Response to Reviewers
Peer Review of "An Intervention Analysis of Exposure to Methylmercury for Consumption of Seafood"

I. INTRODUCTION

The Food and Drug Administration (FDA) and the U.S. Environmental Protection Agency (EPA) jointly issued national advice on consumption of methyl mercury-contaminated fish (March 2001). This advice was targeted to pregnant women and those who may become pregnant, but also considered women who are breast-feeding and small children. Since that time, the National Health and Nutrition examination Survey (NHANES) has observed that approximately 8% of women tested had blood mercury levels in excess of the EPA reference dose of 5.8 µg/L. (Reference dose is described in Rice et al., 2003 and U.S. EPA, 2001). The NHANES study also showed a relationship between blood mercury levels and consumption of fish (Schober et al. 2003).

FDA and EPA are considering ways to improve effectiveness of the national fish advice. FDA has published an exposure analysis for methylmercury from seafood for U.S. consumers (Carrington and Bolger, 2002). This paper described a model for exposure and predicted biomarkers (blood and hair mercury) for all persons, women of child-bearing age and children 2-5 years of age. The document under review (also called poster presentation) presents refinements of the model and expands the list of fish species for which distributions of mercury concentration were defined. This document offers predicted biomarker distributions for women of child-bearing age for several fish consumption scenarios that could be considered in the evaluation of national fish advice.

The document was peer reviewed using EPA contract No. 68-C-02-091. EPA provided the document the charge to reviewers and a description of areas of expertise needed in reviewers. The contractor selected three reviewers (with EPA approval), distributed the document and charge, collected all critiques and compiled a report. The report was completed in August 2003 and is available on the EPA OST website.

FDA responded to reviewer comments by making substantial revisions to the analyses and accompanying text. The text has been expanded to a manuscript for publication EPA and FDA have together summarized the responses to specific critiques in this report.

II. CHARGE TO THE PEER REVIEWERS

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

2. 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.

3. Is the model clearly described? Are modifications supportable by existing data? Modifications include these: expansion of fish categories from 24 to 28; fitted distributions in place of analogues for some species; addition of 0.1 to 2 ppb mercury to blood levels to account for sources other than fish.

4. Data from the Continuing Study of Food Intake by Individuals (CSFII) from 1989-1991 were the basis for distributions of fish consumption. These data were from three days of survey information vs. two days for the later data (CSFII 94-96). Comment on this choice. Comment on the adjustments made to compensate for likely under-reporting of fish consumption by the low consumption portion of the population.

5. In this paper women of child-bearing age are defined as those between 18 and 45 years of age; children are defined as of 2 to 5 years old. Are these the appropriate ranges?

6. Are the fish consumption scenarios logically described, clear and supportable? Comment on the identification of 0.5 ppm mercury or greater as “high mercury fish.”

7. For purposes of applying the scenarios in the exposure assessment, the following boundaries were set for High, Medium and Low mercury contamination of fish species: High, swordfish, shark, tilefish, king mackerel; medium greater than 0.13 ppm; low less than or equal to 0.13 ppm. Comment on these choices. Note and comment on the following: 0.12 ppm is a level of mercury contamination that would permit 12 oz. fish/week without exceeding the RfD.

III. RESPONSES TO REVIEWERS

A. Charge questions and responses

The peer review report was comprehensive and responsive to the charge questions.

1. Reviewers indicated that the document was clearly written for the concise form in which it was presented (a poster and accompanying older paper describing the model). It can be improved by enhanced descriptions of areas of uncertainty, and expanded description of the scenarios.

   Response: Agree. The poster has been expanded to a manuscript for publication.

2. Reviewers made some suggestions as to additional literature to be cited.

   Response: The authors are evaluating inclusion of the references for the manuscript.

3. Generally the reviewers felt that the structure of the model was well described in the *Risk Analysis* paper. Some adjustments and modifications in the poster were considered appropriate and supportable; others (e.g. adjustment of 3 day survey data for long term exposure) were critiqued.

   Response: Additional discussion will be included in the manuscript for publication. Specific comments and responses regarding adjustments and modifications are in section III. B.

4. Two reviewers noted that use of the 3 day CSFII data likely results in underestimation of the number of fish eaters and the amount consumed. They felt that use of the older 3 day data were more appropriate than that of the more recent 2 day survey data.

   Response: We agree with this point and feel that the adjustment from longer term purchase diary data is warranted as well.

5. Definition of women of child-bearing age was considered by one reviewer to be a policy choice. Two reviewers commented that the range of 2-5 years of age for children was probably appropriate. One reviewer suggested use of the NHANES age ranges to improve comparison with the data.

Response: The revised analyses were run using the NHANES age range of 16-49 for women of child-bearing age.

6. All reviewers suggested improvements in descriptions of the fish consumption scenarios.

   Response: We have expanded and clarified the descriptions in the manuscript. Some specific responses are provided in section III.B of this response document.

7. All reviewers noted that the cut off mercury concentration for "high, medium and low" were arbitrary, but two commented that these categories seemed appropriate.

   Response: The categories and cut off points were maintained. Some specific responses are provided in section III.B.

B. Responses to Specific Criticisms

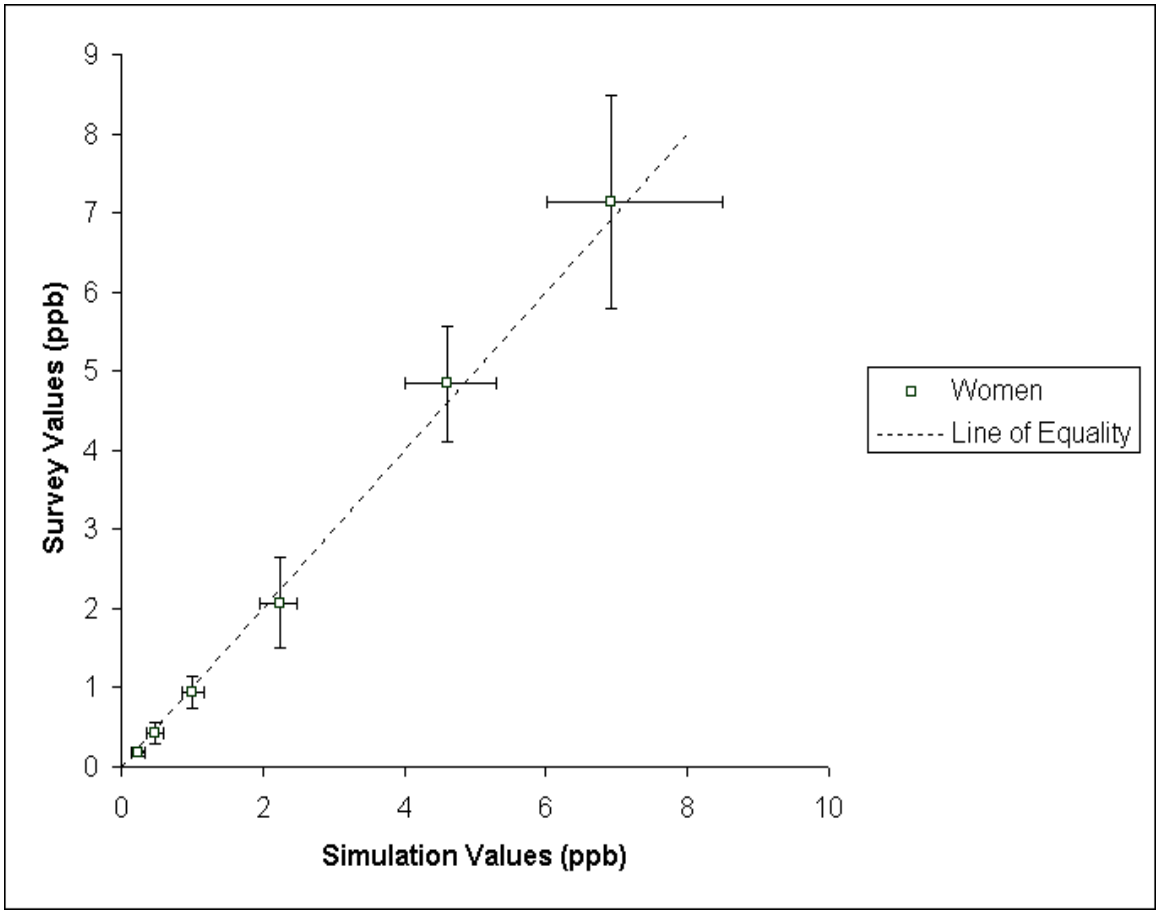
The responses below generally reflect only areas wherein the reviewers had objections to methods, data or interpretation. Most areas of agreement are not noted; exceptions include those items outside the scope of the current analyses.

1. Responses to critiques by multiple reviewers

Comment: Lack of agreement of modeled values with the NHANES data.

Response: All three reviewers commented the lack of correspondence between the model and the NHANES survey blood values. The base case scenario is most comparable to consumption by the general public at the time that the NHANES data were collected. The modeled blood values were within a factor of two of the reported blood levels for women of childbearing age. Generally this would be considered good agreement. We have, however, made some changes to improve modeled estimates.

We have produced a revised version of the model that employs a correction factor for loss of weight during food preparation. These changes resulted in model predictions with increased predicted blood and hair levels. As a result, the values predicted for adult women are in much closer agreement with the NHANES survey values, while the values for children are overestimated to a greater extent than in the previous model.



Quantile-Quantile Comparison of Simulation and Survey Values for Blood

Comment: All three reviewers critiqued the use of an adjustment to CSFII data to account for lack of long term consumption data from this study. One commented that the use of an arbitrary correction detracts from the robustness of the model. None offered suggestions for improving a correction method.

Response: We acknowledge the uncertainty inherent in using the chosen adjustment. However we feel that, as fish is one of the least frequently consumed food items in the U.S. general population, use of the 3 day CSFII data alone would underpredict the number of fish eaters. The longer term purchase diaries were considered the best data available for this purpose. While we acknowledge that the frequency-extrapolation method based on longer term purchase diary (used in the poster presentation) was arbitrary, we still feel it was

reasonable given the information we had at the time. Our newest version of the model, used in the manuscript for publication employs an extrapolation based on the NHANES 30-day fish consumption survey.

Comment: Two reviewers noted that the correction for non-fish mercury exposure is simplistic and not well-supported. It does not appear to have much impact on the final exposure estimates.

Response: The adjustment for non-fish mercury is included to increase the fit at the low end of the NHANES biomarker survey and employs values chosen (i.e. empirically supported by) from the survey itself.

Comment: Two reviewers felt that analyses should consider risk trade off by considering the omega 3 fatty acid content of fish species. It was also noted that analyses, and presumably the EPA/ FDA fish advice should consider PCB contamination of fish.

Response: We agree that the ultimate fish advice (and the scientific basis thereof) should include these factors. This is, however, much beyond the scope of the current analyses.

2. Responses to Reviewer #1.

Comment: "To a large extent, the uncertainty in the model's predictions stems from the uncertainty in the underlying three-day CSFII data which both underestimates the contribution of infrequent consumers, and misrepresents the longer term consumption patterns of more frequent consumers. Unless additional information on usual consumption patterns for those reporting and not reporting during the three-day period are available, there is little that can be done in an objective manner to accurately regenerate the missing data. The approach in this analysis (as described in the Risk Analysis paper) to address the missing data is arbitrary and highly complex leading to a non-robust model whose relationship to the empirical NHANES data on the overall distribution of MeHg exposure appears to reflect curve-fitting rather than a generalizable approach."

Response: All analyses start with a set of assumptions and are arbitrary in some sense. Curve-fitting was used to generate some of the input distributions, but the overall model was not fit to the NHANES data – which is why it doesn't entirely correspond to it. We feel that the use of the long term consumption adjustment does not detract from the model robustness, but rather decreases the degree of underprediction that would occur without its use.

Comment: The reviewer questioned the ability of the model to predict changes in blood mercury of a population as the inputs moved from the base case to alternative fish consumption scenarios.

"… my impression is that the conclusions from this analysis regarding the changes in the patterns of national fish consumption necessary to reduce the proportion of consumers in the high risk group that exceeds the EPA RfD should be viewed with caution. A more useful approach would be to generate an analysis using empirical data on both exposure (hair or blood Hg concentrations) and species-specific fish intake for each individual in a robust sample. It may be that the existing NHANES database contains sufficient data of both types to accomplish such an analysis."

Response: We agree with the reviewer in that the only data on mercury blood levels in the general population are those of NHANES, which in the aggregate reflect the base case. To that extent the only way to test the validity of the model would be to measure blood mercury in test subjects eating fish diets corresponding to the scenarios.

We are considering ways to employ the 30-day frequency data for fish intake that was included in the last release of NHANES data. These data were not available when the current model was being developed and since using this data would require considerable revision of the model, we have not done so yet. Although we are pursuing the matter further, on the basis of a preliminary analysis we doubt that it will be possible to generate accurate predictions for individual blood levels from the frequency data. In particular, the relationship between blood mercury and number of seafood or fish meals eaten is not very strong. In particular, many of the women with high mercury levels (e.g. above the RfD) reported no seafood intake for the previous month. Given the long half-life of mercury in humans, it is likely that fish consumption prior to 30 days before testing could still have and effect on blood level.

We have, however, made use of the NHANES data in the most recent revision of the model. First, the number of seafood consumers was increased to be consistent with the NHANES survey data. Second, the parameters for the equation used to extrapolate long-term frequency of consumption were based on the NHANES survey~~. How? Need a little more explanation.~~ Third, variation among consumers in the types of seafood consumed was based on the NHANES survey data.

Comment: Lack of correspondence of the modeled values is not a function of inorganic mercury; NHANES reported almost no detectable levels of inorganic mercury. "This suggests that model mis-specification rather than confounding measurements of inorganic Hg is responsible for the under prediction of blood

Hg levels in women."

Response: We agree that inorganic mercury exposure is not likely to be a major factor. Investigation of model mis-specification could be considered for future work.

Comment: "Notwithstanding my previous comment regarding the unnecessary complexity resulting from describing species-specific MeHg concentrations in terms of distributions (as opposed to simply using the mean value), the distribution fitting approach described here (with Fig. 2 as an example) as "empirical," is, in fact, not an empirical distribution as the empirical data are used to fit parametric distributions to the data. A true empirical distribution is one in which the distribution is described relative to its percentiles (i.e., a cumulative probability distribution) rather than through function fitting. With such data rich sources a true empirical approach is warranted. Furthermore, if fitted distributions are to be employed, more quantitative tests of curve fit should be provided (e.g., quantile-quantile plots; probability-probability plots; K-S test; A-D test)."

Response: The distributions described as empirical (e.g. those for shark, swordfish) do employ direct data sampling where the "distribution is described relative to its percentiles". The functions derived through curve fitting are described as "modeled". Significance tests of curve fit were not employed because we believe it is a mistake to identify any simple distribution as being "correct". Instead, we employed probability trees that used several different distributions to represent the uncertainty in the statistical form. A quantitative algorithm was used to assign model weights and probability intervals that is similar in spirit to the Anderson-Darling test.

3. Responses to Reviewer #2

Comment: "Exposure model takes a number of approaches that tend to make the consumption profile more uniform across the population and thus remove the potential for high end consumers to be identified. The resulting distribution may thus underestimate the extremes in blood mercury and the number of people above the RfD blood level. This appears to be borne out by the fact that the base model output yields only 3.9% of women above the RfD while NHANES reports nearly 8% in this category. I recognize that there may be other reasons that could contribute to this low estimation of the number of women with elevated blood mercury."

Response: It is true that some of the modifications make the distributions more uniform relative to the short term survey. To some extent, this is intentional

since chronic exposure distributions are generally expected to be more uniform. The degree to which it is more uniform is one of the major uncertainties in the exposure assessment. We have a current version of the model which more closely matches the NHANES data (see general response above).

Comment: "Contributing to the first concern is that the input data for the current modeling effort is insufficient with regards to consumption patterns amongst those individuals who have a preference for a certain fish species. This is especially important to characterize for those species which have substantial amounts of mercury. The use of market share data to "fill in" their consumption profile will tend to average out their behavior with the rest of the population rather than show these individuals as important high end consumers in the population distribution. The current inputs to the model are unable to capture the full range of consumption habits and thus has little chance to capture high end consumers who constitute the tail of the distribution."

Response: We concur that the market share data will not adjust consumption patterns to account for fish eaters who concentrate on a single species. It is likely that only focused studies on such populations will provide such data. In our analyses market share data is used to "fill in", as opposed to using the short-term survey data; this is treated as a source of uncertainty. Specifically, the extent to which market share data is used to predict individual behavior is varied (from 20 to 80% in the poster presentation and 11 to 100% in our more recent version for publication). As a result, the uncertainty analysis reflects a broad range of plausible assumptions. Consumer behavior is highly averaged at one end of the uncertainty distribution, but is hardly averaged at all at the other. Market share will reflect whole distribution – including the ends of the distribution.

Comment: "The model uses a simplified relationship to estimate mercury blood levels from intake rather than incorporating a pharmacokinetic model to estimate blood levels. There is a simple one compartment model that provides reasonable predictions of mercury blood concentrations from acute and chronic intake information (e.g., Stern, Reg. Tox. Pharmacol. 25: 277-288, 1997; Ginsberg and Toal, Risk Anal. 20: 41-47, 2000). This pharmacokinetic model has the advantage of employing a range of parameter inputs that will create a distribution of blood levels for any intake level that will better represent population variability than the current FDA approach. That approach does not really take into account inter-individual variability in pharmacokinetics."

Response: The model is simplified relative to the Stern model in that it assumes steady state kinetics. Given the fact that most toxicological analyses (including the RfD derivation) make assumption that chronic exposure is the relevant dose

metric, we think this is appropriate for current purposes. However, it is not true that population variability is not represented – a distribution is employed which is derived from the Sherlock et al, 1984 study. This distribution is somewhat narrower than the Stern model – this result is attributable to the assumption in the Stern model that blood levels are directly proportional to dose and body weight. It is likely that this assumption causes the Stern model to overestimate pharmacokinetic variability.

Comment: "Numerous states establish consumption advisories for freshwater fish based upon an approach that is geared towards the individual species and the individual consumer. This approach has the goal that each fish species is consumed at the RfD level or less. Thus, it does not worry about how much the general public is now eating (an uncertain quantity) but instead it tells the consumer how much of each species is safe to eat. Of course, this approach must be mindful of the difficulties of risk communication and try to keep the message simple (e.g., general advice plus more specific advice about certain mid-range and high end fish species). The FDA modeling/intervention approach is based upon the average response of the general public to a particular advice scenario. This type of overall population response assessment is most appropriate for a carcinogen where the change in cancer risk among many people is the important risk statistic. In the realm of non-cancer assessment, the lead uptake-biokinetic modeling approach is the only area I am aware of that bases risk management decisions on probabilistic population responses to environmental inputs. This in part is due to the fact that there is no RfD for lead. For mercury, where there is a clear developmental RfD, FDA should consider the species-by-species advisory approach for those high mercury species or commonly eaten species that dominant the public's exposure to methyl mercury. The combination of both the population/probabilistic approach and the species-by-species approach will help harmonize the FDA seafood advisory with what is commonly done at the state level for fish advisories."

Response: First, we acknowledge that the model assumes full consumer compliance, and that this outcome is unlikely. We think that this is appropriate as our goal is to provide advice for consumers who consider lowering their mercury levels to be necessary. Second. it is true that the present model was designed to be used as part of a risk assessment/risk management decision paradigm, rather than as part of an RfD/safety assessment paradigm in which there is no formal characterization of the risk. However, we still believe the model is useful for relating fish intake to mercury tissue levels in the context of a safety assessment. The model does not generate an average response – it generates a population distribution, and we feel this is useful and appropriate for national advice.

At the State or local level it is likely that a few species will dominate the consumption pattern. Our model, or at least portions of it, could be adapted to give species-by-species prediction.

4. Responses to Reviewer #3

Comment: "One distribution in particular warrants additional discussion – canned tuna. The underlying data for estimating distributions for canned "light" vs "white" (albacore) tuna are presumably from Yess (1993)[1]. Yess (1993) reports results for composite samples, with each composite representing 12 cans. If the Yess (1993) data were used to develop distributions of mercury in canned tuna without variance inflation to adjust for the effect of compositing, the resulting distribution of mercury levels in canned tuna would not reflect the distribution for individual cans. The infrequent occurrence of cans with higher mercury levels would be smoothed out by compositing. Given these fish species (light & white canned tuna) represent more than 20% of total fish consumption, it is plausible (though speculation) that this could result in an under-prediction of blood mercury levels in the right tail of the distribution (which is where we are most interested in evaluating the effect of interventions)."

Response: The tuna distributions are based on data from Yess (1993), and the distribution could easily be widened to correct for the effect of compositing. However, since high mercury exposures do not occur as the result of the consumption of a single fish, we would expect the impact of widening the distribution would have very little effect on high end exposures.

The FDA has recently undertaken testing of canned tuna samples and is in the process of analyzing the data. While, preliminary, our results for light and albacore tuna do not depart substantially from those used in the model. The new data can be input to our revised applications.

Comment: "With respect to additional validation work, the modeling of fish consumption behavior and the attempt to adjust CFSII data to better mimic long-term consumption behavior should be better validated if at all possible. It would be of interest, for example, to see the model predicted market share compared to observed market share for fish species."

Response: Additional validation work will be considered.

---

[1] Yess, NJ (1993). U.S. Food and Drug Administration Survey of Methyl Mercury in Canned Tuna. *Journal of AOAC International*, Vol. 76(1):36-38.

Comment: "Regarding model limitations, the authors note in their *Risk Analysis* paper that species consumption patterns for each consumer may be more highly correlated than is specified in the current model. Some additional exploration with sensitivity analyses would be useful."

Response: We agree that additional work could be done in this area. In particular, the 30 day fish consumption frequency data can be used to capture the variation among individuals of the variation in seafood consumption habits. It does appear that some frequent seafood consumers eat one particular species consistently, while others eat a wide variety. These data may provide a basis for differentiating the degree of interindividual vs intraindividual variation on a species by species basis. We are working on a model that is more closely integrated with the NHANES survey.

Comment: A scenario should be included that reflects no consumption of albacore (as opposed to no consumption of medium group fish.

Response: The current draft of the manuscript for publication includes a scenario that limits consumption of albacore to 6 oz., but does not include one with no albacore consumption. We expect that elimination of albacore consumption will have a very minor effect on the blood mercury predictions.