

External Peer Review Report of FDA-EPA's

*Technical Information on Development of
Fish Consumption Advice*

September 16, 2016

Versar Contract No. HHSF223201210011B

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I. INTRODUCTION

The Food and Drug Administration (FDA), in coordination with the Environmental Protection Agency (EPA), has prepared a draft fish consumption advisory document for methyl mercury. The advisory document updates the 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. The purpose of this external peer review is to evaluate the scientific content of the following documents:

1. FDA-EPA Fish Advice: Technical Information (*Draft text for web page – June 28, 2016 version*), and
2. Fish Table for peer review (*A table showing fish species categorized into recommended consumption frequencies for a 4-ounce serving (smaller serving sizes for children)*).

The following background documents that support the main documents were also provided:

3. FDA Memo dated 2/2/16 “Trend Analysis and Evaluation of FDA Mercury Concentration Data”
4. Cladis *et al.* 2014 and Karimi *et al.* 2012 fish tissue mercury documents and FDA analysis of these data in “Summary of Mercury Commercial Fish Data” (1/29/16)
5. IRIS summary sheets for methylmercury RfD
6. Excel spreadsheet with Fish Advice Calculations
7. Peer Review Bibliography

For this peer review, three experts were selected to answer three charge questions and to evaluate and provide written comments on: FDA/EPA's *Technical Information on the Development of Fish Consumption Advice* and the Fish Table for Peer Review.

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. INDIVIDUAL REVIEWER COMMENTS

Reviewer #1

Peer Review Comments on FDA/EPA's *Technical Information on the Development of Fish Consumption Advice*

Reviewer #1

I. GENERAL IMPRESSIONS

It would be helpful to know what will be the text that leads into the table, which will frame the experience of users. For example, lead-in text that highlights the large number of fish choices that are advised for regular consumption might have a different impact than lead-in text that focuses on risks. Also, I think that it will be important to highlight the advice that consumers try to vary the type of fish they consume. I believe this information is in the draft advice. However, I also think it is important that each piece of the advice should be able to stand alone also, since, for example, some doctors may just print out the list itself and hand it to patients, or individuals may print and post it for personal use. Thus, it would be worth reiterating some of the key parts of the message on the table and technical document, too. For this reason, it will also be important to specify on the table and in the technical appendix that this advice is only for women of childbearing age who may become pregnant or who are breastfeeding, and young children, and specify clearly that there are not recommended fish intake limits for older women or men.

I think the advice for children unduly limits intake. It is based on the amount of mercury in the highest fish group among the best choices, whereas other commonly consumed fish in this best choices group has a very negligible amount of Hg that would not result in excess intake even with much greater amounts. I am not aware of any data that show any relationship between child Hg intake and neurocognitive outcomes – so why the extra protection for this group? Given other health benefits of fish intake for children – in addition to beneficial nutrients, evidence suggests that consumption in infancy prevents food allergies – I think the charge is to justify restriction rather than use the cautionary principle here.

I find it hard to go back and forth between the two tables – if I want to figure out which of the fish within the medium intake 1-2 serving/week group is lower or higher in mercury, I think that is hard to determine, even with the sortable table. I suggest adding frequency of intake as an additional column to the mercury concentration table.

Generally, I don't think this guidance provides enough information for those who wish to consume fish frequently. Many individuals and groups make fish a routine part of the diet, and I think that it would be important for this guidance to acknowledge and affirm as well as better accommodate those habits, for example, by suggesting that pregnant women who want to eat a lot of fish every week choose from the very low mercury group (and consider guidance about what that list might be, c.f. Groth. *Env Res* 2010.)

II. RESPONSE TO 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.

1a. 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?

I agree with the use of means for overall guidance. However, in the technical document, it would be worth calling out cases where it is very likely that means under or over represent the likely amount of mercury in a given fish; for example, a very large or very small fish. Additionally, it would be helpful if the technical document provided some measure of dispersion – two fish types with the same mean values could have very different standard deviations.

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).

2a. 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.

Yes, I think using these weights is a reasonable approach. However, I also think it would be reasonable to explicitly highlight the fact that these guidelines assume average weight, and women or children who weigh substantially more or less than average might very reasonably adjust their intake up or down as appropriate.

2b. 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.

I think the reference dose is a reasonable threshold.

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).

3a. 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?

Yes, I agree with the use of the FDA data.

3b. Should the agencies consider other fish species-specific mercury concentration data when generating this table? If yes, what data would you recommend?

I am not aware of other relevant data.

3c. 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?

It would be worth additional investigation into the species that the Karimi paper found would fall into a different category compared with the FDA evaluation. The document (Comparison of FDA to Karimi and Cladis) states that “it is impossible to reproduce the mean estimates without substantial additional information from the original study authors.” However, it shouldn’t be so much work to obtain those data only for the 8 or 9 species for which guidance might be affected.

III. SPECIFIC OBSERVATIONS ON FDA-EPA FISH ADVICE: TECHNICAL INFORMATION
(Draft text for web page – June 28, 2016 version).

Page	Line	Comment
1	1	I suggest the title be modified to specify that the target audience for this information. See general comments above; e.g., instead of FDA-EPA Fish Advice it should be headed FDA-EPA Fish Advice for women of childbearing age and parents of young children
1	13	“the fish advice recommends the consumption of only cooked fish” – is this true for all ages/life stages or just for pregnant women and young children? Should nobody eat sushi or sashimi? I suggest that this sentence highlight especially the importance of not consuming raw fish in pregnancy.
3	2	I am not sure I agree that this advice is ‘cautious and highly protective’ or even exactly what that means, i.e., Highly protective of health? Highly protective of reducing exposure? If you are trying to minimize exposure to Hg then lower consumption would be even more cautious. If you are trying to maximize health, then you should explicitly consider nutrients in fish, since some fish of the same mercury level vary greatly in n-3 PUFA concentration, for example.
3	3	It is misleading to say that the advice is based on the ‘maximum’ amount of mercury that could be in fish when in fact it is based on the average amount of mercury in the fish.

Page	Line	Comment
3	6-7	Suggest some more language explaining the RfD, which is confusing to many; e.g., after this sentence you could add another saying something like: "This means that to experience harm you would have to consume an amount above the reference dose, not during a single meal or a single week, but every week over time."
4	7	The table here does not align so well with the Fish Table. How are readers able to distinguish the best choices from the good choices that are also listed for consumption at 2-3 times per week? Such information will be helpful for those who want to eat fish even more regularly, as I discuss above in overall comments.
5	5-8 and Figure	It took me a while to understand that the figure is based on weekly intake of 2 meals/week, and the guidance is per meal. Suggest you make that clearer. Otherwise from the figure I would assume 1-3 year olds should consume 2 oz per meal, etc. In the text consider "Age 2: 1 ounce per meal or 2 ounces per week"
6	15	It appears that guidance for children is based on the maximum Hg of any fish in the best choices group, whereas in general this guidance is based on averages. Why the difference for kids? See overall comment above.

IV. SPECIFIC OBSERVATIONS ON FISH TABLE FOR PEER REVIEW.

Page	Line	Comment
1	0	I suggest the header include a measure of portion size not just servings, e.g., "Number of 4-6 ounce servings per week"

Reviewer #2

Peer Review Comments on FDA/EPA's *Technical Information on the Development of Fish Consumption Advice*

Reviewer #2

I. GENERAL IMPRESSIONS

I have not checked calculations for accuracy. I did attempt to examine the basis for the 4-ounce meal size. I reviewed the provided link to Title 21 Part 101. It appears that the 4-ounce portion size is derived from Table 2 - Reference Amounts Customarily Consumed Per Eating Occasion: General Food Supply. Specifically, the row for "Fish, Shellfish, Game Meats 10, and Meat or Poultry Substitutes" provides a serving size of 110 g uncooked for entrees without sauce, e.g., plain or fried fish and shellfish, fish and shellfish cake. If this is the basis for the 4-ounce portion, the Technical Information should make this clear. If it is not, the rows in Table 2 used to support the 4 ounce portion size should be identified. Note #4 on this table indicates that FDA considered the mean, median, and mode of the consumed amount per eating occasion, but I could not identify which central tendency measure was used as the basis for the portion size. This should be clear.

Overall, I believe the Technical Information could benefit from a different order of presentation of material. I recommend you begin with the discussion of how FDA and EPA derived categories in the fish chart, then the equations, and then factors used in the calculations. The Sortable Fish Table would in my opinion best follow the presentation of the Table of screening values and how they were used to assign fish species to specific consumption categories (i.e., best, good, avoid). This would provide the reader more contexts for evaluating the Sortable Fish Table.

I recommend that the Sortable Fish Table be expanded to include the sample size and upper confidence limit on the mean. I recognize you provide this on other links, but it is important to make it clear that some of your estimates of mercury concentration in fish species are based on limited data.

The basis for recommending children (and what ages?) only eat fish from the "best choices" category is not adequately explained, and it is not clear how the Chart and last table (Child's serving size...) inform this recommendation. I would think the public will wonder why shouldn't pregnant women only eat fish from the "best choices" category, if that is the recommendation for children. I found it difficult to follow the derivation of values presented in the chart, even after re-reading the text several times.

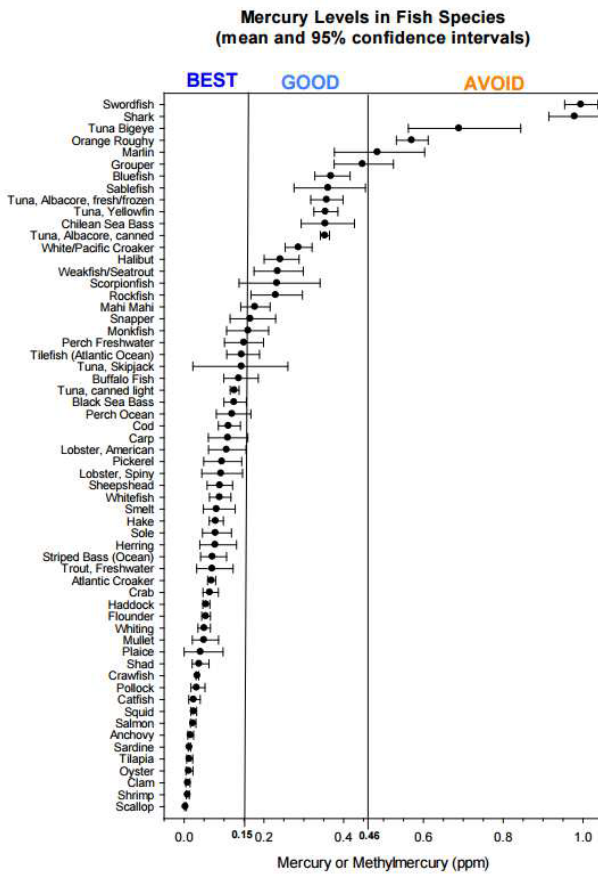
II. RESPONSE TO CHARGE QUESTIONS

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.

1a. 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?

I agree that the mean is an appropriate point estimate to describe mercury levels in fish species for purposes of developing fish consumption advisories. However, I recommend use of the 95th percentile upper confidence limit on the estimated mean. For some fish species, there are hundreds of samples and the estimated mean and upper confidence limit on the mean can be expected to be of similar magnitude (e.g., cod, canned tuna, swordfish, shark). Yet for other fish species sample sizes are much smaller and as a consequence the mean cannot be estimated as reliably, especially for species with considerable variability in mercury levels (e.g., scorpion fish, marlin, monkfish, sheepshead, tilefish, grouper). This is apparent from inspection of Figure 4 in Fish Advice Hg Trend Memo, and reproduced below. For some species, use of the upper confidence limit on the mean would result in a different assignment to fish consumption categories. The upper confidence of the mean will provide a way to take into account the reliability of the estimated mean concentration from available data. This metric is also a fairly standard practice in the development of state recreationally-caught fish consumption advisories.

Figure 4. Estimated Mean and 95% bootstrap confidence intervals for fish species categorized in FDA/EPA Fish Advice.



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).

2a. 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.

I agree that use of age- and gender-specific mean body weight is appropriate and reasonable.

2b. 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.

Presumably your objective is providing actionable information to the public to help them keep fish in their diet while keeping their average mercury dose below levels of concern. In this context, it is reasonable to provide weekly scale information to help with decision-making around consumption of fish. A much longer time scale would challenge consumers to recall past consumption behavior. If you are going to adopt a weekly scale, making sure weekly exposures do not exceed the methylmercury RfD is a reasonably conservative practice. It may also be entirely appropriate for pregnant women so as to protect the fetus during short-term critical developmental windows. Although the RfD is generally considered a lifetime daily dose, for methylmercury, as I am sure you are well aware, the key underlying health data reflects fetal exposure during the later months of pregnancy.

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.

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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).

3a. 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?

The FDA data appear appropriate to use to develop mercury concentration categories for those species where there are a reasonable number of samples. I wonder about the value of presenting species specific data and calculating consumption advice where sample sizes are very small and estimated mean levels have significant uncertainty. I am not aware of an alternative data set other than the US EPA National Coastal Assessment (2000-2006) and National Coastal Condition Assessment (2010) programs.

3b. Should the agencies consider other fish species-specific mercury concentration data when generating this table? If yes, what data would you recommend?

The FDA data list only 9 samples for Northern American Lobster. The US EPA National Coastal Assessment (2000-2006) and National Coastal Condition Assessment (2010) programs have a significant amount of data on composite lobster samples. With a total of 74 composite samples in the EPA NCA/NCCA datasets, the average mercury level was 0.048 milligrams per kilogram (mg/kg), these data indicate mercury levels in American lobster caught in Maine waters are lower than the average presented in the proposed table. Since Maine lobster represents approximately 85 percent of all U.S. landings of American lobster, these data may be a better representation of mercury levels in American lobster in the market that that provided by the 9 samples in the FDA data. At a minimum, these data support including Northern American lobster in the “best choice” category, as is currently proposed based on just 9 samples.

3c. 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?

One limitation is the small sample sizes used to estimate mean levels for at least 15 of the fish species listed in the sortable fish table. This limitation could be made clear by providing the sample size within the sortable fish table, as well as the upper confidence limit on the mean along with the estimated mean. As discussed above, I recommend use of the upper confidence limit on the estimated mean. Also as discussed above, I question the value of providing consumption advice on fish species with very limited sampling data.

III. SPECIFIC OBSERVATIONS ON FDA-EPA FISH ADVICE: TECHNICAL INFORMATION
(Draft text for web page – June 28, 2016 version).

Page	Line	Comment
1	13-14	The statement about the fish advice recommends the consumption of only cooked fish seems out of context here.
3	14	The shift from “category” to “screening level” is abrupt and additional text would help the reader.
3	40	See discussion above about serving size of 4-ounces.

IV. SPECIFIC OBSERVATIONS ON FISH TABLE FOR PEER REVIEW.

Page	Line	Comment
1	1-42	Recommend you distinguish between species than can be consumed two 4-oz meals per week (i.e., 8 oz per week) versus three 4-oz meals

Page	Line	Comment
		(i.e., 12 oz per week).

Reviewer #3

Peer Review Comments on FDA/EPA's *Technical Information on the Development of Fish Consumption Advice*

Reviewer #3

I. GENERAL IMPRESSIONS

The two documents provided for review consisted of text that is apparently to be posted to a web site. The first was entitled "FDA-EPA Fish Advice: Technical Information" (7 pages) and the second was an untitled document with a table on it with three columns denoted as: Line, Fish Type, and Servings Per Week.

Accuracy: The information provided seems to be accurate with regard to cited sources.

Clarity of presentation: Overall these documents were baffling as presented. This was no doubt because they were intended to be a portion of a larger web site that we did not see. They are not successful as standalone explanations. It needs attention from a technical writer not previously embedded in the project who can put it together in a logical way that will make sense to someone not already familiar and be suitable for the web if that is in fact the goal.

Soundness of conclusions (and approach): the overall intent of this project is positive and in keeping with the evolution of advisories. It is desirable to encourage women to consume fish and help them to avoid mercury.

However, it is not at all clear that the data available provide enough certainty in predictions of concentrations of mercury in fish to allow specific advice to be given for all of the types of fish in the database. The implications of using a central tendency estimate and of uncertainty about the overall distribution are troubling and leave open the potential for significant over-exposure of the pregnant women for whom this advice is most important. The approach seems to have been selected without regard to the capability of the data.

II. RESPONSE TO 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.

1a. 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?

The charge questions seem to skip over the first step which would be to assess the validity of the data to allow for accurate predictions of mercury concentrations for the more than 60 fish types specifically addressed.

The overall purpose is to provide more guidance to women who are or may become pregnant and to people who feed children about how to identify fish with relatively safer mercury concentrations. The premise of the advisory draft developed by EPA and FDA in 2014 was to

encourage women and children to eat fish because it has health benefits while also warning them to avoid mercury. Methylmercury is a known neurotoxicant and neurodevelopmental toxicant that passes from a mother to a child in utero through blood. The 2014 draft advisory referred somewhat vaguely to fish that were generally lower in mercury and mentioned shrimp, pollock, salmon, canned light tuna, tilapia, catfish, and cod as good choices. It also identified four types of fish to avoid.

This project is developing guidance for more kinds of fish, effectively creating some kind of a middle category between fish that are recommended with enthusiasm and fish to be avoided. This would be consistent with what the Children's Health Protection Advisory Committee of US EPAⁱ recommended and what many states are doing in their advisory programs for sport or subsistence caught fish (and locally important commercial fish in some cases). The two part message is that it is good to eat fish but important to choose the right ones from those available in the market. This is consistent with the development of the field overall.

The question that seems to have been skipped is to determine for which fish FDA has sufficient data to allow for the development of specific advice. This is a critical issue. To give advice based on expected concentrations in fish, it is essential to accurately predict what concentrations are going to be in fish in the market place.

Maybe I am missing something, but I don't see where these authors have considered or addressed this central issue. This is a threshold issue that would normally be considered before discussion choices for metrics.

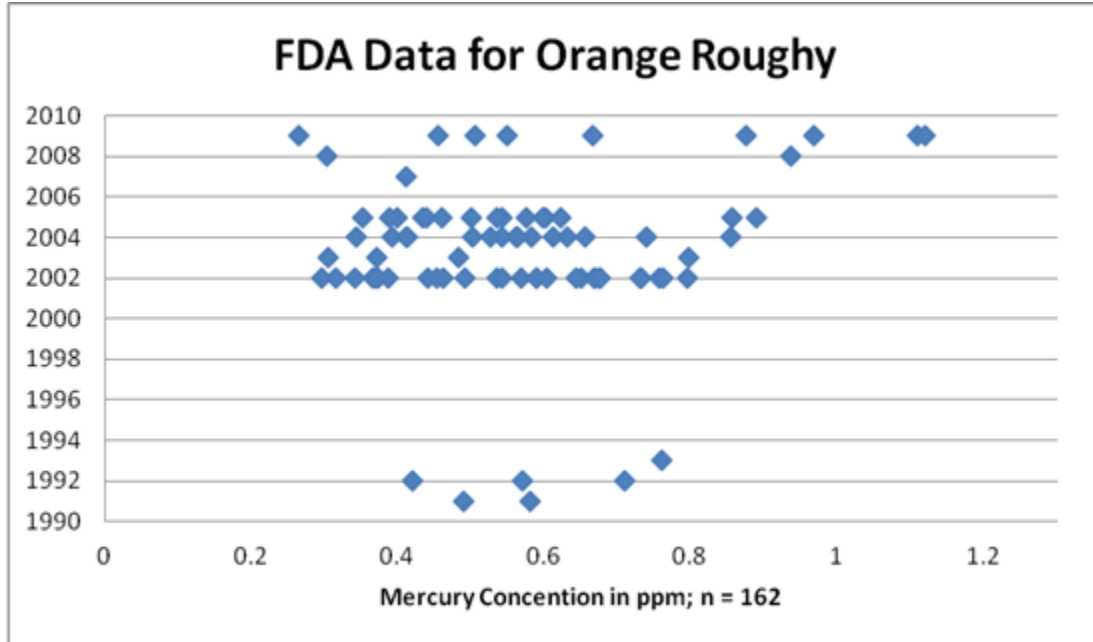
Do the authors conclude that the sampled values represent the population of fish sold through commercial channels and consumed by women and children in the US? This should be discussed and the conclusions substantiated to allow for confidence in the values used in the ensuing public health advice. It almost seems as if the mere presence of data in a database was viewed as evidence of validity for this purpose.

Reviewers don't have much information to use to assess this. There are no geographic identifiers provided with the data or discussion of sampling strategies.

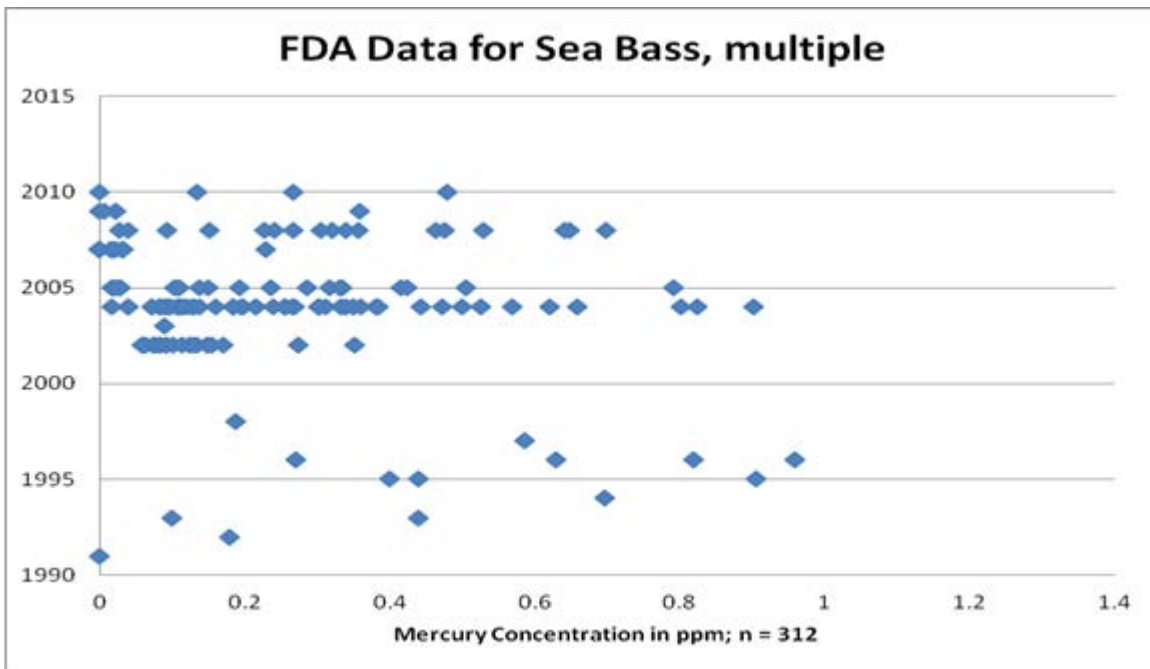
Using a mean to represent fish concentrations

Metrics are evaluated in terms of what they represent about the phenomenon being measured and how they respond to the information needs of the audience. In this case, mean values for measurements of contaminants in biota is informative if the distribution is reasonably normally distributed and if the attribute of concern is the central tendency.

If consumption advice is based on the mean, then, in a normal distribution, you would expect half of the people following the advice to have a higher exposure. For health advice, typically an effort is made to protect more than half of the people from an undesirable exposure. So it would not typically be considered to be a health protective approach. It would be informative to look at what percentage of values in the measured data are above the value estimated as the mean. In the example shown below for Orange Roughy, more than 50% of values are above the cut point, some of them significantly so. I would argue that this fish, for example, would belong in the "avoid" category even though its mean value may be in the so-called "good" category.

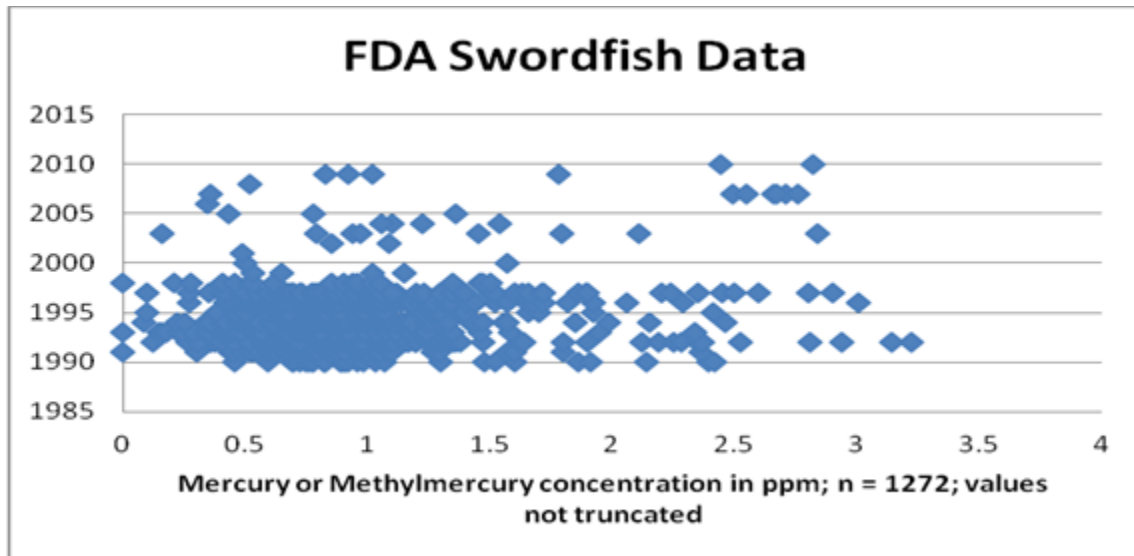


Similarly, the data for Sea Bass show a significant percentage of values above the cut point for a “good” ranking.



It seems more appropriate to select a value at that would be protective for more of the target population.

The document mentions use of a bootstrap method to construct confidence bounds and shows a confidence intervals generated through this method. It does not explain enough how the bootstrapping was done to allow for comment. (Rather, R code is provided without explanation.)



The distribution of swordfish data raises the additional question about whether an action stronger than an advisory is warranted. Note that the scale is extended due to the higher values reported compared to the other fish. It seems that a lot of fish above the allowable level is allowed onto the market.

ⁱ Letter from Sheela Sathyanarayana, Chair, Children's Health Protection Advisory Committee to Gina McCarthy, Administrator, US Environmental Protection Agency, December 2, 2014.

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).

2a. 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.

Using the cited body weight estimates is a common approach for adult women. For the general population, it is appropriate. Again, as an averaging method, it will not be protective for a portion of the population. In this case, those at greater risk would be those with lower body weights than the defaults used here.

There may be concerns for Asian populations. Recent studies are showing higher concentrations of mercury in blood for Asians. Mortensen et al. recently reported higher concentrations for Asians for mercury in whole blood from NHANES. Buchanan and colleagues measured concentrations in hair of Asian women around Chicago and found relatively higher concentrations, associated to some degree with fish consumption. Asian women as a group have a lower body weight than the overall average, which increases the significance of any given dose of mercury. It would be worth considering whether this is something that should be addressed in the advisory.

Some are recommending that women who consume fish regularly seek testing for mercury at the time that they consider becoming pregnant, and this may be something to consider as well. Such an approach was successfully applied in Wisconsin as noted by Knobeloch et al. Obviously there are differences between doing this in a state and addressing it in a national advisory, but it is something to evaluate to recommend for those who may be outside the norms for which the advisory is designed.

- Mortensen ME, Caudill SP, Caldwell KL, Ward CD, Jones RL. Total and methyl mercury in whole blood measured for the first time in the U.S. population: NHANES 2011–2012. *Environmental Research*. 2014;134:257-64.
- Buchanan S, Anglen J, Turyk M. Methyl mercury exposure in populations at risk: Analysis of NHANES 2011-2012. *Environmental Research*. 2015;140:56-64.
- Buchanan, Susan MD, MPH; Targos, Loreen MS; Nagy, Kathryn L. PhD; Kearney, Kenneth E. MS; Turyk, Mary. Fish Consumption and Hair Mercury Among Asians in Chicago. *Journal of Occupational & Environmental Medicine*. 57(12):1325-1330, December 2015.
- Knobeloch L, Tomasallo C, Anderson H. Biomonitoring as an Intervention Against Methylmercury Exposure. *Public Health Reports*. 2011; 126(4): 568-74.

2b. 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.

It is well established that prenatal exposure to mercury can be damaging to children. It is also established that mercury passes in the blood of a mother to the blood of her developing child. It is likely that the RfD does not fully account for this due to under-estimates of the levels of mercury in the fetus, as noted some years ago in papers by Rice et al. and others.

The exact window of vulnerability is not yet established. However, consuming fish with mercury in it can create spikes in blood mercury. This would then be conveyed to a child. Since the duration of exposure necessary for a child to be affected by mercury in the mother's blood is not known but could be short and since the RfD is likely too high anyway, it seems quite prudent and good public health action to try to keep women at or below the RfD on a weekly basis during and immediately before pregnancy.

The applicability of the RfD to children's exposures after birth is largely unknown. In general, because children's brains and nervous systems (as well as other systems) continue to grow and develop until early adulthood, it would also seem that this would be a prudent approach.

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).

3a. 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?

As noted elsewhere, it seems necessary for the project authors to explain how they conclude that the FDA data should be used to characterize the mercury concentrations in fish for purposes of developing an advisory.

With regard to the time trend analysis, I do not understand the reasons for grouping the fish together into the three categories and then trying to assess trends. The more you throw disparate things into a group, the more noise you have.

3b. Should the agencies consider other fish species-specific mercury concentration data when generating this table? If yes, what data would you recommend?

The assumption in the document is that the best or perhaps only way to consider other data would be to create a pooled data set for statistical analysis. This seems too narrow a view. In almost any kind of data analysis, it is relevant to consider results generated by other researchers or analysts looking at the same questions. In fact, this is central to the scientific process to consider what do we know, what is not fully understood, and how does this analysis contribute to the overall knowledge base. Studies that characterize the methods well are particularly valuable to consider and allow consideration of why results might be the same or different. Comparisons could substantiate the values from the FDA data and increase confidence or point out areas where additional data collection may be needed.

Going to pooled analysis of data sets can cause as many problems as it solves due to differences in study design and implementation. However, especially given the limited evidence of validity for the FDA data, it would be valuable to compare it to other studies and assess whether reasons for any observed differences can be identified. For example, use of composite samples, would be expected to dampen variability but not to change estimates of central tendency.

3c. 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?

As noted above, the first assessment of the suitability of data for a particular purpose should come from the data owner who would be most familiar with what the data represent.

Size of fish is also an important predictor of mercury concentrations. We know that larger and older fish have higher mercury concentrations. Fish size isn't addressed in any of the data as far as I can tell. I wonder whether how fish size would compare to fish species as the predictor of mercury concentration. Would we be better off to rule out the worst fish and then advise women to eat small fish rather than to go through the species by species analysis and advice?

A second concern would be with the high degree of precision implied by the way the cut points are set up. The use of cut points with two significant figures implies a lot of precision.

It might be appropriate to consider whether other strategies may be most justifiable for some species. The overall strategy of advising women to continue to eat fish but to move toward species and sizes with lower concentration of contaminants seems to be working and resulting in the same or increased fish consumption without increased body burdens of mercury. The idea of using a universal advisory that tries to give individual women useful advice for many species of fish may be more than is scientifically justifiable to do given the data available. Perhaps greater monitoring or point of use testing for mercury with labeling could provide more accurate information to women making decisions about what fish to consume. Perhaps it would be more appropriate to simply point women toward the species where we have a high degree of certainty that mercury concentrations are low almost all of the time.

The characterization of fish in the middle category as “good” seems overstated. These fish are likely not to be good for many women who follow the advisory. Some of the fish in the “good” range have confidence bounds that go into the “avoid” range. This does not seem to be appropriate. I would encourage women to choose better options instead of eating many of these fish. I don't feel that “good” captures the likelihood that there could be risks. Perhaps “acceptable” would be a more appropriately neutral term.

Lastly, I wonder about the accuracy of the identification of the fish species among the various names used. There is a wide variety of names used in different studies and even among the FDA data. It would seem important to use better identifiers possibly including full scientific names and images for fish species to ensure that the same species are actually being compared. Perhaps this is being done, but if so it is not reflected in any of the materials that we have. The groupings seem ad hoc.

III. SPECIFIC OBSERVATIONS ON FDA-EPA FISH ADVICE: TECHNICAL INFORMATION
(Draft text for web page – June 28, 2016 version).

Page	Line	Comment
1	3 to 7	The piece needs a better introduction. This refers to terms that are not defined here and seems confusing.
1	8	The table deserves a better name and some explanation as to purpose
1	8	Here and elsewhere concentrations are reported as µg/g though in the tissue

Page	Line	Comment
		results they are reported as ppm. Please use one or the other. This is needlessly confusing.
1-2	table	This is about how the two tables compare. Perhaps the mean concentrations could be shown on the fish type table and the servings per week could be added to the fish species and mercury concentration table. Now the only way to see the whole picture is to compare both tables.
1-2	table	Do you believe that you have two significant figures for these values?
3	1	Need to define what are the “categories” and the “fish chart” There are two terms that seem to be used interchangeably – the “categories” of good, avoid, etc., and the number of servings.
3	2	I don't think that the document can claim a cautious and conservative approach in that it is using mean estimates of the fish concentrations that would lead to over exposing a significant percentage of people who follow the advisory. This is not conservative or highly protective. The 10-fold factor for variability is probably not sufficient and so should not be understood as providing a margin of safety in addition.
3	6	It is not correct to say that the RfD is understood to apply over a lifetime when effects related to pregnancy and critical windows of development apply.
3	9-11	Very confusing last sentence. Needs to be unpacked.
3	31	The reference dose may not adequately protect for prenatal exposure. This limitation was identified in 2004 but as far as I know never addressed by EPA. Because the prenatal exposures are so impotent here, this should be addressed in some fashion.
3	40	I am not an expert in serving sizes and don't follow this research, but I believe that 4 ounces is a low estimate for a serving size. Perhaps it would be best to include the ounces along with the number of servings throughout. Many people use a six ounce serving size and some use eight ounces. This would result in an over-exposure.
4	Results	Here again I think the servings should also be expressed as ounces. Do you really believe that you can distinguish these values down to two significant figures? This implies a level of accuracy that I think does not exist.
4	25	Here and elsewhere the audience for this text changes. Here it is directed to a parent, referring to “your” child.
5	graph	You can't tell from this page which column is based on “caloric need” and which on mercury. Need to use cross hatching or something so that we can see which is which. This seems very complicated.

IV. SPECIFIC OBSERVATIONS ON FISH TABLE FOR PEER REVIEW.

Page	Line	Comment
Not specified		I would put ounces on here because the exact amount matters a lot
		This needs a title and short explanation
		I think that grouper belongs in the do not eat group