April 21, 2009

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U.S. Food and Drug Administration
5100 Paint Branch Parkway
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RE: Docket [FDA-2009-N-0018]

Dr. Sundlof:

Environmental Working Group (EWG) is a non-profit public health and environmental research and advocacy organization based in Washington, DC. We conduct research on health risks from exposures to industrial chemicals and pollutants. We advocate for policies that protect public health, including for methylmercury in seafood, a pollutant that is neurotoxic at low levels and that poses particular risks to women of childbearing age and young children.

We are writing to express significant concerns with FDA's January 2009 draft report entitled "Quantitative Risk and Benefit Assessment of Consumption of Commercial Fish" (FDA 2009a). FDA has used this analysis in large part to conclude that the health benefits of eating large amounts of seafood outweigh the health risks from exposures to methylmercury. But the purpose, assumptions, data, models, and conclusions inherent in and derived from this draft assessment are fundamentally flawed and are so far from standard scientific practice that we consider FDA's effort to be beyond repair.

EWG is not alone in expressing significant concerns with FDA's draft report. Upon reviewing an early draft of FDA's assessment, the Environmental Protection Agency (EPA) wrote of the document's "serious scientific flaws," stating that "this is not a product EPA should endorse as it does not reach the level of scientific rigor routinely demonstrated by the Agency" (EPA 2008).

FDA's second draft report, the subject of this review, fails to address many of the concerns raised by EPA and FDA's Peer Reviewers. In new comments submitted to FDA, EPA finds that "While some changes have been made in response to EPA comments on the earlier draft, the analyses themselves are essentially unchanged, and in the opinion of EPA, scientifically flawed" (EPA 2009). Among numerous methodological errors and faulty assumptions EPA describes in nearly 50 pages of comments, the agency notes that FDA relies on science regarding neurodevelopmental risks that "had been completely abandoned by the scientific community as a basis for risk assessment for more than a decade." EPA's review provides dozens of examples in which FDA scientists make questionable, faulty or unfounded choices with the effect of boosting boosting benefits or reducing risks from seafood consumption above what is justified scientifically. EPA concludes that "a fish consumption advisory strategy based on the design of the FDA draft analysis would be highly inconsistent with what is generally considered to be proper public health practice" (EPA 2009).

A renowned expert on neurodevelopmental impacts of methylmercury exposures, Dr. Philippe Grandjean of Harvard School of Public Health, urges that "this draft document should be withdrawn," and a new attempt initiated in a process that includes scientists with expertise in the toxicity of methylmercury for people who eat seafood (Grandjean 2009).

FDA Peer Reviewers raised concerns about the FDA approach and model documentation. One reviewer found that because of FDA's failure to document model assumptions and methods, "guesswork must be repeated every few minutes by a reviewer of this model," and that "it is not possible to determine the validity of the computational implementation" (FDA 2009b, Reviewer #3). Another reviewer noted that "I...could not begin to conduct a true QA/QC (Quality Assurance/Quality Control analysis) of the components of the assessment," again because of FDA's failure to document methods (FDA 2009b, Reviewer #4). When EWG reviewed FDA's model code, we found indications of serious errors. For instance, when seafood eaters in the model are assigned lobster for one of their seafood meals, the model incorrectly assigns mercury levels from halibut and sablefish. No reviewer has yet been able to conduct a complete review of FDA's complex and poorly documented model, but flaws in assumptions and methodology outside of the model code are more than sufficient to support the position that the draft be completely withdrawn.

Given the fundamental flaws in this assessment noted by multiple scientists and EPA and confirmed by EWG, we advocate that this draft be withdrawn, and that any fresh starts involve scientists with expertise in methylmercury toxicity to pregnant women, young children and other vulnerable populations; address all of the basic errors and shortcomings raised in the dozens of pages of comments submitted with regard to FDA's draft; include early and frequent involvement by stakeholders; and involve review of study design and findings by a qualified panel of experts.

Such an effort would most productively focus on producing a list of low-mercury fish that pregnant women can safely eat, to maximize the benefits of seafood nutrients and minimize the harm from methylmercury exposures for a child *in-utero*.

We have attached a detailed list of concerns we identified in our review of the draft assessment. Thank you for your attention to this pressing issue.

Sincerely,

[signed]
Jane Houlihan, MSCE
Vice President for Research

[signed]
Sonya Lunder MPH
Senior Analyst

ATTACHMENT

ATTACHMENT. Environmental Working Group detailed review of FDA's January 2009 draft report entitled "Quantitative Risk and Benefit Assessment of Consumption of Commercial Fish"

Environmental Working Group's (EWG's) review of FDA's January 2009 draft report entitled "Quantitative Risk and Benefit Assessment of Consumption of Commercial Fish" highlights serious shortcomings in the Agency's assessment of mercury exposure, particularly for Americans who eat the most fish. EWG identified numerous errors and faulty assumptions in FDA's draft assessment, The model itself was poorly documented and virtually impenetrable and, therefore, could not be thoroughly reviewed for accuracy. Errors EWG identified in a partial line-by-line review of the model code raise questions about the quality of the entire model. Specific comments from our review of FDA's assessment are below:

FDA incorrectly focuses on the average or typical consumer, not highly-exposed individuals or groups

FDA's current framework attempts to examine the population level effects of fish consumption, but fails to account for high-risk groups. Dietary practices and/or individual physiology could both place an individual at high risk for mercury toxicity. Yet FDA's modeling assumptions limit their ability to quantify risks to these groups.

FDA estimated current fish intake for American adults by extrapolating from short-term consumption studies. These data fail to capture the most highly exposed and vulnerable populations. FDA admits their fish consumption dataset ignores individuals with high consumption: "The assessment is intended to be nationally representative of the U.S. population. It does not address risk to segments of the population whose exposure to MeHg or patterns of fish consumption may be substantially different from the population as a whole..." (FDA 2009a). While FDA lists populations who eat contaminated subsistence or sport fish, this statement clearly also applies to groups with high levels of mercury intake from commercial fish.

Results from CDC's NHANES sampling suggest that 5.8% of American women of childbearing age exceed EPA's Reference Dose for methylmercury. But CDC's modeling doesn't capture sub-populations with high levels of mercury exposure via fish. Hightower (2003) reports elevated mercury levels in 80 patients treated in their medical practice during a 1 year period. The mean level in female patients was 10 times higher than that reported in CDC's NHANES survey, which is designed to be a statistically representative sampling of Americans. Patients at Hightower's clinic were predominantly middle and upper income residents of the San Francisco Bay Area. Additional research has reported higher blood mercury levels in coastal populations (Mahaffey 2009), in certain racial/ethnic groups (Mahaffey 2009, Hightower 2005) and in upper income women (Mahaffey 2009). FDA's analysis focuses on the typical diet of an "average" consumer and is therefore unlikely to capture the risks of mercury to these high-risk groups.

FDA also fails to account for human variability in mercury metabolism. It is well known that mercury is actively transported from maternal blood to the developing fetus. Mahaffey (2005) reports that the partitioning of mercury in these two media is variable, with cord blood mercury levels 3-times higher than maternal blood in 5% of the population, and mercury levels roughly equal in another 5% (Mahaffey 2005). The remainder of the population lies somewhere between these two extremes. A

variety of other physiological factors could place an individual woman, and her gestating fetus, at risk for greater mercury exposure (Rice 2004), and should be accounted for in FDA's model.

Another way that normal human variability is dismissed in FDA's analysis is the modeling of mercury partitioning between blood and hair. FDA bases its model on data from a group of 20 healthy male volunteers, and truncates the data to trim "outliers," which in this case were the men in the upper 20th percentile. Previous comments have questioned the wisdom of basing the model on a convenience sampling of 20 healthy male volunteers.

FDA uses the wrong measure of mercury toxicity to the developing fetus

Given the wealth of data about mercury toxicity, it is baffling that FDA elects to use data from the small and imprecise Iraqi poisoning incident, supplemented with negative findings from the Seychelles study, instead of more sensitive and validated studies of mercury toxicity. FDA mischaracterized the findings from many of the large epidemiological studies to suit their unconventional reading of the literature. In 2000, the National Academy of Sciences (NAS) reviewed the existing evidence of mercury toxicity and concluded that the Iraqi and Seychelles studies should *not* be used to assess mercury toxicity in the United States (NAS 2000).

Iraqi data was gathered after a mass mercury poisoning, and reflects gross toxicity resulting from acute exposures to mercury-contaminated wheat. The scientists gathered data on endpoints including delays in walking and speech. Yet the validity of the data is compromised by an inability to pinpoint children's ages to less than a 6-month range. The Seychelles study was one of the 3 large epidemiological studies reviewed by the NAS, but the only one with purportedly "negative" findings. The Seychelles findings were confounded by the beneficial components of fish eaten, and the author's decision to adjust for post-natal mercury exposure, which could "attenuate the apparent effects of prenatal exposure" (Grandjean 2009).

Several large, epidemiological studies have examined subtle effects of mercury on neurodevelopment, including IQ and other cognitive measures, as well as verbal skill, attention and behavior (Kjellström 1986, 1988, Crump 1998, Grandjean 1999, Oken 2005, 2008a, Debes 2006). The studies use different methods of accounting for the beneficial components of fish. The most valid way to evaluate the risks and benefits in a fish eating population is to model both mercury and omega-3 concentrations as independent variables. This method was employed in an analysis by Budtz-Jørgensen (2007) of data from the large Faroe Islands study, where the predominant source of mercury was ingestion of whale meat with low levels of fatty acids. Researchers found that the impact of mercury-associated deficits roughly doubled when the beneficial components of fish were taken into account (Budtz-Jørgensen 2007). A study of 341 Massachusetts mothers and children modeled the risks of mercury and benefits of omega-3 fatty acids as independent variables and found that both played a significant role in neurodevelopmental outcomes (Oken 2008). These findings are supported by meta-analyses by Cohen (2005 a,b,c). Even a reanalysis of the allegedly "negative" Seychelles' study detected a statistically significant effect of both mercury *and* beneficial components of fish, rather than the "negative" findings initially reported (Strain 2008).

Clearly, FDA had many robust datasets to choose from that could account for impacts to neurodevelopment. Instead, the Agency selected 2 imprecise (Iraq) and confounded (original

Seychelles) datasets to ground their analysis of neurodevelopment. Expert Reviewers and EPA have urged FDA to choose alternate studies considered more appropriate for assessing mercury risks (EPA 2009, FDA 2009b, Expert Reviewers #5 and 7).

FDA has resisted calls to use the most modern and sensitive studies of mercury toxicity, claiming that modeling these data would be impossible because "individual scores on developmental milestones have not been made available from the Faroe Islands study" (FDA 2009a). However, Dr. Philippe Grandjean, a lead researcher for the Faroe Islands study, reports that he offered the data to Dr. Philip Spiller of FDA in a conversation held in 2006 (Grandjean 2009).

FDA does not examine variability of omega-3 fatty acids in fish

The draft document considers exposures to an "average" consumer by ignoring species variability in omega-3 fatty acid concentrations. FDA itself has studied the level of omega-3 fatty acids in commonly eaten fish. The data indicate major variability between species. "Predicting omega-3 levels based on a crude measure of "fish consumption" does not predict serum omega-3 fatty acid levels." (Philibert 2006)

EPA and at least one of the Peer Reviewers consider this to be a major flaw in the FDA model, and a choice that will limit the reliability of modeled scenarios that test the effects of changes in fish consumption. The peer reviewer states, "[T]here is no justifiable reason for not performing comparable and objective analyses for a different biomarker of dietary exposure to another important constituent in fish, i.e., long-chain omega-3 (EPA+DHA) levels." (FDA 2009b, Peer Reviewer #5)

FDA model cannot reliably assess individual-level effects

FDA's fish consumption modeling uses data from the 1989-1991 Continuing Survey of Food Intake by Individuals, which is short-term survey data and sorely out of date. Fish consumption has increased during this period due to greater awareness of beneficial nutrients and fish as a low-fat source of protein, although women of childbearing age may have decreased consumption due to the FDA/EPA advisory.

FDA does not accurately account for the dietary habits of people who eat lots of fish, or who select high mercury species. A variety of studies document excessive risks to sub-groups who eat lots of fish, or lots of high-mercury fish. Women who report eating 12 oz of fish per week on the CDC's NHANES survey have 7 times higher blood mercury levels than non-fish eaters (Mahaffey 2004a). Consumers of subsistence and sport-caught fish are at risk for high mercury ingestion (Knobeloch 2007, Burger 2007, Davis 2008). Dr. Jane Hightower reported elevated mercury hair and blood levels in middle and upper-class patients who reported eating lots of fish (Hightower 2003).

Specific racial and ethnic sub-groups have been highlighted as groups with high mercury levels due to fish consumption. Japanese women residing in Washington State (Tsuchiya 2008a) and those marked as "other racial/ethnic group" in NHANES (meaning Asian/Pacific Islander, Native American and those marking "multiracial" but not designating a primary racial affiliation) (Hightower 2006) are both highlighted. The women in the "other" category were 3 times more likely to have blood mercury levels above the benchmark of 5.8 ug/L than other racial/ethnic groups surveyed by CDC (Hightower 2006).

EPA wisely suggests that FDA model the net impact of fish consumption for these sub-groups, and the impact of various consumption scenarios on these sub-groups, to test hypotheses that consumers could increase average consumption to 12 oz weekly (a 250% increase for the average consumer) without risking impacted fetal development or cardiovascular events.

FDA incorrectly assumes a threshold for mercury toxicity

FDA appears to consider a threshold for mercury toxicity, based on the finding of a threshold for the age of walking and talking. However, this is not believed to be the case for more subtle impacts to neurodevelopment, which would occur at levels of exposure experienced in the U.S. EPA's IRIS assessment for methylmercury states, "It is also important to note that no evidence of a threshold arose for methylmercury-related neurotoxicity within the range of exposures in the Faroe Islands study" (EPA 2001). No threshold was observed in the Massachusetts cohort, either (Oken 2008a).

FDA's model asks the wrong questions

FDA's modeling effort attempts to determine the population-level effect of current fish consumption on fetal neurodevelopment and cardiac outcomes, and test the likely results of certain shifts in fish intake. However, this construction is not only fraught with technical challenges, but also is of limited utility to consumers and health professions who are attempting to distinguish safer fish species and maximize the neurodevelopment and cardiac benefits.

Putting aside the technical concerns and shortcomings detailed above, which cast significant doubt about the accuracy of the model results, we also question FDA's framing of the issue. FDA does not explore options for maximizing benefits and minimizing risks, which is the ideal public health outcome. Some species with high omega-3 levels are also low in mercury, and FDA assessments should explore these species with the intent to sterr populations at risk toward these options (Budtz-Jørgensen citing: Gochfeld 2005, Levenson 2006, Mahaffey 2004, Smith 2005).

For fetal neurodevelopment, the draft report examines scenarios in which adults increase fish consumption or switch to low mercury fish. However, in order to be comprehensive, FDA should have included other combinations. The current draft predicts that the greatest benefit would be if all women of childbearing age ate exactly 12 oz of fish per week but does not specify choosing low-mercury species. FDA specifies that, "Children born to mothers who had to increase their fish consumption (most children) would generally experience increased benefits. However, if their mothers increased their fish consumption by eating a lot of fish that were relatively high in methylmercury, their benefits could be decreased to the point where the net effect for them could become adverse." (FDA 2009a) The results of other scenarios highlight the fact that benefits are focused on changes in dietary FDA should have explored the result in which women eat exactly 12 oz of fish but selected only low-mercury species.

Unlike numerous mercury experts who conclude that the benefits of fish consumption would be maximized by selecting low mercury species (Budtz-Jorgensen 2007, Choi 2008, Domingo 2007, Ginsberg 2000, Mahaffey 2004b, Mahaffey 2008, Mozaffarian 2006, Oken 2008 a,b, Sakamoto 2004, Stern 2005, Tsuchiya 2008b), FDA in its modeling seems to deemphasize this strategy (FDA 2009).

If evidence indeed indicates that Americans would benefit from increasing consumption of omega-3 fatty acids and other seafood nutrients, it is critical that FDA provide species-specific guidance that would allow consumers to minimize mercury-driven risks and that would ensure that pregnant women following the guidance would not expose their fetus to mercury in excess of the Reference Dose. This would require looking at the specific risk-benefit profile of commercial species.

FDA's model itself is very poorly documented, with errors and omissions

FDA's model appears to have been developed without any early input from stakeholders, experts in Federal Agencies, or academia. The FDA model was constructed in Excel, which is highly unusual for a model of this type and complexity and which makes a thorough review of the model nearly impossible.

Excel does not have a true random number generator, and therefore each time the program is restarted the model employs an identical series of "random" numbers as the previous restart. Without deliberately manipulating the input data, duplicate runs of the model will produce identical results. This shortcoming in Excel raises questions about whether the model outcomes truly capture the full variability in the population.

The model is poorly documented. Very little information is provided about its structure or function. Only one expert peer reviewer attempted to validate the model, and noted:

> *"The repeated requirement for 'guesswork' both at the micro level (e.g., what individual lines of code are intended to achieve) as well as at the macro level (e.g., the general lack of documentation as to how the many spreadsheet files interact to form a complete simulation) forbids a formal characterization of the model as being sound. In the end, while no concrete 'fatal' errors were found in the computational implementation, it is simply not adequately documented to allow sufficient scrutiny to support or refute an opinion that the model and corresponding results are technically sound. Any opinion would simply be an opinion on what the reviewer has come to believe is being computed rather than being based in knowledge of precisely what is being computed. Determining the soundness of the model would require either considerably more documentation both within and outside of the model software, or extensive interaction with the author(s) of the code to determine exactly what is being computed, where, and in what order."* (FDA 2009b, peer reviewer #3)

EWG staff reviewed the model and found it difficult if not impossible to track FDA's work. Within 2,400 lines of code, there are only 250 text comments. Of the 250 comments in the code, over 200 simply define the line of code or variable without explaining the purpose of the code block or how it is employed in the program. Several documents were missing from the disk originally provided to EWG by FDA, and linked to 8 help files that were not included.

Nevertheless, we discovered several errors based on our partial review of the code.

1. According to the VBScripts, the data on the "CumulativeIndicies" maps non-specific fish meals to specific species before assigning mercury levels to the meal. The data under "Lobster (Category 52)" is incorrect since it assigns lobster eaters to either contamination

group 12 (Halibut) or 22 (Sablefish) instead of the proper groups 14 (American Lobster) or 15 (Spiny Lobster).
2. The descriptive data on the "CumulativeIndicies" worksheet does not match the species codes used in the "Cross Codes" worksheet. For example, "Ocean Perch (category 54)" should properly read "Ocean Perch (category 64)".
3. Mercury data for at least one species are mislabeled on the "Contamination PTs" worksheet, because both Spiny Lobster and Halibut are assigned "Category 12".
4. CSFII eaters may be improperly assigned mercury from a different species. For example, someone eating "Shellfish mixture and noodles, tomato-based sauce (mixture)" is given an 82% chance that they ate crabs, crawfish, lobster, or shrimp instead of a shellfish as defined under CSFII.

These basic flaws that we identified in our partial review raise questions about the quality of the model as a whole.

Model outcomes are imprecise and implausible

Several of the expert reviewers point out that the different methods for modeling neurodevelopment and cardiac outcomes have very different outcomes. In particular:

> "The end result is that, paradoxically, endpoints with relatively little data (MeHg and neurodevelopment, fish and neurodevelopment) have relatively small uncertainty, whereas endpoints with enormous amounts of data (fish and CHD) have spuriously large (and incomparably calculated) uncertainty." (FDA 2009b, Expert Reviewer #5)

Two expert reviewers point out that some of the confidence intervals for heart disease and stroke are imprecise, undermining faith in the findings. They each gave separate examples:

> *Risk of CHD for older men* - "The resulting uncertainties in the Carrington CHD estimate are so large – ranging from -208,000 to +29,000 CHD deaths in men 46+ due to current fish consumption – as to render the estimate nearly meaningless from a practical standpoint." (FDA 2009b, Expert Reviewer #5)
>
> *Risk of stroke for younger women* - "For [women age 16-45], the "Carrington" stroke model's central estimate is that 127 stroke deaths are being averted for this subpopulation from fish consumption but at the fifth percentile confidence interval it also estimates that fish consumption could be averting up to 6,476 deaths." For this latter estimate to be correct, fish consumption would have to be averting over 4 times more stroke deaths than occur in this subpopulation on an annual basis [1,551]. At the other end of the spectrum – the 95th percentile of the confidence interval – the "Carrington" stroke model predicts that fish consumption may be causing 434 stroke deaths, i.e., roughly one-third of all stroke deaths for women aged 16-45. Such an outcome seems implausible given the nature of the underlying data."
>
> "This reviewer was left wondering if such "implausible" observations at both ends of the dose response model outputs negate these models. Authors need to provide more in terms of what these observations mean for their overall risk assessment." (FDA 2009b, Expert Reviewer #7).

FDA did not address these concerns with their model results directly. A similar range of findings for both outcomes are reported in the January 2009 draft. For stroke only, the central estimate is reported in the findings, and the 95% confidence interval has been moved to Appendix B (Table AB-7). This is not likely the result that Reviewer #7 was hoping for.

If FDA overhauls the model, renews the effort and takes the overall collaborative, transparent and scientifically sound approach that we and other reviewers have suggested, different modeling frameworks and scenarios should be used to evaluate the issue. These should include efforts to determine types of seafood that vulnerable populations can eat to maximize benefits and minimize risks, and to examine the impact to specific subgroups that consume a lot of fish. This effort could also take into account other persistent contaminants, like PCBs, which pose a risk to the developing fetus, and are found in high amounts in some species.

REFERENCES:

Budtz-Jørgensen E, Grandjean P, Weihe P. 2007. Separation of Risks and Benefits of Seafood Intake. Environmental Health Perspectives. 115(3): 323-327.

Bakir F, Damluji SF, Amin-Zaki L, Murtadha M, Kahalidi A, Al-Rawi NY, Tikriti S, Dhahir HI, Clarkson TW, Smith JC, Doherty RA. 1973. Methylmercury Poisoning in Iraq, Science, (181): 230-241.

Burger J, Gochfeld M, Jeitner C, Burke S, Stamm T, Snigaroff R, et al. 2007. Mercury levels and potential risk from subsistence foods from the Aleutians. Sci Total Environ 384(1-3): 93-105.

Carrington, C.D. & Bolger, P.M. 2000. A Pooled Analysis of the Iraqi and Seychelles Methylmercury Studies. Human Ecological Risk Assessment, 6, 323-340.

Choi AL, Cordier S, Weihe P, Grandjean P. 2008. Negative confounding in the evaluation of toxicity: the case of methylmercury in fish and seafood. Crit Rev Toxicol 38(10): 877-93.

Cohen JT, Bellinger DC, Connor WE, Kris-Etherton PM, Lawrence RS, Savitz DA, Shaywitz BA, Teutsch SM, Gray GM. 2005a. A quantitative risk–benefit analysis of changes in population fish consumption. American Journal of
Preventive Medicine, 29(4): 325-334.

Cohen JT, Bellinger DC, Shaywitz,BA. 2005b. A Quantitative Analysis of Prenatal Methyl Mercury Exposure and Cognitive Development. American Journal of Preventive Medicine, 29(4), 353-365.

Cohen JT, Bellinger DC, Connor WE, Shaywitz BA. 2005c. A Quantitative Analysis of Prenatal Intake of n-3 Polyunsaturated Fatty Acids and Cognitive Development. American Journal of Preventive Medicine, 29(4): 366-74.

Crump KS, Kjellström T, Shipp AM, Silvers A, Stewart A. 1998. Influence of Prenatal Mercury Exposure Upon Scholastic and Psychological Test Performance: Benchmark Analysis of a New Zealand Cohort. Risk Analysis, 18(6): 701-713.

Davis JA, Greenfield BK, Ichikawa G, Stephenson M. 2008. Mercury in sport fish from the Sacramento-San Joaquin Delta region, California, USA. Sci Total Environ 391(1): 66-75.

Debes F, Budtz-Jørgensen E, Weihe P, White RF, Grandjean P. 2006. Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. Neurotoxicology and Teratology, 28(3): 363-75.

Domingo JL, Bocio A, Falco G, Llobet JM. 2007. Benefits and risks of fish consumption Part I. A quantitative analysis of the intake of omega-3 fatty acids and chemical contaminants. Toxicology 230(2-3): 219-26.

EPA. 2001. Reference Dose for Methylmercury (MeHg) (CASRN 22967-92-6). US Environmental Protection Agency, Integrated Risk Information System. Available at: http://www.epa.gov/ncea/iris/subst/0073.htm, last viewed April 15, 2009.

EPA. 2008. Memo: Comments from the National Center for Environmental Assessment on the draft FDA report, "An Evaluation of Risks to U.S. Consumers from Methylmercury in Commercial Fish Products, Including a Quantitative Assessment of Risk and Beneficial Health Effects from Fish. Letter from Peter Preuss, Director EPA NCEA to Ephraim King, Director EPA Office of Science and Technology. December 5, 2008.

EPA. 2009. Comments on. January 21, 2009 draft document. US Environmental Protection Agency. Docket FDA-2009-N-0018.

FDA. 2009a. Draft Risk and Benefit Assessment Report. Report of Quantitative Risk and Benefit Assessment of Consumption of Commercial Fish, Focusing on Fetal Neurodevelopmental Effects (Measured by Verbal Development in Children) and on Coronary Heart Disease and Stroke in the General Population. Center for Food Safety and Applied Nutrition, Food and Drug Administration. January 15, 2009. Available at: http://www.cfsan.fda.gov/~dms/mehgrb.html, last viewed April 19, 2009.

FDA. 2009b. Draft Risk and Benefit Assessment Report. Peer Review Report. Center for Food Safety and Applied Nutrition, Food and Drug Administration. January 15, 2009. Available at: http://www.cfsan.fda.gov/~dms/mehgpr.html, last viewed April 19, 2009.

Ginsberg GL, Toal BF. 2000. Development of a single-meal fish consumption advisory for methyl mercury. Risk Anal 20(1): 41-7.

Ginsberg GL, Toal BF. 2009. Quantitative approach for incorporating methylmercury risks and omega-3 fatty acid benefits in developing species-specific fish consumption advice. Environ Health Perspect. 117(2): 267-75.

Gochfeld M, Burger J. 2005. Good fish/bad fish: a composite benefit-risk by dose curve. Neurotoxicology 26:511–520.

Grandjean P, Budtz-Jørgensen E, White R, Jørgensen PJ, Weihe P, Debes F, Keiding N. 1999. Methylmercury Exposure Biomarkers as Indicators of Neurotoxicity in Children Aged 7 Years. American Journal of Epidemiology, 150(3): 301-305.

Grandjean P. 2009. Public Comments on. January 21, 2009 draft document. Docket FDA-2009-N-0018.

Hightower JM, Moore D. 2003. Mercury levels in high-end consumers of fish. Environ Health Perspect. 111(4): 604-8.

Hightower JM, O'Hare A, Hernandez GT. 2006. Blood mercury reporting in NHANES: identifying Asian, Pacific Islander, Native American, and multiracial groups. Environ Health Perspect 114(2): 173-5.

Kjellström T, Kennedy P, Wallis S, Mantell C. 1986. Physical and Mental Development of Children with Prenatal Exposure to Mercury from Fish. Stage 1: Preliminary Tests and Age 4. Solna, Sweden: National Swedish Environmental Protection Board.

Kjellström T, Kennedy P, Wallis S, Stewart A, Friberg L, Lind B, Pine T, Wutherspoon T, Mantell C. 1988. Physical and Mental Development of Children with Prenatal Exposure to Methylmercury from Fish. Stage II: Interviews and Psychological Tests at Age 6. (Draft). Solna, Sweden: National Swedish Environmental Protection Board.

Knobeloch L, Gliori G, and H Anderson. 2007. Assessment of methylmercury exposure in Wisconsin. Environ. Res. 103(2):205-10.

Levenson CW, Axelrad DM. 2006. Too much of a good thing? Update on fish consumption and mercury exposure. Nutr Rev 64:139–145.

Mahaffey KR, Clickner RP, Bodurow CC. 2004a. Blood organic mercury and dietary mercury intake: National Health and Nutrition Examination Survey, 1999 and 2000. Environ Health Perspect. 112(5): 562-70.

Mahaffey KR. 2004b. Fish and shellfish as dietary sources of methylmercury and the omega-3 fatty acids, eicosahexaenoic acid and docosahexaenoic acid: risks and benefits. Environ Res 95: 414–428.

Mahaffey KR. 2005. Mercury Exposure: Medical and Public Health Issues. Transactions of the American Clinical and Climatological Association. (116): 127-154.

Mahaffey KR, Clickner RP, Jeffries RA. 2009. Adult women's blood mercury concentrations vary regionally in the United States: association with patterns of fish consumption (NHANES 1999-2004).Environ Health Perspect. 117(1): 47-53.

Mozaffarian D, Rimm EB. 2006. Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA. 296(15): 1885-99.

Meyers. 2003. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. Lancet 361(9370): 1686-92.

Myers GJ, Davidson PW, Cox C, Shamlaye CF, Palumbo D, Cernichiari E, et al. 2003. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. Lancet 361(9370): 1686-92.

NAS. 2000. Toxicological Effects of Methylmercury. National Academy of Sciences, National Research Council, Committee on the Toxicological Effects of Methylmercury. The National Academies Press, Washington, D.C.

Oken, E., Wright, RO, Kleinman KP, Bellinger D, Amarasiriwardena CJ, Hu H, Rich-Edwards JW, Gillman MW. 2005. Maternal Fish Consumption, Hair Mercury, and Infant Cognition in a U.S. Cohort. Environmental Health Perspectives, 113(10): 1376-1380.

Oken E, Radesky JS, Wright RO, Bellinger DC, Amarasiriwardena CJ, Kleinman KP, Hu H, Gillman MW. 2008a. Maternal fish Intake during Pregnancy, Blood Mercury Levels, and Child Cognition at Age 3 Years in a US Cohort. American Journal of Epidemiology, 167(10): 1171-1181.

Oken E, Bellinger DC. 2008b. Fish consumption, methylmercury and child neurodevelopment. Curr Opin Pediatr 20(2): 178-83.

Philibert A, Vanier C, Abdelouahan N, et al. 2006. Fish intake and serum fatty acid profiles from freshwater fish. Am J Clin Nutr. 84: 1299-307.

Rice DC. 2004. The US EPA reference dose for methylmercury: sources of uncertainty. Environ Res 95(3): 406-13.

Sakamoto M, Kubota M, Liu XJ, Murata K, Nakai K, Satoh H. 2004. Maternal and fetal mercury and n-3 polyunsaturated fatty acids as a risk and benefit of fish consumption to fetus. Environ Sci Technol 38(14): 3860-3.

Smith KM, Sahyoun NR. 2005. Fish consumption: recommendations versus advisories, can they be reconciled? Nutr Rev 63: 39–46.

Strain JJ, Davidson PW, Bonham MP, Duffy EM, Stokes-Riner A, Thurston SW, et al. 2008. Associations of maternal long-chain polyunsaturated fatty acids, methyl mercury, and infant development in the Seychelles Child Development Nutrition Study. Neurotoxicology 29(5): 776-82.

Stern AH. 2005. Balancing the risks and benefits of fish consumption. Ann Intern Med 142(11): 949.

Tsuchiya A, Hinners TA, et al. 2008a. Mercury exposure from fish consumption within the Japanese and Korean communities. Journal of Toxicology and Environmental Health-Part a-Current Issues. 71(15): 1019-1031.

Tsuchiya A, Hardy J, Burbacher TM, Faustman EM, Marien K. 2008b. Fish intake guidelines: incorporating n-3 fatty acid intake and contaminant exposure in the Korean and Japanese communities. Am J Clin Nutr 87(6): 1867-75.