low sensitivity of the parameters is typical of a physiological model; no single factor determines the time course of methylmercury, all of them have some effect in parallel. The sensitivities work together and nothing gets diluted out; if a factor is a direct determinant of the dose-metric of interest, it will have a sensitivity of one.

The panel reached consensus that the documentation on the PBPK model and the Monte Carlo analysis was acceptable. The data were presented, and justifications for choices were provided. Some comments suggested that the revised model provided an incomplete

justification for the distributional form of some of the inputs to the Monte Carlo analysis of the PBPK model. This presents some problems in principle for the interpretation of the significance of the output of the Monte Carlo analysis. Nonetheless, the general agreement of the variance predicted by the revised model with the variance predicted in the previous Monte Carlo analyses of USEPA (1997) and Stern (1997) suggested that the selected distributional shapes provided reasonable approximations. Given the uncertainty in the reported literature values, different choices could reasonably have been made for central tendencies of key input distributions. This could have resulted in some differences in the central tendency of the output distribution of the average daily intake corresponding to the BMDL hair level. This was acknowledged by ICF and was addressed in the discussion of uncertainty factor adjustments.

Issue 4 - Explanation for Why Selected Parameters Differ From Those of Stern and EPA.

One reviewer stated that he found the fairly close estimation in variability between models encouraging and noted that the differences are based on different choices of literature values. He asked how ICF adjusted the hair:blood parameter to a steady state when it was reported at end of pregnancy without having a steady-state hair:blood ratio a priori. ICF responded that the change in hair:blood between steady state and the end of pregnancy was calculated by the model and is, regardless of the hair input, the relationship due to the change in plasma volume. They ran the model iteratively, with different steady-state values, until the observed end-of-pregnancy hair:blood was predicted.

One reviewer questioned how ICF derived a specific value and distribution shape for the key parameter of hair:blood ratio, particularly their use of data summarized by correlation coefficients (r2), when standard deviations were not available, and how much error this introduces. ICF responded that in Appendix F they explain how one could use a regression approach to compute the standard deviation of the ratio, using a strict algebraic relationship between r2 and the standard error of the slope. Another reviewer asked where the intercept is taken into account in Appendix F. ICF responded that they assumed that one would get the same regression slope with or without the intercept; for those with actual data including the intercept or not had made virtually no difference in the slope. Another reviewer indicated that when he did this with the small number of data sets available, he found that the slope value was always smaller than the ratio value, because some of that ratio is taken up by the intercept. This reviewer acknowledged that given there is a lot of variability in data sets reflecting differences in populations, there is no one correct answer for the hair:blood ratio, resulting in a lot of uncertainty in how one parameterizes that distribution.

ICF also stated that for the hair:blood ratio they calculated a broad distribution and did not think they could have underestimated variability. In cases where they were not certain about whether data reflected parameter uncertainty or population variability, they assumed that it was variability. This combination of uncertainty with variability leads to an overestimation of variability.

The panel agreed that ICF has added appropriate text and explanation.

Issue 5 - Uncertainty and Variability Need to be Better Described and the Sensitivity Analysis Needs More Discussion.

The panel agreed that the uncertainty and variability were better described in the revised document and that the sensitivity analysis was adequately discussed.

The panel agreed that ICF has added appropriate text and explanation.

Issue 6 - Discussion of Varying the Hair:Blood Ratio and Distributions From Seychelles Versus Pooled Data.

The first part of this issue, why varying the hair:blood ratio did not have a large effect on the results, was discussed above.

ICF indicated that in response to the reviewers' comments at the first meeting, they realized they had put too much emphasis on this one study and noted the double counting of the Seychelles variability. In the revised document they used a global distribution to represent a diverse U.S. population, rather than the more narrow Seychelles distribution. They pooled many studies (see Table E-2), assuming that the diverse U.S. population would include all of these types of people and that the differences were not due to analytical technique (which may actually be the true reason for differences in variation).

The panel agreed that ICF has added appropriate text and explanation and that these additions will inform the panel's discussion of uncertainty and modifying factors.

Issue 7. Better Justification for a Database Factor of 1 and Appropriate Uncertainty and Modifying Factors.

Reviewers raised a number of issues that influenced their preferred selection of uncertainty/modifying factors.

ICF proposed that an uncertainty factor of 3 for database limitations be applied to the distribution of intake values to derive a corresponding distribution of RfDs. This factor is recommended to account for some results in the New Zealand and Faroe Islands studies, which could be construed to suggest the possibility of effects at maternal hair concentrations below 10 ppm. In addition, concerns about the possibility of sequelae can not be completely ruled out.

At the January meeting, the panel had agreed to an intraspecies uncertainty factor of one. The animal to human, subchronic to chronic and LOAEL to NOAEL uncertainty factors

were not needed. Therefore, the database uncertainty factor and the modifying factor were the basis for this meeting's discussion.

One reviewer pointed out that given that the critical effect is developmental effects to children exposed in utero, and since all members of a population are at some point fetuses, the use of a BMD at 10% increase in the effects, does not really focus on a sensitive population. Thus, the part of the UF for within human dynamic variability, discounted in the present RfD and in the RfD on EPA's IRIS, may still be needed.

One reviewer felt that an uncertainty factor of 3 for the potential for chronic sequelae may be needed. Without this concern for sequelae, no uncertainty factor would be needed, rather one could use the dose response with aging factored in. This reviewer thinks there are three important areas for consideration of uncertainty factors, that were either not addressed in the ICF document or the emphasis was misplaced. First, this reviewer thinks that it is clear that we do not know what the threshold might be, but there is some evidence from Minimata (Harada 1995) of patients with relatively low exposures who were asymptomatic, becoming symptomatic with aging. Second, the Rice and Gilbert (1995) paper reported results from an objective test (vibration sensitivity) administered to monkeys exposed to levels as low as 10 ppm up to age 4, with significant effects seen at 10 and 25 ppm. Third, the paper of McKeown-Eyseen and Ruedy (1983a and b) which identifies effects in at least one population that increases with age. The reviewer acknowledged that the study does carry some caveats relating to possible uncorrected confounding, but the authors conclude that after adjustment for potential confounders, a significant positive association was found.

ICF pointed out that in the Rice and Gilbert (1995) and Rice (1996) studies there was no dose-response (impairment at 10 and 25 ug/kg/day, but not 50 ug/kg/day), and that these animals were only tested at one time period, which did not allow for classifying this as a delayed effect. The corresponding concentration in maternal hair for the 10 ug/kg/day monkey was 40-80 ppm.

A number of reviewers thought that for a chemical with a data base this size an uncertainty factor of 1 is most appropriate. For example, one reviewer mentioned that there are more data now than in 1992 when EPA assigned an uncertainty factor of 3 to the data base uncertainty factor (as currently shown on EPA's IRIS). This reviewer stated that if ever one was going to assign a factor of one, it would have to be for a chemical such as this.

Another reviewer summarized support for an uncertainty factor of one as follows: first, the reviewer did not believe that a two generation reproductive study in rodents would yield a lower dose, and the human epidemiology studies do not suggest a concern for reproductive effects. Second, the reviewer does not think that chronic exposure at the BMD will evoke neurological damage; if the threshold is not exceeded for infants in utero, then these individuals as adults will not be impaired. This opinion is based, in part, on the appearance that infants are the more sensitive individuals and that some of the studies in humans at low levels of fish consumption show no neurological effects in

adults. This latter point, however, is where the reviewer could be talked into a factor of three. This reviewer also thought the Seychelles and New Zealand data appear consistent with each other and would like to see a BMD for the Faroes when the data are available.

Another reviewer pointed out that while the Seychelles study was not designed to identify neurological impairment in mothers, the fact that this large population has been exposed for a lifetime and there are no reported observations of people exhibiting adverse effects. The absence of anecdotal mention of effects in this and other studies from Peru, New Zealand, Canada and the Faroes is a powerful argument to support the use of a modifying or data base uncertainty factor of 1. Another reviewer took exception concerning the lack of anecdotal evidence, stating that one cannot assume there is no effect since only one study was designed to measure any effects on the mothers.

One reviewer identified the question of interest as whether one would see chronic sequelae at the selected BMD or RfD, not whether methylmercury exposure results in chronic sequelae. This reviewer found no reason to believe that there are chronic sequelea at this low level. This reviewer found the Harada data less than convincing; the doses were high and presented anecdotally (not presented as an objective epidemiological study). In addition, taking the good epidemiological studies together, they do not suggest that animal reproductive studies are needed. The Seychelles database is so strong this deserves an uncertainty factor of 1.

ICF stated that they thought at this low dose range that given the lack of effects in the Seychelles population, along with all the other animal and mechanistic studies, it is highly unlikely that there would be chronic sequelae later. But, since they cannot prove that with absolute certainty, they are proposing a total factor of three to take that into account.

A reviewer raised the issue of whether and how much conservatism is built into this assessment in the calculation of the BMD, and asked ICF to identify these. ICF indicated that there were many opportunities in the methodology to choose values that lead to a smaller (more conservative) value, including the use of the lower end of the BMD range (21), using the lower bound on the BMD, including uncertainty in the distributions of parameter variability, and use of the sensitive subgroup in the Seychelles. Other reviewers disagreed that there is a conservative bias, citing several reasons, including (1) the assessment contains few conservative assumptions because the study and database are so good; (2) the BMD approach itself reports what is actually known; and, (3) there are assumptions made in the model choice, etc. that introduce uncertainty.

After the initial polling, many reviewers preferred that an uncertainty factor of 1 was sufficient to generate a RfD, while two reviewers preferred a factor of three or more to account for the various uncertainties discussed above. The chair then asked the group whether it could form a consensus on an uncertainty factor of 3. This factor would be for applied to consider uncertainties in the choice of parameters for the Monte Carlo and PBPK models, for potential adverse sequelae, and for the results in the New Zealand and Faroe Islands studies which could be construed to suggest the possibility of effects at

maternal hair concentrations below 10 ppm. The group agreed to this consensus position. One reviewer preferred a value of 5 for the following reasons:

Finally, one reviewer suggested using a benchmark dose of 21 rather than 20, since the recalculated BMD range was from 21 to 26 ppm maternal hair concentration. ICF indicated that they rounded down to 20 to make it one significant digit as well as to be conservative. The effect of such a change would be linear, so the distribution would be moved intact about 5% upward. After rounding the distribution values to one digit, the results are the same values as that generated with 20 ppm. The panel agreed that 21 would be more appropriate and easier to explain.

Issue 8 - Use of Distribution to Communicate RfD vs. a Point Estimate, and Derivation of a Site-Specific RfD

The panel discussed how to express this RfD as a distribution rather than a single point estimate on ITER. It was suggested that one could describe the shape of the distribution mathematically, along with the mean and standard deviation, as well as list the first, fifth, ten, etc. percentiles. A reviewer asked ICF whether one could express this as a mean and standard deviation or mean and confidence limits. ICF thought the percentile distribution would be the best way to do this. A percentile distribution of the ingestion of mercury in fish, similar to Table 4-8 was suggested. Some reviewers were strongly opposed to identifying just one point estimate.

One reviewer stated that using a distribution to express a RfD is an excellent idea and his organization has struggled with where to make the cut on which percentile to use with no strong basis for choosing one over another. He advocates returning the distribution back to the risk manager and local regulators so that the project team can make a decision for themselves about what is appropriate under their circumstances. With the usual reference dose that choice is not available and the risk managers deserve that choice.

Another reviewer thought that presenting this RfD as a distribution advances the science and forces people to face the fact that it is a distribution; it is constructive to lay out the data. Perhaps guidance is needed for interpretation and use. The recent article in Science points out that there is concern about being too restrictive for a fish eating population and this opportunity should be provided to risk managers.

There was a short discussion on how to explain (or interpret) what an RfD distribution represents. One reviewer said -- take a BMD of 21 ppm and get a distribution of doses and use an UF of 3, then you have a distribution of RfDs consistent with a BMD of 21 ppm maternal hair. This spans a range of approximately 3-fold. Another reviewer thought the RfD corresponding to a particular percentage in the distribution would indicate the percent chance that the critical hair concentration would be exceeded. Another reviewer believes the percentage corresponds to that percent of the population not protected.

A reviewer indicated that he was not greatly concerned with the misuse of this RfD, at

least in the U.S., since most exposures will be from eating fish and this will be most useful for that exposure scenario. Another reviewer suggested putting the word fish in parentheses after methylmercury to make it clear that this RfD was developed for humans chronically ingesting fish containing methylmercury.

One reviewer asked that the RfD be qualified for use as a remedial action value, rather than one that could be used to justify additional releases of mercury. Another reviewer disagreed, saying that this RfD is a risk assessment, and such qualifiers are in the realm of regulation. This second reviewer thought the best way to qualify this is as an RfD for fish eating populations.

The panel reached consensus that the RfD should be expressed on ITER as a distribution and should include a caveat that this is a site-specific RfD for fish-eating populations. A subgroup of peer reviewers was formed to recommend language to best communicate what the distribution means for inclusion in the meeting summary and the ITER database; this text follows:
"This RfD is for humans chronically ingesting fish containing methyl mercury, and has been developed specifically for Lavaca Bay, Texas, USA. This distribution shown in the figure and table illustrate the probability that a given rate of ingestion of fish containing methyl mercury will result in a level of 7 ppm mercury in maternal hair (equivalent to a benchmark dose of 21 ppm divided by an uncertainty factor of 3). The science underlying this RfD generates a distribution, not a single value. Selection of any single percentile or number as the RfD is a risk management decision or a regulatory policy."

The ITER summary will include a figure which shows the distribution of methyl mercury ingestion rates associated with the 7 ppm mercury in maternal hair derived by ICF in its pharmacokinetic analysis. The value of 7 ppm in hair is the BMDL from the Seychelles (21 ppm) divided by a factor of 3 to account for some uncertainties

This table of the distribution of RfD values will also be included in the ITER summary.

Distribution of RfD Values

Percentile	RfD (ug/kg/day)
1	0.29
5	0.35
10	0.38
25	0.44
50	0.53
75	0.63
90	0.77
95	0.86
99	1.10

This table accompanies the figure described above, and shows that the RfD derived in the ICF analysis ranges from 0.3 to 1 ug/kg-day, that 0.5 is the 50th percentile, 0.4 is the 10th percentile, etc.

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Appendix A
Managing Potential Conflicts of Interest
(approved 2/26/98)

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. These statements were discussed at the beginning of the February 26, 1998 conference call meeting and were agreed to by all. One reviewer noted that this meeting was the first time that two people from the same organization were on a panel together; however, the panel did not think this was a problem.

Robert Bornschein - Dr. 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, however Dr. Bornschein was not able to make the conference call.

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.

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 after 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 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 decided that they did not perceive this to be a conflict of interest and agreed that Dr. Stern may participate fully in the discussions and consensus.

William M. Stiteler - Dr. Stiteler works for Syracuse Research Corporation. He does not have any conflicts. The panel decided Dr. Stiteler 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, however, Dr. Weis was not able to make the conference call.