

FDA and EPA's Response to External Peer Review on the FDA-EPA's Technical Information on the Development of Fish Consumption Advice

I. INTRODUCTION

The Food and Drug Administration (FDA), in coordination with the Environmental Protection Agency (EPA), has prepared a draft fish consumption advice document for methylmercury. The advisory document updates the 2014 draft consumption advice and recommends that women who are pregnant (or might become pregnant) or nursing and anyone who prepares food for young children eat certain amounts and types of fish in order to improve health and developmental outcomes while minimizing risk from methylmercury in fish. Fish species vary in the extent to which eating the fish poses a risk of methylmercury exposure to the consumer. To support updated advice to consumers on the consumption of several fish species, FDA and EPA developed a method to categorize fish species into consumption frequencies that will be linked to recommendations that minimize the risk for such exposure while encouraging fish consumption.

Below are the names and affiliation of the peer reviewers:

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II. CHARGE TO REVIEWERS

Charge Questions:

1. The grouping of fish into “categories” for frequency of consumption is based on the mean mercury content for species of commercially available fish, as compiled by FDA, and the EPA IRIS reference dose (RfD) of 0.1 µg/kg/day for methylmercury.
 - a. Do you agree that these mean mercury concentrations are appropriate to use to categorize the mercury levels in the fish species? If not, what alternative measure of mercury concentration should we consider, and why?
2. The Technical Information uses a mean body weight of 75 kg for pregnant women based on EPA Exposure Factors Handbook (2011), with support from 2003-2010 NHANES data for pregnant women of 78 kg. For children, we used female body weights because they tend to weigh less than males (CDC 2012 Anthropometric Reference Data for Children and Adults).
 - a. Is the use of the mean body weight for pregnant women and the mean body weight for children from age 2 through 18 appropriate and reasonable in developing recommended consumption frequencies? If not, please explain and propose an alternative approach.
 - b. Please comment on the appropriateness of keeping pregnant women’s and children’s exposure to mercury at or below the RfD on a weekly scale in the analyses.
3. The Technical Information relies on mercury levels in commercial fish and shellfish in FDA’s monitoring database (found at <http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm115644.htm> and <http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm191007.htm>).

This database contains data for 66 commercial fish species over a period of decades (1990-2012), and is supplemented with data from the 1978 National Marine Fisheries Service (NMFS) report and the 2000 Gulf of Mexico Report (as noted in the database). In the analysis we grouped some similar fish types together, such as canned and fresh/frozen albacore tuna and freshwater and ocean perch, and ended up with 64 fish types that were grouped into consumption categories.

FDA evaluated available FDA mercury concentration data in fish species from the past 20 years to determine: (1) trends for mercury levels over time in each of the three consumption categories (best, good, avoid); and (2) the arithmetic mean mercury concentration for each fish species and 95% bootstrap confidence intervals of these means. Overall, there was no significant trend for mercury concentrations over time in each fish category (i.e., no statistically significant increase or decrease; see FDA memo 2/2/16).

FDA considered two other datasets of mercury in commercial fish: Karimi *et al.* 2012 and USDA (Cladis *et al.* 2014; see FDA Analysis of Summary of Mercury Commercial Fish Data, 1/29/16).

- a. Do you agree that the FDA data are appropriate to use to develop mercury concentration rankings, or categories, for the fish categories listed in the table? If not, what alternative data should we consider, and why?
- b. Should the agencies consider other fish species-specific mercury concentration data when generating this table? If yes, what data would you recommend?
- c. Please comment on the limitations to the data used that could impact the scientific bases for the fish consumption categories. For example, is there a reason to believe the data do not accurately reflect current levels of methylmercury in the fish species evaluated? If there are data limitations, can you suggest ways that they could be articulated in the Technical Information?

III. SUMMARY OF PEER REVIEWER COMMENT AND FDA-EPA RESPONSE

General Impressions

Overall, the reviewers agreed upon the necessity of mercury fish advice for pregnant women, those trying to get pregnant, and children, to encourage fish consumption while helping to avoid mercury. They were generally supportive of the technical information and methodology used to support the scientific basis for the fish consumption recommendations. The reviewers made suggestions to improve clarity, transparency, and presentation, and to enhance the scientific underpinnings of the fish advice. They suggested supplementing the FDA data on mercury levels in seafood with other published sources to support the fish categorization for species with small sample sizes and/or large variability in mercury levels.

Reviewers provided various suggestions of where additional details could be added to aid the reader and support the conclusions.

Question 1. Use of Mean Mercury Concentration in Fish

Two of the reviewers believed that using the mean mercury concentration in fish was sufficient for the purpose of the advice to limit undesirable mercury exposure to vulnerable populations, while promoting consumption of fish lower in mercury. The other reviewer expressed the concern that by using the mean, half the people following the advice would have a higher exposure.

Reviewers noted the large variability in the mercury data for some fish species and made recommendations to address this concern, with one reviewer suggesting that the suitability of the data

for the purpose of the advice needed to be better explained. One reviewer suggested including a statement about the variability of the data, saying the estimated mean mercury concentration could be under or over- represented in different fish depending on the number of fish representing that species. This reviewer suggested providing some measure of dispersion to acknowledge the differences in standard deviations. Another reviewer suggested using the 95th percent upper confidence limit on the mean, especially for fish species with small sample sizes where the mean cannot be estimated as reliably. This would provide a way to increase the reliability of the data and become more protective, while considering the smaller sample size for some species. Another reviewer expressed concern over how protective the advice is based on the mean, and proposed looking at the percentage of values in measured data that are above the estimated mean value.

One reviewer recommended that the advice be more explicit about which fish data are representative of the commercial fish population that would reach children and pregnant women. This reviewer also requested more details on the bootstrap method used to conduct the confidence bounds.

FDA-EPA Response:

We appreciate the reviewers' comments regarding the use of the mean mercury concentration in fish. The reviewers generally endorsed the use of the mean, while communicating a need for: 1) augmentation of the number of samples for some fish species, and 2) application of other measures to assure that the advice is protective. In response to the reviewers' comments, we implemented the following specific measures:

- We added text to explain that the advice is now based primarily on FDA data, supplemented with several other sources to ensure a robust sample size sufficient to support the development of the advice.
- We sought out additional data from other published sources [Karimi et al. (2012), EPA's Mercury in Marine Life Database (2003), EPA NCA/NCCA data, Health Canada (2007), Cladis et al. (2014)] to increase the number of samples used in determining the appropriate fish category. Some fish were moved into a more restrictive category (e.g., Best Choices to Good Choices) based on consideration of the supplementary data for the species in question and/or the 95th percent upper confidence interval on the mean.
- In a few cases, the supplemental data supported keeping the fish in a category based on the mean level.
- Fish that did not have sufficient data (i.e., fish with < 30 FDA samples, and no additional published data) were removed from the advice.
- We confirmed all fish on this advice are commercially available.

We expanded the discussion in the technical appendix to identify the several supplemental mercury fish data sources that were used to categorize the fish, modified the sortable fish table to include the sample size and 95th percent confidence intervals on the mean, and provided more information on the bootstrap method used to determine the confidence bounds.

Question 2. Use of Mean Body Weight for Women and Children

2.a. Appropriateness of the body weight for pregnant women and children

Reviewers agreed this was a reasonable approach for the general population of pregnant women and children. One reviewer suggested the advice explicitly state that those women who weigh more or less than average should adjust their intake of fish accordingly. Another reviewer mentioned the population of Asian women, who generally have a lower average body weight. This reviewer cited a study conducted by Buchanan et al. (2015) that found higher concentrations of mercury in hair samples of Asian women were associated, in some degree, to fish consumption.

One reviewer recommended considering advising women who consume fish regularly to seek testing for mercury before attempting to become pregnant, citing successful implementation in Wisconsin documented by Knobeloch et al. (2011).

FDA-EPA Response:

We appreciate the reviewers' comments and support regarding the appropriateness of body weight used to develop the advice. We have added language to the Questions and Answers document that advises women who weigh less than average to adjust their intake of fish accordingly. While mercury testing could be useful in some cases, it is beyond the scope of this advice, which focuses on broadly applicable information for fish consumers.

2.b. Appropriate use of RfD on a weekly scale

All reviewers agreed that keeping pregnant women's and children's exposure to mercury at or below the RfD on a weekly scale is a conservative approach and prudent measure to protect public health.

Two reviewers mentioned the uncertainty of the window of developmental vulnerability, and believed that using the RfD was a conservative practice to protect the developing fetus. Another reviewer commented on the passage of mercury from the mother to the developing fetus through the bloodstream and thought that, while the RfD may not fully account for this transition, its use in this advice is still a conservative approach.

One reviewer highlighted that the applicability of the RfD to children's exposures after birth is unknown, but that it is prudent to use the RfD for assessing children as their nervous systems continue to develop into early adulthood.

FDA-EPA Response:

We appreciate the comments and the agreement that keeping pregnant women's and children's exposure to mercury at or below the RfD on a weekly scale is a conservative approach and a prudent measure to protect public health.

Question 3. Use of FDA Data

3.a. Appropriateness of FDA data in developing mercury concentration ratings

One reviewer completely agreed with the use of FDA data in developing mercury concentration categories, while one reviewer agreed the FDA data appear appropriate where there is a reasonable number of samples. The third reviewer expressed some reservations and requested additional explanation to support the use of FDA data in developing the advice.

One reviewer questioned the value of presenting estimated mean levels for fish species with small sample sizes because of the large uncertainty. To address this issue, this reviewer suggested that FDA-EPA supplement their data with the EPA National Coastal Assessment (NCA) and National Coastal Condition Assessment (NCCA) data.

Another reviewer indicated that FDA-EPA should clarify how they determined the FDA has sufficient data to allow for the development of specific advice. Additionally, this reviewer requested further explanation for grouping the fish into categories in a time trend analysis, noting that it creates more noise in the analysis.

FDA-EPA Response:

We thank the reviewers for their comments on the use of FDA data in developing mercury concentration ratings. As suggested, the technical information identifies additional supplementary data sources (Karimi et al. 2012, EPA's Mercury in Marine Life Database (2003), EPA NCA/NCCA data, Health Canada (2007), Cladis et al. 2014), and other considerations that support the fish category and recommended fish servings per week. After considering these supplemental sources, we are confident that the sample size data are sufficient to support this advice and address the peer review comments. We added additional text to the technical information to clarify that for any fish species with fewer than 30 samples in FDA's dataset, we examined other published sources to categorize the fish.

The time trend analysis was prepared to show that mercury levels in fish have been fairly stable over time. The fish were grouped to increase sample size for improved statistical reliability.

3.b. Consideration of other fish species-specific mercury concentration data

While one reviewer felt the FDA data used was sufficient, the two other reviewers believed comparison to other data would be beneficial to improve the confidence in the results. One reviewer noted limitations to FDA data, and believed that a comparison using other composite samples would allow for improved validity and support for the advice. One reviewer specifically notes the benefits of using EPA NCA/NCCA data for the North American Lobster, which would provide a sample size of 74 composite samples as compared to FDA's 9 samples. The reviewer believes the EPA lobster data collected in Maine are appropriate to consider because 85% of the lobster consumed in America comes from Maine.

FDA-EPA Response:

We appreciate the reviewers' comments regarding fish species-specific mercury concentration data. The technical information now identifies additional data sources [Karimi et al. (2012), EPA's Mercury in

Marine Life Database (2003), EPA NCA/NCCA data, Health Canada (2007), Cladis et al. (2014)] and other considerations that support the fish categorization and recommended fish servings per week.

We combined the spiny and American lobster FDA data to increase the sample size to n=22, and considered data from the EPA NCA/NCCA and Health Canada to support the lobster category.

3.c. Limitations to the data that could impact scientific bases for consumption categories

One reviewer recommended that FDA-EPA evaluate the fish data in Karimi et al. (2012) further, especially for 8 or 9 fish species for which the advice might be affected. Another reviewer reiterated the limitation of the small sample size for some fish in the FDA data, and recommended the use of the upper confidence limit on the mean, and questioned the value of providing advice on fish with limited data. Additionally, this reviewer suggested including the sample size and upper confidence limit in the sortable table.

Another reviewer mentioned again that FDA-EPA need to better explain the suitability of the FDA data for supporting the fish advice. That reviewer questioned whether the data support reporting category thresholds with two significant figures.

Because fish size is an important indicator of mercury concentrations, one reviewer wondered how fish size might compare to fish species, and questioned if the advice should advise women to eat small fish, rather than list advice by species. This reviewer noted success with an overall strategy of advising women to eat fish lower in mercury, but questioned whether the data support providing advice on individual fish species. The reviewer also suggested more point of use testing and labeling of fish containing mercury.

One reviewer also added that the “good” category seems overstated, because some fish have confidence bounds for mercury that overlap the “avoid” category. Instead, this reviewer suggested using “acceptable.” One reviewer suggested the advice also include the full scientific names and images for fish species to ensure proper comparisons because there are a wide variety of names used in the different studies.

FDA-EPA Response:

We appreciate the recommendations from the peer reviewers. As discussed previously, we further evaluated the Karimi et al. (2012) data, and used these data, along with other supplementary sources to augment the FDA data. Some fish were moved into a more restrictive category (e.g., Best Choices to Good Choices) based on consideration of the supplementary data for the species in question and the 95th percent upper confidence interval on the mean. Fish that did not have sufficient data from any source were removed from the advice. The distinction between the categories has been refined through consideration of additional data as described above. Most of the mercury fish data are reported to three or four significant figures, so we believe this supports the use of two significant figures for the category thresholds in the advice.

While we appreciate the suggestion to include the full scientific names and images for fish species in the advice, we are concerned that this information would not be useful to consumers in selecting fish at

point of purchase. The suggestion to provide for point of use testing and labeling is beyond the scope of this advice.

IV. SPECIFIC OBSERVATIONS ON THE FDA-EPA FISH ADVICE: TECHNICAL INFORMATION

Specific comments and concerns were addressed and text changes were made to the technical information.

Comments to Improve Presentation of Technical Information

All of the reviewers felt the clarity and organization of the presentation could be improved. One reviewer suggested re-organization of the document to start with how we derived the categories, then equations, then factors used in equations, and screening values, followed by the sortable fish table. In reference to the sortable table, one reviewer suggested including the sample size and upper confidence limit, and another reviewer suggested adding the frequency of intake, while also distinguishing between 2 and 3 servings. Another reviewer suggested that the table have a more specific name to the target population, and some explanation as to its purpose. One reviewer requested an expanded introduction and another additional text when transiting from “category” to “screening level.”

Two reviewers, acknowledging the materials they were given were part of a larger project, thought the documents should be able to stand alone. For example, they thought key parts of the message should be reiterated in the technical document and table that contains the recommended consumption frequencies.

One reviewer suggested that ounces be included along with serving sizes throughout the document.

One reviewer suggested clarification for the term “maximum” amount of mercury that could be in fish, when the advice is based on averages.

One reviewer noted it is confusing to report mercury levels in the tissue as both $\mu\text{g/g}$ and ppm.

FDA-EPA Response:

We appreciate the reviewers suggestions to improve the presentation of the technical information. We have adopted a number of the peer review recommendations, including an improved introduction, the suggested re-organization, and other modifications to improve clarity. Furthermore, the sortable fish table was updated to include the 95th percent confidence intervals on the mean, sample size and recommended fish categories. The technical information identifies additional data sources [Karimi et al. (2012), EPA’s Mercury in Marine Life Database (2003), EPA NCA/NCCA data, Health Canada (2007), Cladis et al. (2014)] and other considerations that support the fish categorization and recommended fish servings per week.

Comments on Clarifying Target Population

Two reviewers felt the technical information should explicitly state the target populations (children, pregnant women and those trying to get pregnant), and specify that the advice does not extend to women outside of these categories or to men. One reviewer thought the advice did not provide sufficient information for those who wish to consume fish frequently and suggested that pregnant women who want to eat a lot of fish every week choose from the very low mercury group. That reviewer also thought it was important to highlight that consumers should vary the type of fish they consume.

FDA-EPA Response:

We have added text to the technical information to clarify that this advice is for women of childbearing age, pregnant and breastfeeding women and parents and caregivers of young children. With regard to varying the type of fish they consume, other advice materials stress eating a variety of fish lower in mercury.

As stated in the Question and Answers that accompany the advice, “This advice is specifically for women who are pregnant, might become pregnant or are breastfeeding, and for young children, but everyone can follow this advice.”

Comments on Children’s Fish Consumption

Two reviewers felt that the advice “unduly limits intake” of fish by children, and that the health benefits offered from consumption of fish should be highlighted when offering the advice. Additionally, another reviewer noted that children were only advised to eat fish from the “Best Choices” category, and requested further explanation for the limited intake for children but not for pregnant women. One reviewer noted that evidence on the adverse neurodevelopmental effects of mercury on children is lacking.

One reviewer made suggestions to improve the figure in the technical information on children’s portions to improve clarity because it is based on 2 meals/week and the guidance is per meal. The reviewer also suggested the text include “Age 2: 1 ounce per meal or 2 ounces per week.” This reviewer also questioned why the children’s guidance is based on maximum mercury in fish, whereas the pregnant women guidance is based on averages, and suggested that this needs a better explanation.

FDA-EPA Response:

We appreciate the recommendations from the peer reviewers and we agree that the advice should highlight the health benefits offered from consumption of fish. For children, we provided a range of recommended fish intake that considers both calorie need and keeping exposure to mercury below the RfD for children as they grow. The children’s portion sizes should be smaller than adult portions and right for a child’s age and physical activity level. We recommend children eat a variety of fish 1-2 times per week, and emphasize fish low in mercury. FDA-EPA agree with the concern of the reviewer who observed that although the applicability of the RfD to children’s exposures after birth is unknown, it is prudent to use the RfD for assessing children as their nervous systems continue to develop into early

adulthood. In addition, selecting fish from the Best Choices category assures that children receive the benefits of consuming fish in portions consistent with their calorie needs without reducing portion size to keep their mercury intake below the RfD.

While the commenter asserts that the children's guidance is based on maximum mercury in fish, in fact it is based on the highest average mercury level, and the technical information was clarified to reflect this information.

Comments on Serving Size

Two reviewers requested more information on the basis of the 4 oz serving size, and thought this seemed low. One commented that many people use a 6 oz serving size.

FDA-EPA Response:

We thank the reviewer for this comment and have expanded the text to include more information on the basis of the 4 oz serving size.

The 4 oz serving size is based on the FDA Reference Amount Customarily Consumed (RACC) for fresh or frozen fish consumed without sauce (e.g., plain or fried fish and shellfish, fish, and shellfish cake), which is 85 g for fish on the cooked basis (equivalent to 110 g on the raw basis)

(http://www.ecfr.gov/cgi-bin/text-idx?SID=fc8a10331e1e0e7210be26e86ae512fb&mc=true&node=se21.2.101_112&rgn=div8). This RACC was determined based on analysis of numerous factors, including the mean, median, and mode of fish intakes reported in the What We Eat in America (WWEIA)/National Health and Nutrition Examination Surveys (NHANES) for ages 4+ years. RACCs (e.g. 85 g for cooked fish, 110 g for raw fish) are used as the basis for nutrient declarations on Nutrition Facts panels on food packages, and to use any other basis for categorizing fish based on mercury contents could be confusing to consumers. It should be noted that mean/median/modal amounts of fish consumed as part of a mixture would be much lower than four ounces per eating occasion.

In addition, the 4 oz serving size is consistent with the *Dietary Guidelines for Americans 2015* (<http://health.gov/dietaryguidelines>) and USDA's MyPlate guidelines (<http://www.choosemyplate.gov/ten-tips-eat-seafood>) which recommend consumption of 8-12 ounces of a variety of seafood per week. This is equivalent to 2-3 four-ounce servings (raw basis) per week.

Data in a publication by Tran et al. (2012) indicate that 85 g cooked finfish is well above the median amount consumed per eating occasion by women of childbearing age (16+ y), and that 85 g cooked shellfish is well above the 75th percent intake per eating occasion by this age group.

Comments on the RfD

Two reviewers suggested additional text to explain the RfD to emphasize this is protective of the critical window of development for a fetus during pregnancy, and not a lifetime exposure. One reviewer suggested the including the text, "this means that to experience harm you would have to consume an

amount above the RfD not during a single meal or a single week, but every week over time.” One reviewer indicated the RfD may not be adequately protective for prenatal exposure.

FDA-EPA Response:

FDA and EPA underscore their approach in the advice of keeping weekly exposure to mercury from fish consumption below the RfD, and additional text has been added to the technical information for further clarification.

Comments on Consumption of Only Cooked Fish

One reviewer suggested the document highlight the importance of not eating raw fish when pregnant, and that this would not apply to others who might eat sushi or sashimi. Another reviewer indicated the statement that the advice recommends the consumption of only cooked fish seems out of context on page 1.

FDA-EPA Response:

The Questions and Answers that accompany this advice address the issue regarding raw fish. We reorganized the technical information, and clarified the target audience as noted previously.

Comments on Health Protectiveness of Advice

Two reviewers were unclear what “cautious and highly protective” meant and did not agree with the use of this term. One reviewer stated that the 10-fold uncertainty factor in the RfD for variability may not be sufficient.

FDA-EPA Response:

FDA and EPA endeavored to follow an approach in the advice that is conservative and health protective with regard to the adverse neurodevelopmental effects of mercury. We edited the technical information to address this comment. The RfD includes a 10-fold uncertainty factor to allow for variability among individuals and groups, including individuals who are not pregnant.

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