Responses to Comments of the Peer Review Panel and Public Comments on Methylmercury

Note: The following comments addressed the original background document submitted to the peer review panel for review. The final document, which is the basis for the IRIS summary, is Chapter 4: Risk Assessment for Methylmercury, in the *Water Quality Criterion for the Protection of Human Health: Methylmercury*, Final, January 2001.

1. Is the document logical, clear and concise? Are the arguments presented in an understandable manner?

Peer Review Panel Comment:

All the reviewers found the document well-written and logical, however specific suggestions were made regarding references to the NRC report and clarification of neuropsychological terms and tests for the lay reader. Specific recommendations are as follows:

a. Section 1, "Background" should include a summary discussion of the OSTP [Office of Science and Technology Policy workshop on the Scientific Issues Relevant to Assessment of Health Effects for Exposure to Methylmercury, November, 1998; NIEHS, 1999] meeting and subcommittee deliberations.

EPA Response:

EPA agrees and has done so, pp. 4-10 to 4-12 of the revised background document.

Peer Review Panel Comment:

b. In Section 1, and throughout the report, citations of the NRC report should be more direct, with specific page numbers and in the electronic form, direct links to the NRC document.

EPA Response:

EPA has referenced specific page numbers in the revised background document.

Peer Review Panel Comment:

c. Create three new tables to assist the reader in understanding the tests, results and implications of the three main studies (New Zealand, Seychelles, and Faroes) referred to in this document. These tables would be placed in Section 2.1 to highlight the key information presented in pages 9-23 of the draft document. The first table would be similar to Table 5-10 of the NRC report, i.e., a methodological summary, but only including the three studies. The reader can be referred to the NRC report for tabular summaries of other relevant studies described in the text. The second table would focus

on the various neuropsychological tests that were administered in these studies. It is envisioned that this table would have three columns with headings such as, "Test Name", "Domain Evaluated", and "Clinical Relevance". The third table would summarize the results of the various neuropsychological tests administered in the main studies. This table would have three columns with headings such as, "Study", "Tests Administered", and "Findings". It may be possible to collapse this information into fewer than 3 tables.

EPA Response:

A table was added in the revised background document (Table 4.3, p. 4-51) describing the tests that showed a significant effect, domain assessed, and societal relevance. The other information requested is either in the text of the revised document or is provided in tabular form in the NAS report.

Peer Review Panel Comment:

d. A limited amount of text describing neurobehavioral testing should be added to accompany these tables. Issues such as differences between global and domain-specific testing, sensitivity and predictiveness of various tests, and appropriate ages for testing should be included. Which tests were run in each study and how they were conducted should also be briefly described. Appendix D includes one reviewer's assessment as an example as to how these areas can be addressed.

EPA Response:

Appropriate text added (pp. 4-53 to 4-56) in the revised background document.

Peer Review Panel Comment:

e. Section 1.2, "Risk Assessments Done by Other Groups", should be reduced to a few succinct paragraphs referring to other documents but not including a detailed description or citation of numbers. This abbreviated discussion should then be incorporated into Section 1, "Background".

EPA Response:

This section was necessary for the Water Quality Criterion Document, and was not changed. See Section 4.1.2 of the revised background document.

2. Given the limited scope of the document, has the appropriate literature been cited? Are there publically available, peer-reviewed papers that should be included? Please provide copies of any papers or reports for consideration.

Peer Review Panel Comment:

All reviewers agree that the key literature has been included in the Draft RfD document. Suggestions were made to add citations that are either needed for completeness or represent publications not considered in the recent NRC report and that the panel felt EPA should consider. Suggested additions to background discussion include:

a. Ramirez, 2000.

EPA Response:

This is added to Section 4.5.4.1 of the revised background document.

Peer Review Panel Comment:

b. Four papers on the Seychelles study published within the last two months.

EPA Response:

These studies were added to the appropriate sections of Section 4.2.1 of the revised background document.

Peer Review Panel Comment:

c. A discussion of animal test results. These are supportive of the RfD and are not confounded by exposures to PCB's or other chemicals. There is also a paper on animal test results on methylmercury effects in an aging rat population (Newland and Rasmussen, 2000).

EPA Response:

This section has been added, Section 4.1.1.3, pp. 4-6 to 4-7 of the revised background document. The paper on aging was added to Section 4.5.5.2, p. 4-85 of the revised background document.

3. The National Academy of Sciences (NAS) Committee reviewed three studies that it considered suitable for quantitative analysis: the Seychelles Islands study, the Faroe Islands study, and the New Zealand study. The NAS Committee chose the Faroe Islands study as the most appropriate study on which to base an RfD. EPA concurs with this assessment. Please comment on the choice of the Faroe Island study as the appropriate study.

Peer Review Panel Comment:

All reviewers agreed that the Faroe Islands study is the best choice for the basis of the RfD. However, there were several recommendations regarding expanding the justification of that study. The recommendations are:

a. EPA needs to justify more fully the use of the Faroe Islands study in Section 2.2.8 [of the draft background document]. Specifically, they should discuss such issues as: domain specific testing, age at evaluation, sensitive population, ability to detect subtle effects, and that the effect of methylmercury is still statistically significant after controlling for PCB exposure for some endpoints.

EPA Response:

Most of these points are added in Sections 4.2.2.7, 4.2.2.2, and 4.2.2.8 of the revised background document. EPA believes that the discussion of the power of the studies to detect an effect was sufficient in the draft document, so this was not changed.

Peer Review Panel Comment:

b. In Section 2.2.2.5 [of the draft background document], "PCB Exposure in the Faroes Population", additional arguments regarding the confounding of PCB exposure should be included. This discussion should address whether PCB exposure in the Faroes study is substantially different than in other areas.

Supporting information for this can de developed from other studies reporting geometric mean concentrations for umbilical cord tissue and milk fat in other populations. Appropriate studies are: Grandjean [sic] (1997) for umbilical cord tissue concentrations; Grandjean [sic] (1995), Steuerwald [sic] (2000), and ATSDR toxicological profile for methylmercury for PCB's in milk fat; two Dutch studies: Lanting [sic] (1998) for PCB's in cord blood and Patandin [sic] (1999) in milk fat; and "Mass Expert Review Panel" for serum PCB's in the U.S. A combined review of these data may indicate that the lowest tertile Faroes group in the Budtz-Jorgenson, et. al., (1999) analysis is likely to have PCB exposures similar to the background levels found in the Netherlands.

EPA Response:

This is added to Section 4.2.2.2, see especially pp. 4-37 to 4-38 of the revised background document.

Peer Review Panel Comment:

c. To Section 2.2.8, "Selection of Study", add a discussion regarding the New Zealand study, in particular, i) acknowledge the uncertainty in the BMD model with and without the exclusion of the extreme data point and ii) relate this outlier uncertainty in the BMD determination (study) to the integrative analysis approach encouraged by the NRC.

Issues were also raised on the animal test results. Attempts to estimate an RfD based on the animal literature generally support the RfD estimated here, and the animal studies are not confounded by exposures to PCB's or other chemicals (Gilbert and Grant-Webster, 1995; Rice, 1996). A review of behavioral effects on methylmercury and PCBs provide strong support for the recommendation that PCB exposure be considered in evaluating the results of the Faroe Island study, as there are overlapping effects and even possible interactions between these neurotoxicants (Newland and Paletz, in press). Recent studies indicating that methylmercury effects may appear in aging populations (e.g., Kinjo et al., 1993) are also supported by a paper on animal test results on methylmercury effects in an aging rat population (Newland and Rasmussen, 2000).

EPA Response:

This issue is expanded in Sections 4.2.1.4 and 4.2.31 (pp. 4-49 and 4-50) of the revised background document.

The Kinjo et al. study is discussed in Section 4.5.5.2 of the revised background document.

Peer Review Panel Comment:

d. Section 3.5, "Integrative Analysis" is too brief to be a stand-alone section. It is recommended that a new section be created entitled "Supporting Studies" and added to Section 2.2.8, "Selection of Study." The results of an integrative approach should be considered as supporting information for the choice of the Faroes study as the basis of the RfD. This section should be based on a similar section in the NRC report.

EPA Response:

Section 4.2.3.4 was added and includes this information.

4. The NAS Committee considered a number of endpoints from the Faroe Islands study as possible endpoints on which to calculate an RfD. The Committee chose the Boston Naming Test as the appropriate endpoint, even though this was not the most sensitive endpoint identified in that study. This was based on the fact that the most sensitive endpoint, Continuous Performance Reaction Time, was based on only half the total cohort. EPA concurs with this choice. Please comment on the choice of endpoint.

Peer Review Panel Comments:

The reviewers concluded that the use of the Boston Naming Test (BNT), without controlling for PCB exposure, is not endorsed. The reason that the use of the BNT without adjustment for PCB exposure could not be endorsed, is that of all the endpoints showing an association with methylmercury exposure, this was the one showing the strongest evidence for a

PCB effect. (See comments of Reviewer D in section 3.2.) However, the panel did endorse use of the BNT with adjustment for concurrent PCB exposure, along with three other options discussed below for RfD derivation.

a. Use of the BMDL for the BNT with correction for concurrent PCB exposure. As this recommendation was in partial conflict with NRC's recommendation (i.e., NRC recommended use of BNT without correction for concurrent PCB exposure), the panel asked the Faroe Islands research group for additional analyses to further explore an apparent PCB effect. Budtz-Jorgensen and colleagues graciously provided the panel with BMD and BMDL determinations for the 1993 BNT data (i.e., BNT data for which PCB cord tissue data was available) without any PCB adjustment, as well as a series of BNT residual plots before and after controlling for PCB and all other covariates but methylmercury exposure. The BMD and BMDL (P0 = 5%, BMR = 5%, K-power model) for the 1993 BNT data without adjustment for PCBs was reported to be 112 mg/L and 59 mg/L, respectively. These new BMD/BMDL determinations can be compared to the BMD and BMDL of 183 mg/L and 71 mg/L obtained from the same data with PCB adjustment (Table 7-4, NRC Report). This comparison indicates a substantial increase in the BMD upon adjusting for PCB exposure that cannot be attributed to reduced sample size and any increase variability in BMD determination. These new results confirm the panel's prior conclusion of the need to adjust for concurrent PCB exposure in deriving a BMDL from the BNT data; the prior conclusion being based on the original regression analyses of Grandjean et al. (1997), the PCB tertile analyses of Budtz-Jorgensen et al. (1999), and the comparison of the BMD determinations on the PCB unadjusted full cohort versus the PCB adjusted 1993 data (Table 7-4, NRC Report).

b. Another alternative is to consider using the California Verbal Learning Test as the critical endpoint. Although this test is not the most sensitive endpoint, it is useful for clinical relevance as well as predictive value and there is less evidence for any significant PCB confounding from either the multivariate regression analyses (only small changes in regression coefficients), PCB tertile analyses, or comparison of BMDs with and without PCB adjustment. In contrast, panel deliberations revealed that the CPT Reaction Time test has issues with reproducibility and clinical correspondence. These concerns are reinforced by the fact that valid results from this test were reported for only one of the two years of the Faroes study. While this particular endpoint might seem attractive as a basis for deriving the RfD (highly significant results, least apparent influence by PCB's), the panel felt that the CPT Reaction Time test should not be used as a stand alone endpoint for RfD derivation. However, it can be considered for inclusion if BMDLs are composited for RfD derivation (see next recommendation).

c. An alternative to using a single test result is to develop a composite index across several measures within the Faroes study. For example, the BMDL's from the four statistically significant tests could be developed, evaluated for effect of PCB's and then composited as appropriate (e.g., geometric mean BMDL across four endpoints). If this alternative is selected, the method of compositing should consider a weighting scheme to account for

different sample sizes for the various tests (i.e., if some tests are PCB-adjusted, the N will be smaller).

d. Take a within-study integrative, multivariate approach using factor analysis to analytically create a composite factor that combines results across tests with overlapping functional domains. This factor would then represent the endpoint from which the RfD would be derived. The reviewers recognized that this alternative would require important decisions about the most appropriate statistical methodology since different approaches to factor analysis may yield different results. This would require a substantial effort by Faroes investigators and may not be appropriate at this point in the process.

EPA Response:

There was extensive discussion at the peer review meeting concerning choice of endpoint recommended by the NAC and EPA. A discussion of EPA's response to Question 4 is in Section 4.2.3.5 of the revised background document. EPA agrees that different endpoints in the Faroe Islands have different strengths and weaknesses. In addition, comments from the public recommended inclusion of data from other studies in some manner. EPA therefore generated RfDs based on four of the endpoints from the Faroe study, corrected and uncorrected for PCBs, and based on the subset of subjects in the lowest tertile with respect to PCB exposure (Table 4-8, p. 4-61 of the revised background document). See also Table 4-7, p. 4-58 of the revised background document for a summary of BMD and BMDLs for all three studies. Also included are smoothed values for the Faroe and New Zealand studies, and the integrative analysis of all three studies (i.e. including the Seychelles). The majority (19) of the RfDs generated are 0.1 µg/kg/day, with 4 at 0.05 and one at 0.2 µg/kg/day. The integrative analysis yielded an RfD of 0.10 µg/kg/day. This analysis provides further confidence that the RfD of 0.10 µg/kg/day is based on converging evidence derived from a rich data base.

5. The NAS Committee believed that benchmark-dose analysis was an appropriate method of ascertaining the appropriate point of departure for derivation of an RfD, and EPA concurs and derived the RfD from a calculated benchmark rather than a LOAEL or NOAEL. Please comment on this choice.

Peer Review Panel Comment:

The reviewers are in complete agreement that the benchmark dose approach is preferable to the LOAEL/NOAEL approach for RfD derivation from the epidemiological datasets under consideration for methylmercury. However, there was a suggestion that EPA further justify the use of a BMR of 0.05 in this calculation.

EPA Response:

See Issue 6.

6. The EPA concurs with the NAS Committee's decisions concerning the choice of model (K-power model with $K \geq 1$), and the choice of $P_0=0.05$ and BMR=0.05. Please comment on the choices of model and process.

Peer Review Panel Comment:

All the reviewers agree on the choice of the K-power model. Suggestions were made regarding further evaluation of the appropriateness of using a BMR of 0.05.

a. EPA should report the value of K that provides the best fit and provide goodness of fit statistics on the selected value.

EPA Response:

Budtz-Jørgensen et al. (1999), in their BMD modeling of the Faroese data under contract to the U.S. EPA, report that for the K power model K=1 provides the best fit (see also Budtz-Jørgensen et al., 2000). This has been added to the IRIS summary (p. X).

Peer Review Panel Comment:

b. The use of a BMR of 0.05 needs further justification given that it is a departure from the BMR of 0.10 used in deriving the current methylmercury RfD. It is the panel's understanding that it is also a departure from a BMR of 0.10 that has been used in all IRIS RfDs based on benchmark dose modeling (Crump et al., 2000). Appropriateness of the selected BMR should be based upon stability of BMDLs when using different models (as per EPA, 1995) and based upon comparing BMDLs at the 0.05 level to effect levels seen when the Faroes dataset was disaggregated (Grandjean, et al., 1997). Such an assessment may find that the size and statistical power of the Faroes study to detect low dose methylmercury effects is sufficient to support the use of the BMR = 0.05 model input. This would provide stronger justification than that which is currently provided in the draft RfD document.

EPA Response:

First, it is important to point out that EPA has no policy on the choice of BMR, which is to be chosen on a case-specific basis. Therefore there is no need to justify a value different from 0.10. Budtz-Jørgensen et al. *(1999, 2000) reported that the logarithmic model provides a better fit for at least some endpoints than the linear or K=1 models. In all cases, the logarithmic model yielded BMDLs considerably lower than the K=1 (or linear) model, as is demonstrated in Table A-1. Budtz-Jørgensen* et al. *also compared*

results at BMR 0.05 and 0.10. The ratio of the BMDLs was in all cases between 1.6 and 1.7 for the K=1 model, suggesting that BMDLs are stable in the range between 0.05 and 0.10. In contrast, the ratio for the logarithmic model varied between 3.1 and 44.2 for the BMD, and 2.5 to 6.2 for the BMDL. The BMDL was less for the logarithmic model in all cases, with ratios from 2.3 to almost 20. EPA used the K=1 model because of concerns about the stability of the logarithmic model at low levels, as well as questions concerning the plausibility of a supralinear response at low mercury exposure. EPA chose BMR=0.05 because it believes that a tripling of the background rate of abnormal responses (BMR=0.10) is not justifiable, particularly given that effects were found on a number of neuropsychological endpoints representing a range of functional domains. Examination of Table A-1 reveals that the choice of the K=1 model and a BMR of 0.05 yields BMDLs that avoid the extremes of the possible choice combinations. Therefore EPA believes that this approach is a justifiable one for risk assessment purposes. Budtz-Jørgensen et al. *also point out that the linear model, unlike the logarithmic model, is particularly sensitive to a few observations at high levels (not low levels); when the child with the highest blood mercury level was excluded from analysis, BMDLs decreased by 10-20%.*

Peer Review Panel Comment:

c. The justification for the cutoff for abnormal responses ($P_0 = 0.05$) is not clear. It can be clarified by stating the basis for this selection along the lines described by Crump et al., (2000) that this parameter value is "suggested by the convention of considering 95% of the clinical response in healthy individuals to define the normal range." Alternative language along similar lines would certainly be appropriate.

EPA Response:

Discussion was added as suggested to Section 4.3.3 of the revised background document and to the IRIS summary.

Table A-1. Results of benchmark calculations in the Faroe Islands study using the cord-blood mercury concentration (µg/l) as the dose parameter. (adapted from Budtz-Jørgensen *et al*., 1999)

	Motor speed (finger tapping)					**Attention (CPT reaction time)**					**Visuospatial performance (Bender)**				
Model	*K* power		Logarithmic		ratio *K*/log	*K* power		Logarithmic		ratio *K*/log	*K* power		Logarithmic		ratio *K*/log
	BMD	BMDL	BMD	BMDL		BMD	BMDL	BMD	BMDL		BMD	BMDL	BMD	BMDL	
BMR=0.05	139.73	82.87	51.60	7.92	10.4	71.75	48.37	3.03	1.60	13.8	241.57	113.97	270.82	12.66	9.0
BMR=0.10	234.01	136.46	761.34	38.04	3.6	120.15	80.29	9.31	3.96	20.1	404.56	179.88	11930.24	78.71	2.3
ratio BMR 0.10/0.05	1.7	1.6	14.8	4.8		1.7	1.7	3.1	2.5		1.7	1.6	44.2	6.2	

	Language (Boston Naming Test)					**Short-term memory (California Verbal Learning Test)**				
Model	*K* power		Logarithmic		ratio *K*/log	*K* power		Logarithmic		ratio *K*/log
	BMD	BMDL	BMD	BMDL		BMD	BMDL	BMD	BMDL	
BMR=0.05	84.98	61.22	6.46	3.1	19.7	246.31	110.05	49.51	7.56	14.5
BMR=0.10	142.32	102.22	27.94	9.66	10.5	412.49	176.11	711.34	35.45	5.0
ratio BMR 0.10/0.05	1.7	1.7	4.3	3.1		1.7	1.6	14.4	4.7	

7. EPA used a one-compartment model for conversion of the benchmark dose from a level of methylmercury in cord blood to an ingested dose of methylmercury which would support that blood level. Please comment on the model choice as well as on the values which EPA used for the model parameters.

Peer Review Panel Comment:

All reviewers commenting on this charge agreed that the one compartment model is sufficient for the purpose of dose conversion in RfD derivation. However comments were made regarding the appropriateness of using a higher body weight for a women without consideration of the apparent dependencies between body weight, blood volume, and fraction of absorbed dose described in Swartout and Rice (2000).

a. EPA should acknowledge that the value of "f" used in their calculations (0.059) is based upon data combined across both men and women. EPA should mention that limited data (Sherlock et al., (1984) as described in the ATSDR toxicological profile) suggest a gender difference. However, this evidence is limited by a small "n" in this study (6 women and 14 men) and there are no data describing the value of "f" during pregnancy. While the panel recommends that EPA acknowledge this issue, it does not recommend that a separate value specific to women be used.

EPA Response:

This is now explicitly stated in Section 4.4.2.3 of the revised background document (p. 4-74).

Peer Review Panel Comment:

b. EPA should be aware of the correlation between blood volume and body weight and evaluate the current value used for blood volume given the increased value that was used for body weight. EPA may also want to give consideration to adjusting "f" for the increased blood volume based on the data of Swartout and Rice (2000). See specific reviewer comments in Section 3.2.

EPA Response:

We described the correlations determined or assumed in Swartout and Rice (2000) or Stern (1997) in subsections of 4.4.3.2. After consideration of the reviewer comments and re-analyses of some of the parameter discussions in the above papers, EPA decided to set V = 5L. EPA chose to use f=0.059, which is intermediate with respect to the published values.

8. EPA used a factor of 3 for both interindividual variability and uncertainty in methylmercury pharmacokinetics. Please comment on choice of this uncertainly factor and whether the arguments in support of the choice are adequate.

Peer Review Panel Comments:

This charge asked whether a 3 fold uncertainty factor was appropriate to represent a combination of inter-individual variability and toxicokinetic uncertainty. The panel generally agreed that this choice is appropriate and well documented by Table 5-1. One reviewer noted that the NRC concluded that a factor of 2 was sufficient to account for 95-99% interindividual variability and uncertainty when using cord blood as the biomarker (versus hair). However it was felt that the additional variability/uncertainty and the uncertainty introduced by the fetal blood to maternal blood extrapolation was a persuasive argument for maintaining a full 3-fold uncertainty factor. In addition, the reviewers felt that it would be helpful if EPA could clarify what percentage of this uncertainty factor is due to variability and what percentage is due to uncertainty.

The panel recommends that EPA perform a distributional assessment of the one compartment model (e.g., Swartout & Rice, 2000) incorporating an estimate of uncertainty about the cord blood:maternal blood ratio. This analysis should be used to assess whether a 3-fold uncertainty factor is appropriate.

EPA Response:

The variability estimates in Table 4-9 based on maternal blood are from 1.4-2.2 for the 50th/5th percentile, and 1.7-3.0 for the 50th/1st percentile estimate. EPA chose the upper end of this range for the UF. This is also consistent with the typical strategy of setting UFs in half-log units, although this was not a primary reason. EPA considers this UF of 3 to represent PK variability.

In addition, there is variability and uncertainty concerning the ratio of cord to maternal blood mercury levels. Additional analysis by EPA, in Section 4.5.4.1 (pp. 4-79 to 4-81) of the revised document, provide evidence that the cord:maternal ratio converges on 1.7 based on the available literature. The variability and uncertainty around that number are unknown, but data from two studies suggest they are greater than a factor of 3. Therefore a total factor of 3 for PK variability and uncertainty may be too low.

EPA agrees that a distributional analysis of cord blood:maternal blood would provide valuable information concerning whether a 3-fold factor is sufficient. EPA will undertake such an analysis in the future if appropriate raw data sets are available from primary investigations.

9. Part of the reasoning in the use of a pharmacokinetic uncertainty factor dealt with reported differences in mercury levels in cord blood vs. maternal blood. Specifically, there is evidence from some publications that cord blood levels are higher than those of the mother. The extent (and even the consistency) of this difference is variable, as described in section 4 of the draft RfD document. EPA chose to assume equality of maternal and fetal blood levels in the dose conversion and to deal with the likelihood of difference as an area of uncertainty. Please comment on this decision. Would it be more appropriate to take a fraction of the fetal blood level when converting to maternal blood for the dose conversion? If so, what should that fraction be?

Peer Review Panel Comments:

In this question EPA is asking whether it is appropriate to consider the methylmercury maternal blood:cord blood ratio as equal for the purposes of dose conversion and to add the uncertainty around this assumption to the overall toxicokinetic uncertainty factor. All reviewers acknowledged that this is a potentially important area of variability and uncertainty in the dose conversion estimate. The panel felt that EPA did not adequately describe this uncertainty. Some reviewers felt that EPA should make more of an effort to critically review the published literature on cord blood to maternal blood ratio to determine whether an adjustment is needed. Specifically, the panel recommended that EPA undertake a more comprehensive and critical review of the studies on methylmercury levels in maternal and cord blood. The Agency should include the additional studies in such a review: 1) Ramirez, 2000; 2) Yang J, et al., 1997; 3) Baglan RJ, et al., 1974; 4) Vahter M et al., 2000. EPA should also include the studies that present ratio data cited in Section 3.2 (under charge question #9) in its review, plus the human data in Tsuchiya, 1984; this latter paper was included in the RfD document reference list but not in discussions of this issue in Sections 4.2.1 or 5.4.1.

Section 3.2 of this report provides data summaries from a number of human studies documenting mercury in maternal blood and cord blood; this information has been provided by two of the reviewers to assist EPA in identifying some of the key datasets and to show what appears to be the general trend for the ratio in these data. It was also stated in the panel discussion that the animal literature generally supports a cord:maternal blood ratio greater than 1.0 insofar as mercury levels in fetal tissue or blood levels are usually higher than those in maternal tissue. The fetal:maternal ratios range from about 1.2 to 2.0, but with some organs (reported in Wannag) it can be even higher. Some supporting references are listed below (Burbacher et al., 1987; Inskip, M. J., & Piotrowski, J. K. 1985; Rice, 1989; Wannag, 1976).

To the degree possible, EPA should evaluate the central tendency and variability (thru distributional analysis) in the maternal blood/cord blood ratio based upon the available studies. This may lead to using the central tendency estimate of the ratio as a discrete factor in the dose conversion model and to adding the variability in the ratio database to the overall PK variability factor.

EPA Response:

Section 4.5.4.1 (pp. 4-79 ff.) of the revised background document provides a more detailed discussion of the issue of cord:maternal blood ratios, including references provided by the reviewers. Based on studies in which mercury was speciated, cord:maternal ratio of methylmercury converge on about 1.7 based on 9 studies (Table 4-81).

EPA retrieved all available literature on cord blood and maternal blood mercury levels. Ratios were calculated for all papers which reported appropriate data. No determination of data quality was done at this time. Discussion of these results was incorporated into section 4.5.4.1. Preparation of a distributional analysis must await the retrieval of some raw data as well as evaluation of data quality.

As a result of our analysis, EPA decided not to make a numerical adjustment for potential differences in cord vs. maternal blood levels of mercury. EPA will work towards a scientifically justified cord blood:maternal blood numerical adjustment.

10. EPA applied an additional factor of 3 for database insufficiency. EPA included the following in the basis for this choice: lack of data on toxicodynamic variability, inability to quantify long-term sequelae, and uncertainty as to selection of critical effect (insufficient data on cardiovascular effects and lack of a two-generation reproductive effects assay) . Please comment on choice of this uncertainty factor.

Peer Review Panel Comment:

This charge asked whether a 3 fold uncertainty factor is appropriate for methylmercury in addition to the toxicokinetic factor described above. The panel agreed that this combined factor for toxicodynamic uncertainty, endpoint uncertainty, and database deficiencies is appropriate. While EPA's justification for this factor mentions the key points, the panel recommends that the justification be clarified so that the relative importance of the various areas of uncertainty becomes transparent. This will help focus methylmercury research priorities and will also let risk assessors know whether the uncertainties/variabilities that might be important in a local population of exposed women have or have not been weighted by EPA in this uncertainty factor.

EPA Response:

This issue has been clarified in the revised background document (p. 4-87). This additional factor of three addresses uncertainty regarding TD variability. Lack of information concerning other endpoints is raised as a concern, but not formally included in the UF.

Comments from the Public

Note: The following comments addressed the original background document submitted to the peer review panel for review. The final document, which is the basis for the IRIS summary, is Chapter 4: Risk Assessment for Methylmercury, in the *Water Quality Criterion for the Protection of Human Health: Methylmercury*, Final, January 2001.

Public comments were submitted by four groups: Toxicology Excellence for Risk Assessment (TERA), Electrical Power Research Institute (EPRI), Edison Electric Institute, and the Utility Air Regulatory Group. Most of the issues were addressed by the peer review panel as part of their response to the charge, or in EPA's response to the peer review panel. These include the potential confounding of the effects of methylmercury by PCBs in the Faroe study, the choice of endpoints, the choice of the BMD model, dose conversion, and the choice of the UFs. Additional comments, not addressed above, are the following.

Comment: *The Faroe Islands study is not an appropriate choice because exposure in that population was episodic high-level exposure via whale meat meals, which is not representative of exposure in the U.S. population.*

EPA Response: First, EPA is unaware of any data on whether methylmercury in whale meat is more or less bioavailable than methylmercury in fish tissue. EPA assumes that bioavailability from these sources is equivalent.

Second, this objection is predicated on the assumption that episodic exposure results in greater toxicity to the fetal brain than an equal total amount of methylmercury ingested by the mother on a more continuous basis. While this may be a reasonable hypothesis, EPA is unaware of any studies directly addressing this issue. A comparison with the effects of ethanol is not appropriate, since ethanol distributes very quickly in total body water (including the fetus) whereas methylmercury does not (see below).

Third, the actual pattern of mercury exposure in the Faroe Islands study is unknown. Much of the exposure from whale was likely by "snacks" of dried whale meat consumed on a regular basis, so that for many individuals exposure was likely not very "episodic". It must also be remembered that this population also consumes fish on a regular basis (about three times a week on average), which is a continuous source of low-level mercury exposure. It is also completely unknown the degree to which any "spikes" in mercury intake would be integrated (attenuated) moving through the numerous compartments between the mother's stomach and the fetal nervous system (particularly brain). These unknowns represent very significant information gaps, such that no conclusion can be drawn regarding the issue of the importance of episodic exposure in this study, if it indeed exists.

Fourth, EPA is unaware of the existence of any data sets that directly combine data on frequency of fish intake and mercury levels in fish in relevant samples of the U.S. population. It is probably true that in some individuals in the U.S. with elevated mercury levels, exposure was

through ingestion of fish with relatively low mercury levels on a frequent basis. However, it is clear that fish in inland waters can have high levels of methylmercury.

Fish available in the United States contain methylmercury at levels in excess of 1 ppm and in many situations considerably over 1 ppm. Such elevated concentrations have been reported in New England, New York, the Southern states, and Hawaii. For example, the North East States Coordinated Air Use Management summarized data from New England's freshwater fish in the "Mercury Study: A Framework for Action" by the Northeast States and Eastern Canadian Provinces (1998).

Table A-2. Maximum Mercury Concentrations in Selected Fish Species

Fish Species	***Maximum Mercury Concentration in ppm***
Largemouth bass	8.94
Smallmouth bass	5.0
Yellow perch	3.15
Chain pickerel	2.81
Lake trout	2.70
Walleye	2.04
Brown bullhead	1.10
Brook trout	0.98

These levels do not simply reflect a maximum far above the remainder of the data. From the report cited above, additional data shown that:

- 8% of Connecticut's largemouth and small mouth bass had mercury concentrations > 1 ppm. The highest concentrations for these species were 2.65 and 2.32 ppm, respectively.

- Monitoring data from Massachusetts showed 29% of chain pickerel over 1 ppm with a maximum of 3.2 ppm, 9.2% of largemouth bass exceeded 1 ppm with a maximum value of 2.6 ppm, 20.6% of smallmouth bass exceeded 1 ppm with a maximum of 5.0 ppm, and 7.3% of white perch exceeded 1 ppm with a maximum of 2.2 ppm; 6.3% of yellow perch exceeded 1 ppm with a maximum of 2.5 ppm.

- Similar maximum values, and a similar percent of fish above 1 ppm were reported from New Hampshire for these same species. It is estimated that in the New England states approximately 10% of selected species of freshwater fish contain over 1 ppm mercury.

  Additional data are available for New York State (Simonin and Meyer, 1998).

- In New York State, maximum mercury concentrations over 2 ppm were seen for the following species: walleye (3.2 ppm), striped bass (5.4 ppm), white perch (3.2 ppm) Northern pike (2.1 ppm), smallmouth bass (3.34 ppm), largemouth bass (2.39 ppm), rock bass (2.7 ppm), drum (1.4 ppm), channel catfish (2.0 ppm), sunfish (1.2 ppm), American eel (1.6 ppm), Lake trout (2.7 ppm), white sucker (1.2 ppm), black crappie (1.4 ppm), and carp (5.8 ppm).

These higher mercury concentrations are not limited to New England and New York. Fish with mercury concentrations in the 1 to 3 ppm range are also found in Southern states and Hawaii. King mackerel frequently contains mercury in excess of 1 ppm and samples as high as 3.5 ppm have been reported from North Carolina. Samples containing up to 1.6 ppm mercury have been found in samples of King mackerel obtained offshore from Texas. Hawaii State Department of Health has identified mako shark and thresher shark samples containing up to 2.7 and 2.75 ppm methylmercury respectively. Data from Florida have identified mako shark containing 3.9 ppm methylmercury, and black tip and sand sharks with 2.9 and 2.7 ppm methylmercury.

A recent study from Florida collated 206 samples of fish of various species in retail stores between October and December 2000 (Florida Department of Agriculture and Consumer Services, Food Safety Division). Mercury levels of 36 samples of tuna steaks or fillets ranged from 0.07 to 1.19 ppm, with a mean of 0.56 ppm. Two samples had mercury levels over 1.0 ppm. Mercury levels in 10 samples of fresh king mackerel or mackerel ranged from 1.59 to 4.02 ppm, with all six samples exceeding 1.0 ppm. Of a total of 33 samples of swordfish, 24 exceeded 1.0 ppm, with ranges between 0.48 ppm and 3.55 ppm. Analysis of 118 samples of canned tuna averaged 0.28 ppm total mercury, with a range from below the limit or detection of the methodology to 0.77 ppm. The data from the fresh samples clearly demonstrate that fish available for purchase in retail stores can have high levels of mercury, comparable to whale meat in the Faroe Islands study.

In addition to data on mercury levels in fish, it would be useful to know the consumption pattern of people who eat fish, particularly from inland waters. There are some data available from studies in anglers on the consumption pattern of fish caught in inland waters (Tables A-3, A-4).

In the Oswego study on the effects of consumption of contaminated fish on neuropsychological development, pregnant women were recruited between 1991-1994, 840 non-fish-eaters and 477 who ate fish from Lake Ontario. Frequency of fish consumption, based on 28 species of Lake Ontario fish, was as follows (P. Stewart, personal communication):

Table A-3. Frequency of Lake Ontario fish consumption by pregnant women who ate Lake Ontario fish in the Oswego Study

Frequency	Number of People	Frequency	Number of People
1/year	59	3/month	28
2-6/year	63	1/week	41
7-11/year	51	2/week	45
1/month	59	3-4/week	33
2/month	63	5/week	35

In a study of older (over 50 years old) fish eaters in Michigan recruited in 1980, the pattern of eating sport-caught fish in 1994 of the total cohort was as follows (S. Schantz, personal communication):

	Frequency (n)			
# meals/season	Spring	Summer	Fall	Winter
0	17	16	32	39
1-3	37	31	38	39
4-6	24	27	22	16
7-9	11	15	10	10
10-13	15	14	9	7
13+	15	16	8	8

It is clear from these tables that a substantial proportion of anglers eat caught fish at frequencies between once a week and once a month, or less than once a month. This intake pattern is comparable to that of intake of whale meat, with fresh whale meat being consumed on average less than once a month and dried whale meat perhaps more frequently. From the data available, it seems likely that some individuals consume fish potentially contaminated with high levels of mercury with a frequency pattern comparable to that in the Faroe Islands.

These tables do not include consumption of other fish in these cohorts, including marine fish. Consumption of high-mercury marine fish such as tuna steak, sword fish, or shark is more likely to be episodic (once/week to once/month or less) than continuous.

Recent analysis of NHANES 99+ data documents that greater than 10% of women of

child-bearing age in the general population have blood mercury concentrations exceeding that assumed by an intake based on the proposed RfD (MMWR, 2001). It is prudent to assume that the elevated mercury levels in some unknown proportion of these women is the result of episodic exposure via high-mercury fish.

Comment: *Data are needed regarding mercury levels in the U.S. population, and levels of sources of mercury in fish in various areas.*

EPA response: EPA agrees. Hair and blood mercury data are being evaluated in NHANES 99+, and first-year data are recently published (MMWR, 2001). Collecting data on sources of mercury in the food chain is part of EPA's Mercury Research Strategy (2000). However, these issues are not directly relevant to determination of the RfD, but are important for management of risk to the U.S. population.

Comment: *"Comparison of fish consumption between the U.S. and Faroe Islands should not be used, in part, as a basis for the choice of the critical study."*

EPA Response: The meaning of this is unclear, since EPA did not base the choice of the critical study on a comparison of fish consumption between the two populations.

Comments: *"Uncertainty in toxicodynamics does not reflect database insufficiency." "The NAS does not call out a need for this uncertainty."*

EPA Response: In fact, little or nothing is known about the variability in TD, as opposed to TK, in the human population, so we have used a default factor of 3. In addition, both the Faroe and Seychelles populations are relatively homogeneous compared to the U.S. population. Also, NRC did state that an overall uncertainty factor of 10 was appropriate.

Comment: *Other comments about choice of UF included disagreement with the inclusion of other endpoints (e.g. delayed neurotoxicity, cardiovascular).*

EPA Response: The revised background document discusses these as areas in which more information is needed, but does not include them in the UF.

Comment: *"[A] question that has not been adequately addressed ... concerns the failure of the Faroes studies to observe significant effects of PCBs [given the high exposure levels]...."*

EPA Response: In fact, the Faroe study did identify PCB effects on four endpoints, that assess the domains found to be affected in the Michigan study. These effects became nonsignificant when the variance shared by mercury and PCBs was removed, which is not surprising. It is also important to point out that the Michigan study did not measure mercury in fish or in human tissue, so effects in that study attributed to PCBs could have been the result of methylmercury exposure instead of or in addition to PCB exposure.

Comment: *"The use of benchmark dose analysis and the choice of BMR of 5% resulted in a [greatly elevated] RfD compared to the use of a NOAEL approach and/or choice of a BMR of 10%." (There were several comments along these lines.)*

EPA Response: The comparison of a 5% and 10% BMR is included in the response to the comments of the peer review panel for Question 6. It can be observed that the association for the BMDL for the various endpoints of the Faroe study is orderly and results in a difference of 1.6-1.7 greater for 10% compared to 5%. EPA takes the position that deriving an RfD that may result in a doubling of the background incidence of abnormal response is more acceptable than an RfD that allows a tripling of children with abnormal responses. This is particularly true since deficits on several functional endpoints were identified in the same range of exposures.

As for comparison between BMD and NOAEL, the study referred to in the comments compared quantal data from animal studies with small n's (i.e. typical numbers for an animal study). These results are not applicable to continuous data from a large epidemiological study. Moreover, the BMD is quite different from a NOAEL, and there is no reason to compare the two. In addition, in the Faroe study, analysis by the Faroe investigators demonstrated that for some endpoints, the logarithmic model fit the data better than the *K* power or linear. For the *K* power models, the best fit was *K*=1. These analyses certainly provide no evidence for detection of a threshold within the range of methylmercury exposures in the Faroe Islands study.

Comment: *PCB exposure in the Faroe Islands is high, and infants are exposed to very high PCB levels via breast feeding.*

EPA Response: EPA recognizes that exposure to PCBs in the Faroe cohort was likely to be high, based on data from a subsequent cohort (Steurwald *et al*., 2000). This is discussed in the revised background document (pp. 4-37 to 4-38). However, the Dutch PCB study, which was designed specifically to study the contribution of prenatal versus postnatal PCB exposure to neuropsychological impairment, has clearly identified cognitive deficits associated with prenatal but not postnatal exposure (Patandin *et al*., 1999). The PCB exposure of concern is therefore *in utero* and not postnatal exposure through breast milk. Moreover, any contribution of an unmeasured variable (intake of PCBs from breast milk) would simply add noise to the dependent variable if it was not highly correlated to the independent variable(s) being measured, and thereby decrease the probability of identifying association with independent variables that were measured (i.e. methylmercury). In order for postnatal PCB exposure rather than methylmercury exposure to be the cause of the observed effects, there would have to be a high correlation between prenatal methylmercury exposure and postnatal PCB exposure. EPA knows of no reason to hypothesize such an association.

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