DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

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Dear Ms. Houlihan and Ms. Callendar:

This letter is in response to "Information Quality Appeal Requesting Correction of FDA Seafood Advisory Entitled, "What You Need to Know About Mercury in Fish and Shellfish: 2004 FDA and EPA Advice for Women Who Might Become Pregnant, Women Who Are Pregnant, Nursing Mothers, Young Children," dated March 15, 2005, sent to Dr. David Acheson, Director of Food Safety Defense and Outreach, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration (FDA) (referred to herein as the "request for reconsideration" or RFR). In the RFR, you ask for reconsideration of Dr. Acheson's response to a Request for Correction submitted by the Environmental Working Group (EWG) dated December 22, 2003 (the Request). The Request for Correction was sent pursuant to the Information Quality Act, Pub. L. No. 106-554, § 515 (2000).

As Dr. Acheson explained in his response to your Request, the "Guidelines for Ensuring the Quality of Information Disseminated to the Public" of the U.S. Food and Drug Administration (FDA) (http://aspe.hhs.gov/infoquality/Guidelines/fda.shtml) (FDA Guidelines) provide that when the agency disseminates information in draft form, the agency may consider the request in connection with agency comment procedures. Thus, rather than responding immediately to the Request, FDA considered it as a comment on the 2003 Draft Advisory (2003 Draft Advisory) and took it and other comments by EWG, the FDA Food Advisory Committee (FAC), and others into account when we refined the 2003 Draft Advisory into the 2004 Advisory, "What You Need to Know About Mercury in Fish and Shellfish" (2004 Advisory or Advisory) (*see* www.cfsan.fda.gov/~dms/admehg3.html).

In the RFR, you challenge both Dr. Acheson's response and provisions of the 2004 Advisory. In keeping with your designation, I will handle it as a request for reconsideration to me, as Dr. Acheson's immediate supervisor and the Director of FDA's Center for Food Safety and Applied Nutrition. *See* 21 C.F.R. § 10.75 and FDA Guidelines VI.B.

Development of the 2003 Draft Advisory

Although Dr. Acheson provided much of this information in his response, I think it is helpful to set out here the history of the development of the 2003 Draft Advisory and the 2004 Advisory.

FDA and the Environmental Protection Agency (EPA) worked jointly to develop and review the 2003 Draft Advisory and the 2004 Advisory. The Draft Advisory language was developed following a series of stakeholder meetings. The Draft Advisory was then presented to the FAC in December 2003 and the comments following that meeting were used to develop the final Advisory. The background materials, transcripts, and meeting minutes, including the FAC recommendations, are provided on the web at http://www.fda.gov/ohrms/dockets/ac/cfsan02.htm.

The 2003 Draft Advisory had its origins in an advisory on the subject of methylmercury in fish that FDA first issued in the mid-1990s and had most recently revised in 2001 (the 2001 Advisory). In July 2002, FDA asked the FAC to provide recommendations on ways in which the Advisory could be improved. The FAC recommended that FDA clarify the language of the 2001 Advisory, develop a quantitative exposure assessment, and increase monitoring for methylmercury, including levels in fish, and the use of human biomarkers. The FAC also recommended that FDA and EPA issue a joint advisory and that it address both commercial fish and fish caught by sports anglers.

The agencies addressed the FAC recommendations as follows :

- FDA and EPA jointly held four stakeholder meetings between July 29 and July 31, 2003, regarding methylmercury in fish (http://www.cfsan.fda.gov/%7Edms/mehg703.html). The meetings consisted of a series of formal presentations from FDA and EPA, followed by a general discussion in which participants provided comments on the progress toward a joint advisory.
- FDA conducted focus group testing in November 2003 to assess consumers' understanding of the then-current draft of the Advisory. Changes reflecting the respondents' comments were incorporated into a new draft that was tested in focus groups in early 2004.
- The exposure assessment that FDA conducted underwent a peer review in August 2003 and was published in a peer reviewed journal. [1]
- FDA collected additional fish monitoring data from 2002 to 2003.

FDA made revisions to the 2001 Advisory in response to the above information and the FAC's prior recommendations. FDA and EPA issued the 2003 Draft Advisory on December 10, 2003.

On March 10, 2004, the FAC provided additional recommendations for the FDA and EPA to consider, as follows:

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[1] Carrington CB, Montwill B, Bolger PM. An intervention analysis for the reduction of exposure to methylmercury from the consumption of seafood by women of child-bearing age. *Regul Toxicol Pharmacol.* 2004 Dec;40(3):272-80.

- "Specifically address the impact of canned tuna on the risk [exposure] assessment.
- "More resources for research, to include; working with industry to get industry data, acquire better consumption data, the need for more fish data on species, sub species, and geography
- "Make the joint FDA/EPA advisory positive
- "Make portion size consistent between variety and frequency of consumption
- "Clarify the portion size to make it easier to understand
- "Include a list of low-levels mercury content fish that are safe to eat
- "Include a list of common names of fish (for clarity)
- "Design 1 advisory to be understood by more than just original target audience (avoid multiple advisories)
- "Include website in the advisory (for those who might want further information)
- "Reconsider what fish should be included on the 'do not eat' list[.]"

Letter, Sanford A. Miller, Ph.D., Chairman, Food Advisory, to Robert E. Brackett, Ph.D., Director, Center for Food Safety and Applied Nutrition, March 10, 2004. [2]

FDA and EPA considered these recommendations, along with other public comments, including those submitted by EWG, as they refined the 2003 Draft Advisory into the 2004 Advisory.

The 2004 Advisory

On March 19, 2004, FDA and EPA jointly released the 2004 Advisory. The purpose of the 2004 Advisory, as described in the "backgrounder" document released simultaneously, is to inform women who may become pregnant, pregnant women, nursing mothers, and parents of young children how to get the health benefits from eating fish and shellfish, while reducing their mercury exposure. The backgrounder document is available at www.fda.gov/oc/opacom/hottopics/mercury/backgrounder.html.

The 2004 Advisory provides the following three principal consumption recommendations for women who might become pregnant, women who are pregnant, and nursing mothers (referred to in this letter as "the target population") (www.cfsan.fda.gov/~dms/admehg3.html):

1. Do not eat shark, swordfish, king mackerel, or tilefish because they contain high levels of mercury.
2. Eat up to 12 ounces (two average meals) a week of a variety of fish and shellfish that are lower in mercury.

[2] Available at http://www.fda.gov/ohrms/dockets/ac/03/briefing/4010b1_Ltr%20of%20recommendation-Dr%20Miller.pdf. The letter erroneously refers to FDA's exposure assessment as a risk assessment.

- Five of the most commonly eaten fish that are low in mercury are shrimp, canned light tuna, salmon, pollock, and catfish.
- Another commonly eaten fish, albacore ("white") tuna has more mercury than canned light tuna. So, when choosing your two meals of fish and shellfish, you may eat up to six ounces (one average meal) of albacore tuna per week.

3. Check local advisories about the safety of fish caught by family and friends in your local lakes, rivers and coastal areas. If no advice is available, eat up to six ounces (one average meal) per week of fish you catch from local waters, but don't consume any other fish during that week.

With respect to young children, the consumption recommendation is to follow the recommendations for the target population (listed above) when feeding fish and shellfish to young children, but to serve them smaller portions.

EWG's Request for Reconsideration

In Section A of the RFR, you allege that Dr. Acheson's response to your December 2003 Request for Correction is inadequate for five reasons. I set out below these allegations and our response to them in the order in which the RFR presents them.

Section B of the RFR is a lengthy discussion of EWG's position with respect to the policy and legal ramifications of the Advisory. Insofar as you are challenging the agency's policy recommendation in the Advisory, I note that the Information Quality Act request for correction process is designed to address concerns regarding the quality, objectivity, and utility of disseminated information, not the process or policy or legal implications of the information.

In several places in the RFR, you present the Advisory as a statement by FDA (and EPA) that EPA's reference dose represents a "safe" level of mercury in fish. *See, e.g.*, RFR at 6, 12, and 13. As we have previously indicated, the purpose of the Advisory is not to establish a safety level for mercury in fish, but rather to provide information to the target population to enable them to reduce the risks of mercury exposure from fish, and at the same time avail themselves of the health benefits of fish consumption.

1. "The Advisory's recommendations violate objectivity guidelines requiring accuracy and completeness, and comprehensive information on risk." (RFR at 5).
    a. "The Advisory's recommendation to eat up to 12 ounces of a variety of fish and shellfish per week violates standards for accuracy, completeness and comprehensiveness because, if followed, it will cause the vast majority of women and children to increase exposure to mercury to the point of exceeding safe levels of mercury exposure."

We disagree with this argument for three reasons.

First, as noted above, the Advisory is not about what level of mercury exposure is "safe"; instead, it is about risk reduction.

Second, the Advisory is soundly supported by data generated by EPA, FDA, and other experts within and outside of government. For example, as Dr. Acheson described in his

response, FDA has conducted and made available the results of sampling done over a 13-year period (1990-2003), including analyses of mercury concentrations in 28 species of finfish and 7 species of shellfish. These data are available at http://www.cfsan.fda.gov/~frf/seamehg2.html. In 2004, we collected and are currently analyzing 17 species of fish for total mercury (including 280 samples of canned and fresh tuna and 255 samples of imported and domestic fish). FDA plans in FY 05 to collect additional data on shrimp, tilapia, clams, and tilefish. The webpage cited above will be updated with these new data once analysis is complete.

The Advisory is also supported by FDA exposure mitigation modeling, which showed that if seafood consumers follow FDA's advice to limit their overall fish consumption and eat less of certain species, the estimated proportion of women who are exposed to methylmercury at levels over the reference dose would decline.[3]

The Advisory reflects the ample and growing body of scientific literature supporting a determination that a well-balanced diet that includes a variety of fish and shellfish can contribute to the health of adults and children. During the July 2002 meeting, the FAC recognized and accepted the approach of recommending 2-3 meals of fish and shellfish per week, and heard evidence that it is consistent with recommendations by the American Dietetic Association, the American Heart Association, and the U.S. Dietary Guidelines.

A comparison of the Advisory with a number of standards, including EPA's reference dose (RfD) for methymercury (MeHg) (0.1 micrograms per kilogram per day), indicates that consumption of fish pursuant to the Advisory will reduce exposure to methylmercury.[4] The "reference dose" is defined by EPA as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime."[5] As you agree in the RFR (at p.6), the reference dose is not a bright line standard that can never be exceeded. Indeed, with respect to MeHg, the reference dose has a 10-fold uncertainty factor built into it.[6]

Finally, there is no evidence that women have increased their fish consumption in response to the Advisory, which is the fundamental premise of EWG's argument. Instead, there is some limited evidence that the target population reacts to federal fish consumption advisories by reducing fish consumption in keeping with the Advisory.

For example, a large study conducted in eastern Massachusetts around the time FDA issued an earlier advisory on fish consumption (the 2001 Advisory) provides further evidence about the likely response of the target population of women to the 2004 Advisory.[7] That study, conducted by researchers from the Harvard Medical School, involved a cohort of 2235 pregnant women who visited obstetric offices in eastern

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[3] See reference at n. 1.

[4] See reference at n. 1.

[5] Methylmercury (MeHg), EPA's Integrated Risk Information System, CASRN 22967-92-6) USEPA, www.epa.gov/iris/subst/0073.htm) at 2. See also National Academy of Sciences. Toxicologic effects of methylmercury. Washington, DC; National Research Council: 2000 (on derivation of RfD); available at www.nas.edu.

[6] See ref. at n. 1.

[7] Oken E et al, Decline in fish consumption among pregnant women after a national mercury advisory. Obstset Gynecol. 2003 Aug. 102(2):346-51.

Massachusetts and completed dietary questionnaires at intervals during pregnancy. The study compared the dietary questionnaire responses given before and after FDA's January 2001 Advisory. The researchers found that, compared with responses to questionnaires from 1161 women surveyed before the 2001 Advisory, the questionnaires from 904 (different) women surveyed after the Advisory[8] reported consuming less dark meat fish, canned tuna, and white meat fish (which essentially means a drop in consumption of all finfish), with decreases resulting in a statistically significant reduction of fish consumption of about 1.4 servings per month (95% CI 0.7, 2.0). There was no change in shellfish intake. The mean intake of fish and shellfish declined from 7.7 to 6.4 servings per month, including a decline in canned tuna from 2.9 to 2.1 servings per month and dark meat fish (including salmon) from 1.3 to 1.1 servings per month. The proportion of women who consumed more than three fish servings per week declined significantly, from 15% to 11%. As the authors noted, adjustments for age, race or ethnicity, and education did not materially change the results, although it is possible that women participating in a similar questionnaire-based study conducted elsewhere in the U.S. would have responded differently. As the authors stated, "[t]he results of this time series analysis suggest that pregnant women in this cohort acted in accordance with the federal guidelines to reduce fish consumption. Further research specifically asking pregnant women about their awareness of and responses to this Advisory would be needed to confirm that the decrease in consumption resulted from the warnings, as opposed to other factors."

Consistent with the Oken study, in a 2005 analysis of the Bureau of Labor Statistics Consumer Expenditure Survey, an annual cross-sectional collection of all household expenditures, Shimshack and colleagues looked at the response to the 2001 Advisory among households with young or nursing children, compared to other households, for a two week period.[9] Households of married women under 46 years of age without children were excluded from the analysis. Specifically, the analysis looked at differences in household expenditures on canned fish over the course of a two-year period (1999-2002) with roughly half of the 10,537 observations in the two years before the Advisory and half in the two years after the Advisory. The authors found that educated households with young and nursing children reduced their canned fish expenditures by 29%. There is no information in the study about what if any food purchases were made in lieu of canned fish or whether purchase of canned fish is an indicator of overall fish intake (i.e., canned, fresh, and frozen). The authors used a differencing methodology that controlled for price changes, so the change in consumption of canned fish was not a result of changes in price.

EWG's comments with respect to children are addressed below in response to #3.

2. [Also numbered "1" in RFR.] "The Advisory's claim that following the recommendations will reduce exposures to mercury's effects contradicts existing

[8] An additional 170 women who were surveyed both before and after the 2001 advisory were not included in the analyses.

[9] Shimshack, Ward, and Beatty. Are mercury advisories effective? Information, Education, and Fish Consumption. 2005 Tufts Department of Economics Working Paper. Available at http://www4.nationalacademies.org/webcr.nsf/(MeetByDocID)/9217C1D3D2BCEB0F85256FBD007178C2?OpenDocument..

science, in violation of objectivity guidelines and standards for influential information." (RFR at 7).

a. "The claim regarding reduction of exposures to mercury's effects violates objectivity guidelines for accuracy because it makes an unsupported scientific claim and directly contradicts existing data on fish consumption."

I disagree that the Advisory violates objectivity guidelines because, as FDA's exposure modeling suggests, following the Advisory leads the target population to choose fish and shellfish with lower mercury concentrations. As a result, these individuals have reduced their exposure to the harmful effects of methylmercury while still taking advantage of the health benefits of fish and shellfish consumption.

I note that the RFR does not provide data supporting your assertion that the Advisory is confusing to consumers. On the contrary, in focus group research conducted by FDA to evaluate the clarity and impact of the draft of the 2004 Advisory, most of the respondents indicated that the salient "take-away" messages were easy to find and understand.[10] Some of the participants said that they will eat less fish as a result of the Advisory, and some of the pregnant women said that they probably would avoid fish altogether while they were pregnant to make sure that they did not get exposed to methylmercury. Some participants also said that they would serve less fish to their children. Finally, many participants said that they would tell others who are not in the at-risk groups about the risks of fish because if fish can be risky for pregnant women, it probably isn't good for other people. [11]

b. "To the extent that this statement is serving as FDA's safety standard for the purposes of the Advisory, the statement fails to meet guidelines for influential information because it is not based on the best available, peer-reviewed science."

As Dr. Acheson noted in his Reply and as I have pointed out elsewhere in this letter, the issue is whether the Advisory helps the target population reduce the risk of exposure to methylmercury. The RfD is not a bright line threshold. FDA's Advisory was based on risk reduction modeling that was peer reviewed, as described above, and has been published in a peer-reviewed journal.

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[10] Halverson L. Consumer Reactions to the Draft Advisory on Methyl Mercury in Fish: Focus Group Research. 2004. Unpublished research report. Prepared by ORC Macro International for the Division of Market Studies, Center for Food Safety and Applied Nutrition, Food and Drug Administration. Available at http://www.cfsan.fda.gov/dms/admehg3g.html.

[11] This focus group research is qualitative and based on small samples. It should not be viewed as nationally representative or projectable. Quantitative experimental data are necessary to make reliable and verifiable conclusions. The focus group findings are based on observations recorded by the observer, as well as post-group discussions with the focus group moderator and other observers. While respondents seemed to clearly understand the intended message in the draft advisory, their responses were dependent on their own levels of risk aversion; hence, many participants indicated that they would simply stop eating seafood and stop feeding it to their families.

Furthermore, the baseline analysis of the risk indicates that current blood levels of mercury in the target population are very low. In an analysis of 4 years of NHANES data, Jones and colleagues reported that just under 6% of women 16-49 years old had blood mercury levels greater than or equal to EPA's RfD (5.8 μg/L).[12] Women above the RfD were within an 8-fold safety factor.

EWG recommends that FDA "revise the Advisory to provide recommendations that will help women maintain a level of mercury exposure from fish that is below the established reference dose for mercury." However, getting all women in the target population below the EPA's RfD for mercury was not the goal of the Advisory. The recommendations in the 2004 Advisory were largely based on the recommendations made in July 2002 by the FAC in regards to the 2001 Advisory. While the exposure assessment did examine a scenario in which virtually all members of the target population would be below the RfD (and other standards),[13] this scenario was dependent on much greater restrictions in the types and amounts of fish that could be consumed by the target population. Such a scenario did not consider the potential loss of benefits from consuming fish, and since FDA has to consider the overall public health impact, it would have been inappropriate to make such sweeping changes that went beyond the recommendations made by the 2002 FAC without the science to back it up. As you may be aware, there are new studies being undertaken on the risk-benefit analysis of fish consumption. These include a project by the Food and Nutrition Board of the Institute of Medicine entitled "Nutrient Relationships in Seafood: Selections to Balance Benefits and Risks," which is funded by the National Oceanic and Atmospheric Administration (NOAA) and began in late September 2004,[14] as well as work by the Harvard Center for Risk Analysis and a panel of experts focused on various aspects of the risk tradeoffs involved in eating or avoiding fish.[15] As these new analyses emerge FDA will consider what further revisions, if any, would need to be made to ensure the optimal public health balance in the advice they provide to women who may become pregnant, pregnant women, nursing mothers and young children about consuming fish.

3. [numbered 2 in RFR] "The Advisory's guidance regarding children's portions is vague, in violation of utility guidelines." (RFR at 10).

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[12] CDC. Blood mercury levels in young children and childbearing-aged women, United States, 1999-2002. 53 MMWR 43 (2004): 1018-1020.

[13] See reference at n. 1. As indicated by Figure 5 in that article ("comparison of scenario outcomes to various safety standards"), several of the exposure scenario outcomes were compared to various standards including the RfD, the minimal risk level (MRL), and provisional tolerable weekly intake (PTWI), a standard set by the World Health Organization—Joint Expert Committee on Food Additives (WHO-JECFA). All three of these scenarios resulted in exposures below the MRL and PTWI. Two of the scenarios resulted in small percentages exceeding the RfD, while the third (12 oz. low methylmercury fish only) was below the RfD.

[14] Information on this project is available at http://www4.nas.edu/webcr.nsf/5c50571a75df494485256a95007a091e/eea3c8a5c270f3a385256f3f006e2b7d?OpenDocument&Highlight=0,fish.

[15] These papers are in press and will be published over the next several months. See, e.g., Cohen JT et al. Evaluating risk/risk rradeoffs in fish consumption advisories to address the risks of methylmercury. Abstract. Presented at the 2004 Annual Meeting of the Society for Risk Analysis. Available at http://birenheide.com/sra/2004AM/program/singlesession.php3?sessid=P3&order=4#4.

EWG argues that the Advisory's suggestion to feed children smaller portions than those recommended for adult women is "imprecise and incomplete." EWG suggests that FDA should "issue specific guidance on a safe quantity of seafood that young children could eat regularly without exceeding the reference does for safe levels of mercury exposure." RFR at 10.

As Dr. Acheson noted in his response, the 2004 Advisory was reframed from earlier versions to promote, for adult women and young children, informed dietary choices that reduce risk while maintaining the benefits of consumption of fish and shellfish. The 2004 Advisory indicates that women can eat up to 12 ounces a week of a variety of fish and shellfish that are lower in mercury (and provides specific and detailed information about which fish and shellfish those are); the Advisory adds that the same recommendations should be followed when feeding fish and shellfish to young children, but by serving smaller portions.

FDA's FAC recommended that the message in the Advisory about fish be stated in positive terms, include a list of fish that have low levels of mercury and are safe to eat, make portion size consistent with variety and locale, improve the clarity of the tuna message, and consider adding body weights versus amounts for children. FDA considered this advice and made changes reflective of it.

With respect to children, FDA is not aware of specific scientific data that would allow a determination of how much fish children should consume at specific ages, although there are data that fish consumption in childhood has health benefits. However, suggesting serving sizes and consumption levels somewhat lower than what adults consume is consistent with the practice of other federal dietary guidance information. The current USDA food guidance system, the 2005 MyPyramid, described in the 2005 Dietary Guidelines, follows the practice of recommending smaller serving sizes and consumption for young children.[16] *See also* the previous food guidance system for children, the 1999 USDA Food Guide Pyramid for Young Children (recommending that young children consume serving sizes about 2/3 of regular Food Guide Pyramid servings).[17]

4. [numbered 3 in RFR] "The Advisory did not undergo a rigorous peer review process, in violation of standards for influential information." (RFR at 10).

EWG argues that FDA "did not respond to the majority of the expert panel's comments on the Advisory, and did not ultimately receive approval from the expert panel prior to releasing the Advisory, in violation of transparency standards for influential information." EWG argues that FDA "must enlist qualified experts from outside the Agency...and create an Advisory that meets the expert panel's approval." However, as

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[16] MyPyramid Food Intake Patterns, USDA Center for Nutrition Policy and Promotion, April, 2005. http://www.mypyramid.gov/downloads/MyPyramid_Food_Intake_Patterns.pdf ; USDA and DHHS 2005 Dietary Guidelines for Americans, Appendix A-2, http://www.health.gov/dietaryguidelines/dga2005/document/pdf/dga2005.pdf http://www.healthierus.gov/dietaryguidelines/)

[17] U.S. Department of Agriculture. Tips for Using the Food Guide Pyramid, 1999 http://www.cnpp.usda.gov/KidsPyra/PyrBook.pdf, http://www.cnpp.usda.gov/KidsPyra/; USDA The Food Guide Pyramid, revised 1996, http://www.cnpp.usda.gov/pyrabklt.pdf, http://www.cnpp.usda.gov/pyramid.html.).

noted above, the process used by FDA in developing the Advisory is not reviewable under the Information Quality Act.

EWG also asserts that because Dr. Acheson's letter "did not challenge the categorization of the Advisory as influential scientific information," FDA has conceded as much (RFR at 4), and that FDA "does not question the appropriateness of a peer review for the Advisory" (RFR at 10). The Advisory reflects a policy judgment based on scientific information, much of which is peer reviewed. It is important to note the process by which the Advisory was produced was in keeping with the FDA Guidelines, even those for influential information.

FDA's review process is extensive and was used as appropriate to the particular information to be disseminated. We have a rigorous internal review, clearance, and approval process that is required before information is made public. With respect to the 2004 Advisory, during its development we diligently sought the advice and opinion of experts, including the FAC, worked with EPA, and involved the public in stakeholder and public meetings and focus group testing. Furthermore, much of the underlying research and analysis was also subjected to extensive internal, external, and/or pre-publication peer review, including FDA's exposure assessment.

FDA complied with its standards for influential information, which provide that the agency should use a "participatory process" and that "[t]he process for generating information defined as influential should be transparent." FDA Guidelines VII.B. Several approaches for accomplishing these objectives are set out:

> "One approach is to invite public comment on the information to be disseminated and encourage stakeholders to submit scientific data and information that can be used in preparing the information. As appropriate, we will solicit advice and opinions of advisory committees as well as peer review from experts within and outside of the agency. To the extent practicable under confidentiality laws, we will strive to make supporting data and analyses available to the public for technical review and comment. This can be accomplished by posting the information on our web pages and providing printed copies as requested."

Id.

Under the FDA Guidelines, FDA may achieve transparency, as that term is used in the Guidelines, in a number of ways, many of which were used in producing the Advisory. Without repeating the details of the development of the 2004 Advisory that I described earlier in this letter, I note that the content and tone of the Draft Advisory was considered by the FAC (and recommendations by the FAC were followed in crafting the language of the 2003 Draft Advisory and 2004 Advisory) and was the subject of four stakeholder meetings.

5. [Numbered 4 in RFR.] "<u>The documentation that FDA has released supporting the Advisory is inadequate and inconsistent with sound scientific practices, in violation of objectivity guidelines, utility guidelines, and requirements for influential information</u>." (RFR at 13).

    a. "The analyses and data supporting the recommendations in the Advisory fail to meet objectivity and utility guidelines for transparency."

EWG argues that "FDA has not released analyses and data to support statements that it is safe for a person in the Agency's target population to follow the Agency's consumption advice..." This assertion is incorrect; as noted above, we have made available to the public all analyses and data supporting the Advisory. To the extent EWG's argument here is that FDA's documentation does not support a finding of "safe," I note again that the Advisory is about reduced risk, not safety.

As Dr. Acheson noted in his response, the information used to revise the 2003 Draft Advisory into the 2004 Advisory is documented and publicly available. The document entitled, "Backgrounder for the 2004 FDA/EPA Consumer Advisory: What You Need to Know About Mercury in Fish and Shellfish" (www.fda.gov/oc/opacom/hottopics/mercury/backgrounder.html) provides a summary of the changes made to the 2003 Draft Advisory for the 2004 Advisory. The transcripts for the FAC meetings, which detail the scientific information considered and the discussion of those data relative to the development of the advisories are also available (http://www.fda.gov/ohrms/dockets/ac/03/briefing/4010b1.htm). FDA obtained a peer review for the FDA exposure assessment, and the agency carefully considered the comments, responded to those comments, and made both the peer review comments and our responses available to public view (see FDA's Food Safety website at www.cfsan.fda.gov/seafood1.html or http://www.fda.gov/ohrms/dockets/ac/03/briefing/4010b1-12-%20EPA.pdf).

We also sought advice from experts concerning the content and language in the 2003 Draft Advisory. Our review process is extensive and appropriate to the particular information to be disseminated. Beyond the FAC, we involved the public in stakeholder meetings and performed focus group testing. The underlying scientific data and assessments presented at the December 2003 FAC meeting are available on the web for those who are interested in additional details (http://www.fda.gov/ohrms/dockets/ac/03/briefing/4010b1.htm). We have made available to the public the citations to the data sources and, where possible, the sampling and analysis plans. The mercury testing data used in the exposure assessments come from three sources: the FDA Food and Cosmetics Compliance Program/ Toxic Elements in Food Survey and Special Assignments (1990-2003), Gulf of Mexico Report (2000), and National Marine Fisheries Service Report (1978).

General information about the FDA Compliance Program is available in the Compliance Program Testing Manual: www.fda.gov/ora/cpgm/default.htm. This information includes: the Food and Compliance Testing Programs: www.cfsan.fda.gov/~comm/cp-toc.html; and Toxic Elements in Food and Foodware, and Radionuclides in Foods-Import and Domestic: http://www.cfsan.fda.gov/~comm/cp04019.html.

b. "FDA failed to use sound scientific practices required for influential scientific information in its risk mitigation scenarios, use of analog data, assumption of exposure time and documentation of sampling and analysis plans."

    i. "FDA's risk modeling relies on unsound assumptions regarding compliance."

The RFR also argues that FDA's risk mitigation modeling scenarios[18] inappropriately assume 100% compliance with the Advisory. However, EWG does not suggest a compliance rate correction that Drs. Carrington and Bolger could use in a reanalysis of these data.

ii. "FDA's use of analog mercury distributions in place of further testing is not scientifically sound."

I disagree with this assertion. First, the analog approach was used only for certain species for which only mean values were available; these species represent minor species from a market-share standpoint, and they contribute very little to population methylmercury exposure and have a negligible impact on the statistical outcomes of the predicted blood mercury levels. Second, FDA continues to sample various species of fish for mercury concentration, and as more data are collected we will be able to use these data instead of modeled data.

iii. "FDA's assumption of exposure time corresponding to the reference dose does not comport with scientifically sound practices."

As EWG did in the initial Request for Correction, the RFR cites in support of this assertion comments by one of three experts who reviewed FDA's model scenarios (RFR at 15). The two most common measures of toxicokinetic dose are average steady-state concentration and peak concentration. The derivation of the methylmercury reference dose follows the convention of using average daily dose as the dose metric. Although there is room for further exploration of the relationships between toxicokinetic dose and effect, the way in which FDA conducted this analysis was correct and in fact EWG has offered no correction. If exposure assessments are to be consistent with current toxicologic analyses, they must use average exposure as the relevant metric. *See, e.g.*, Grandjean *et al.* 2003[19] (Faroe Islands research group conclusion that average exposure is the better dose metric). The peer review comment to which EWG refers came from a reviewer who reviewed a poster presentation. Modifications were made to the work and as noted it has subsequently been published in a peer reviewed journal. The reviewer's comment was rejected because it was against the convention accepted by most experts in the field.

[18] See reference at n. 1.

[19] Grandjean P. Neurotoxic risk caused by stable and variable exposure to methylmercury from seafood. Ambul. Pediatr. 2003 Jan-Feb; 3(1):18-23.

Conclusion

In light of the foregoing, I do not believe that at this time the Advisory needs to be corrected pursuant to the Information Quality Act. However, I concur with Dr. Acheson that EWG's comments were helpful in refining the 2004 Advisory.

Sincerely,

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Director
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