COMMENTS ON the FDA Report on its "Quantitative Risk and Benefit Assessment of Commercial Fish Consumption," Submitted by the Mercury Policy Project/Tides Center

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To The FDA:

We are commenting on behalf of the Mercury Policy Project (MPP), a project of the Tides Center, 1420 North St., Montpelier, VT. MPP is a non-governmental organization that coordinates policy work on mercury among environmental and public-interest health organizations. Comments were prepared for MPP by Dr. Edward Groth, an independent food safety and risk communication consultant residing in Pelham, New York.

At the outset, we considered two possibilities: First, that the FDA analysis of risks and benefits may be scientifically sound and essentially accurate. If so, the analysis suggests that the benefits of fish consumption are diffused across the population, while the risks from methylmercury exposure fall primarily on a small minority of consumers who eat large amounts of high-mercury fish. Basically, we already knew that. So, if it is valid, the FDA analysis adds relatively little to available information, and does not alter the need for focused, effective risk communication, aimed at persuading those consumers who need to do so to choose low-mercury fish.

The alternative possibility is that the FDA analysis is not scientifically valid, that it contains errors, arbitrary elements and uncertainties that render its results scientifically questionable at best, and perhaps even seriously wrong. If that is the case, then this FDA analysis should not be used as a basis for policy decisions, and a scientifically sounder analysis of benefits and risks of fish consumption may still be needed. In the meantime, it is still possible to maximize benefits and minimize risks (whatever their relative size) by the same strategy: Effective risk communication that promotes fish consumption and emphasizes choosing low mercury fish.

Having reviewed the FDA draft report in detail, we are persuaded, unfortunately, that the latter possibility—that the analysis is substantially flawed and its results may be seriously in error—seems the much more likely of the two. Our comments therefore are focused on issues where we believe FDA's analysis is deficient. We emphasize three aspects: Flaws and limitations in FDA's model for exposure to and risk from methylmercury; improved

ways to conceptualize and communicate about differences in mercury content of different fish; and emerging evidence on the risks and benefits of fish consumption.

In the latter context, we focus neurocognitive effects, both those associated with prenatal exposure to mercury from maternal fish consumption, and those that may be occurring in other subpopulations who eat large amounts of high-mercury fish. Our comments concern primarily the risk assessment side of FDA's endeavor. We also have a few comments on the prenatal neurocognitive benefits, but do not address the possible positive and adverse effects of fish nutrients and methylmercury on cardiovascular health, not because we feel they are unimportant, but because our primary interest and expertise lies elsewhere.

Our comments address the following general topics:

(1) Inappropriateness of assessing risks and balancing benefits against risks in the same analysis (violates basic principles of risk analysis).

(2) Biases, weaknesses, errors and arbitrary assumptions built into FDA's quantitative benefit-risk model that seriously degrade the scientific credibility of the results.

(3) Improved approaches for addressing methylmercury exposure associated with fish consumption, especially for risk management and risk communication purposes.

(4) Critical recent evidence on the prenatal neurodevelopmental effects of maternal fish consumption, including evidence FDA largely ignored in its analysis, and evidence the agency appears to have misinterpreted and/or should re-interpret in light of recent data.

(5) Possible adverse effects of mercury in populations other than women of childbearing age, which need to be considered in formulating risk-management strategies.

To supplement these general comments, we include a Technical Appendix with detailed, page-by-page comments on the FDA's draft report.

(1) FDA's Analysis Violates Basic Principles of Risk Analysis

The international food safety expert community, with active participation by US experts, has developed extensive principles for food safety risk analysis (FAO/WHO 2005, FAO 2006). A fundamental principle of risk analysis is the need for "functional separation" of risk assessment from risk management. In practical terms, this means that scientific tasks, including carrying out a risk assessment, and value-laden risk-management tasks, such as balancing risks against benefits, should be handled by separate teams. In many countries, in fact, these quite distinct tasks are conducted in separate agencies.

Such functional separation is required, the principles state, "to protect the scientific integrity of the risk assessment." Risk management relies to a large extent on weighing and comparing values. However, when value-weighted judgments enter or influence a

risk assessment, they can bias the outcome and undermine the objectivity and scientific soundness of the risk assessment.

FDA not only houses risk assessors and risk managers in the same agency, it formed a team including individuals from both groups to prepare the subject report, and it gave that team a statement of task that conflates risk assessment and risk management objectives. If someone had wanted to design a method for undermining the scientific integrity of a risk assessment by commingling it with value issues arising in risk management, they could hardly have devised a more effective approach than the one FDA knowingly chose to use in this instance.

Exactly this problem—risk-management approaches that influenced and undermined the soundness of the risk assessment—is evident in this FDA analysis. The stated purpose of the analysis is to "balance risks and benefits," clearly a risk management activity. While there is certainly a need to perform such balancing, FDA has attempted both to assess the risks of methylmercury in fish, and to balance the risks and benefits of fish consumption, in the same analysis. As we make clear later in these comments, this approach has clearly compromised the accuracy and credibility of the risk assessment.

In fact, the model developed by FDA may or may not be suited for assessing benefits of fish consumption, but it is highly inadequate for assessing the risks of mercury in fish. By force-fitting the risk assessment into this largely benefits-driven model, FDA's analysis has marginalized and effectively obscured some critical aspects of mercury risks.

(2) Flaws, Biases, and Errors in FDA's Analysis

A. The Analysis is Based on Fundamentally Flawed Concepts

Before we describe the numerous and serious biases, errors, misconceptions and poor scientific decisions in FDA's benefit-risk analysis itself, we must address fundamental problems with the way FDA has framed the issue, defined the purpose of the analysis, and tried to place the effort in a policy context.

1. Risk/Risk Trade-Offs Are Not Inevitable

FDA's initial framing of the issue sets up a classic false dichotomy: Consumers have to choose either to eat fish, thus gaining the nutritional benefits, but also accepting the risk of methylmercury exposure, or to avoid fish, minimizing mercury risk but also missing out on the nutritional benefits. This mind set—that the choice is a stark "either/or," with risk to health no matter which option one picks—permeates the FDA's analysis.

In fact, this lesser-of-two-evils choice is almost a complete illusion. The obvious "win/win" solution is to teach consumers to eat fish often but to choose low-mercury fish. This approach had by far the best outcome in the risk/benefit analysis of fish consumption by the Harvard Center for Risk Analysis (Cohen et al. 2005a). It is highlighted in the 2006

NAS/IOM committee report on benefits and risks of fish and seafood consumption (IOM 2006), recommended by virtually all authors of scientific studies on this topic, and is the central premise of the 2004 EPA/FDA joint advisory on fish and mercury.

FDA's focus on an essentially false choice suggests that policy should depend on the relative magnitude of overall benefits and risks from fish consumption, rather than on strategies that increase benefits and simultaneously reduce risks. It undermines current government advice, encourages interest groups that hope FDA will rescind that advice, and promotes fruitless debate over whether or not pregnant women should eat fish. (Of course they should eat fish—low-mercury fish.)

More effective risk communication built around the message that women—and everyone else—should eat more low-mercury fish would benefit public health immeasurably. We believe those benefits to public health could be achieved, without significant economic harm to the fishing industry, if all stakeholders would unite behind that message.

MPP believes strongly that some population groups should eat much less of certain high-mercury varieties of fish and shellfish. But the number of people who need to consider doing that is probably less than 20 percent of the population. Included are women of childbearing age, people above the 95th percentile in total fish consumption, and people who currently prefer to eat high-mercury fish. However, since many if not most people in the first two groups already eat primarily low-mercury fish, the true extent to which fish-consumption behavior needs to change is undoubtedly far smaller than the size of these combined population categories might suggest.

If consumers are given sufficient accurate information about both the benefits of eating fish and the mercury content of different fish, we believe increased consumption of low-mercury varieties should more than offset reduced consumption of higher-mercury fish. There would inevitably be some redistribution of market share; for instance, people may eat less tuna and swordfish, and more salmon and shrimp. The market is already driving such changes, for a variety of reasons unrelated to benefits and risks. But we believe no basis exists to fear that more accurate information about mercury risks, more effectively communicated, would make Americans eat less fish overall.

2. "Net Effect" is a Largely Meaningless, Misleading Construct

FDA's central approach seeks to calculate *net effects* of fish consumption, by expressing both benefits and risks per serving of fish, and then essentially subtracting adverse effects from beneficial effects. The primary results suggest that for most individuals, there is a net benefit (i.e., benefits are greater than risks).

This approach is conceptually flawed. Calculating net effects for the average individual makes no sense, because risks and benefits have very different distributions (**Figure 1**.) Comparing aggregate benefits and risks for the population as a whole, on the other hand, is misleading if, as is very likely the case here, the beneficial effects are spread diffusely across the population, while risks affect a small subset but affect at least some of them

relatively intensely. In that situation, the aggregate benefit may be much greater than the aggregate risk, but the latter may nevertheless be a substantial public health concern that requires risk reduction, even at the cost of some benefits.

FIGURE 1. RELATIONSHIP BETWEEN MERCURY DOSE PER SERVING OF FISH AND NUTRITIONAL BENEFIT, AS MERCURY CONTENT OF FISH INCREASES

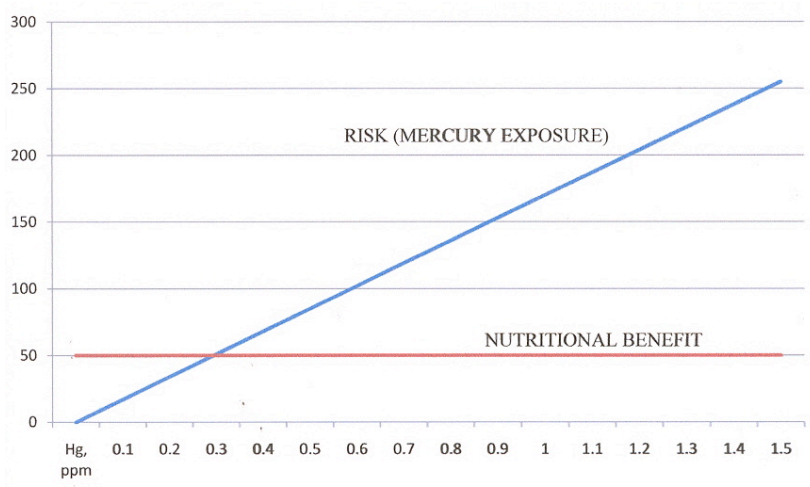


Figure 1 indicates that benefits are constant for any given serving of fish, while risk (in micrograms of mercury per 170-gram serving) rises linearly with the mercury content of the fish consumed. When assessing benefits, it may or may not be appropriate to treat all fish alike; i.e., to express positive effects per serving of fish, without regard for type(s) of fish consumed (see later discussion). But this approach is unequivocally inappropriate for assessing mercury exposure. The risk-management implications of the differences in mercury content of different fish are examined in Section (3), below. Here, we simply stress that the idea of a "net effect per serving of fish," which crops up again and again in FDA's analysis, is scientific nonsense. While the benefits may be roughly proportional to the number of fish servings consumed, mercury risk is driven more strongly by types of fish chosen than by amounts consumed.

The point where the lines cross (i.e., where risk begins to exceed benefit as fish mercury content increases) is likely to vary for different individuals and subsets of the population, and is essentially unknown. The point of intersection shown in Figure 1 merely illustrates the general concept; it is not meant to be quantitatively exact.

3. Quantitative Risk-Benefit Analysis on This Issue is Neither Feasible Nor Necessary

As our comments in Sections (2) B, C and D and in our Technical Appendix will make clear, FDA's effort to quantify benefits and risks of fish consumption must be judged a failure many ways. A basic problem is that there are too many data gaps and uncertainties in the evidence to support a credible analysis. The only practical way to carry out such an analysis is to make dozens of arbitrary, sometimes untenable assumptions, each of which

diminishes the reliability of the outcome. With so many arbitrary decisions built into it, the model must inevitably produce arbitrary, scientifically questionable results.

On some issues, the results of a flawed, scientifically challenged model might be better than nothing. In this case, there is no need for such an analysis. It is already clear that educating at-risk populations to choose low-mercury fish is the optimal policy approach. No elaborate quantitative analysis is likely to contradict the common-sense, obvious fact that simultaneously promoting benefits of fish consumption and reducing mercury risks offers the best long-term public health outcomes. As FDA notes, most fish and shellfish consumed by Americans are low in mercury. Teaching people who need to avoid higher-mercury fish how to do so requires modest changes in fish-consumption behavior.

In short, an obvious win/win solution to this problem is already known and is already the basis of EPA/FDA policy. Attempts to quantify risks and benefits, with all their attendant uncertainties, do not change this qualitatively sound knowledge. FDA should get on with educating consumers to eat more low-mercury fish. Why the agency chose instead to put several years and so much resources into a scientifically flawed risk-benefit analysis built around untenable concepts is a mystery to us.

B. The Analysis is Permeated With Serious Biases

Although it is presented by its authors as a purely scientific analysis, and by implication, might be presumed to be as objective as possible, the FDA report is thoroughly saturated with biases. Some of these are scientific biases, which influence multiple judgments and choices in developing and running the model. Some are value biases, subtle and not so subtle indications that different weights have been given to risks, benefits, and specific types of evidence of one effect or the other. Both kinds of bias have severely influenced the results of the analysis.

1. Scientific Biases: Feed The Model

In general, the scientific biases are explicit in the report, although their influence on the outcomes is often understated. Briefly, the main form of bias is one typically encountered in modeling exercises: Choices and decisions are driven primarily by what will work for the model, rather than by more scientifically appropriate criteria, such as data quality and relevance, congruence with published results, or similar criteria. Many specific instances of this general bias are cited in our Technical Appendix.

For example, the adverse effects of methylmercury on cognitive development have been measured on dozens of different outcomes. FDA had to choose from the broad literature those effects to include in its model as the basis for its risk dose-response component. It chose just a few effects that have also been associated with benefits of fish consumption, so that "net effects" could then be calculated.

In making this choice, FDA based its risk assessment for prenatal cognitive effects on a very small subset of the available evidence—excluding large amounts of data that might

have led to different results. Did it choose the narrow data sets it relied on because that evidence was strongest, scientifically? The least subject to uncertainty? Representative of effects with the greatest public-health significance? Consistent with results of the best recent studies? No. It chose those data because the "net effects" model required it, and because FDA had already done this segment of the analysis, nearly ten years ago.

Modelers with a sense of humor often compare some of the choices they must make in building their analyses to a drunk's decision to look for his lost car keys under the lamp-post, because that's where the light is better. That might seem like a pragmatic choice at the time, but it seldom yields a useful outcome. At many points in most such exercises, an analyst must confront data inadequacies or basic holes in scientific understanding that threaten to defeat the modeling effort. When there are a great many such obstacles, as is the case here, tempered scientific judgment often leads investigators to stop the analysis. Once it becomes clear that the number of artificial and arbitrary components of a model is so great that the validity of the results is doubtful, most scientists will pause the effort, and seek better data.

The fact that FDA did not pause this effort to seek better data, but instead pressed on, and is publishing this report as a proposed basis for future policy, suggests that this particular modeling effort was driven by more than a desire for credible scientific analysis. Hints as to what may have driven this exercise may be found in the next sub-section.

2. Value Biases: Spotlight on Benefits

A second and less explicit form of bias also pervades the FDA report. It seems clear to us that the authors were much more interested in documenting and quantifying the benefits of fish consumption than in assessing the risks of methylmercury exposure. This bias is clearly evident at multiple points, and it skews the results and downgrades the quality of the analysis in numerous ways. These value biases are not acknowledged, and although they are obvious to the reader, it is less clear whether the authors are even aware of them. However, their effects on the results are no less severe than the scientific biases.

We acknowledge a bias of our own in this regard: Our professional focus has been on documenting and communicating about mercury risks. But we offer here the following evidence of a clear "slant" of the FDA analysis toward benefits, and provide detailed examples in the Appendix.

The stated purpose of the analysis is to estimate the "net effects" of fish consumption on public health: The benefits of nutrients in fish, and the adverse effects of methylmercury exposure. Those benefits and risks are examined in the context of effects of maternal fish consumption on prenatal cognitive development, and benefits and risks of fish intake for cardiovascular health (fatal heart attacks and strokes). The cognitive development model indeed does compare nutritional benefits and detriments due to mercury. But the model for cardiovascular effects examines only benefits. Assessing the adverse effects mercury may have on cardiovascular health proved too scientifically difficult, the authors explain

(on page 38). So this critical assessment was simply not done, and the goal of comparing "net effects" on public health became impossible. In this respect, the analysis failed.

The FDA report includes a second major document, a research review. That review is concerned only with summarizing evidence on benefits of fish consumption. We are not entirely sure why FDA felt a need to generate its own literature review on this subject, given the several comprehensive, authoritative recent reviews by expert organizations that are cited in the FDA document. On the other hand, the last major US expert reviews on methylmercury risks were those by the National Research Council in 2000, and by EPA in its 1997 Report to Congress.

There has been a proliferation of recent research on methylmercury effects, especially in populations with comparatively low levels of exposure. A strong case could easily have been made that an authoritative, expert review of current epidemiological evidence on mercury risk would be at least as useful for FDA's analysis as a review of evidence for benefits of fish consumption. Yet FDA neither conducted nor (if FDA felt it lacked the expertise in epidemiology) commissioned such a review.

As a result, the scientific portions of FDA's draft report have an asymmetrical emphasis on benefits, with the strong associated implication that the agency, or at least the authors of this report, placed greater value on promoting the benefits of fish consumption than on managing the risks of methylmercury exposure.

The analytical sections of the FDA report show many instances of a similar bias. In some cases, this bias is combined with scientific ineptitude (see next section), leading to errors of interpretation. Generally, those errors tend to exaggerate benefits, and/or to downplay or minimize risks. Specific examples are detailed in the Appendix.

Another way that this bias expresses itself is in the report's strong emphasis on benefits and risks to average consumers. Benefits may or may not be best viewed as averaged out over the whole population, but risks must be viewed differently. Risks fall almost entirely on sub-populations who are either physiologically vulnerable (i.e., fetuses and pregnant women, young children), or at risk because of behavior (i.e., very high fish consumption, preference for high-mercury fish). A risk assessment needs to focus squarely and acutely on analyzing exposures of and risks borne by those specific vulnerable populations. Risk to the vast majority of the population or to the average individual matters far less.

By its very structure, a benefit-risk assessment loses most of that needed acuity, focusing largely instead on aggregate benefits and risks across the population, or "net" effects for the average individual. This perspective biases the analysis in favor of benefits and tends to marginalize and obscure critical risk issues. As we stated in Section (1), by combining the risk-management objective of "balancing risks and benefits" with the scientific goal of assessing the risks, FDA has compromised the scientific integrity and utility of the risk assessment, in several obvious and serious ways.

One final sign of this bias is evident from the peer review process. FDA sent the draft out for review by seven external scientists. At least one of them is an expert in, and a strong public advocate of, the beneficial nutritional effects of fish consumption. But none of the peer reviewers has done any epidemiological research on methylmercury in fish (though one appears to have studied ethylmercury in vaccines). The choice of reviewers suggests that FDA put lower priority on having its mercury risk assessment subjected to effective, expert critical review, and that the agency may therefore be less aware of the many and serious deficiencies a more competent external review might have revealed.

3. Questionable Judgments: Biased Results of "What If" Scenarios

The analysis includes four scenarios modeling the net impacts on cognitive development of possible changes in fish consumption among women of childbearing age; FDA calls them "What If" scenarios. The scenarios are biased in at least two ways that profoundly affect their outcomes, and thus the main conclusions of the analysis.

The first bias is one of omission. The four scenarios are as follows: Scenario 1 assumes that women are advised to limit fish consumption to 12 ounces a week, but not to change the types of fish they eat. Given the risk and benefit functions built into the model (which we believe are flawed—see Section 2C, below), this scenario results in a net loss of 0.015 IQ points per child, because women who had been eating more than 12 ounces of fish per week reduce their consumption to 12 ounces.

Scenario 2 assumes that all women eat exactly 12 ounces of fish per week, again without changing the types of fish they eat. This produces a net gain of 0.57 IQ points per child, because most women increase fish intake significantly, and the increased benefits offset the loss seen in Scenario 1. Scenario 3 assumes women limit their intake to 12 ounces per week, and choose only low-mercury fish. This scenario results in a net loss of 0.006 IQ points, because limiting high-end consumers to 12 ounces offsets the gain from avoiding mercury. Scenario 4 assumes that women choose only low-mercury fish but don't change how much they eat, i.e., some women still eat more than 12 ounces. This scenario results in a net gain of 0.18 IQ points per child.

Overall, Scenario 2 has the best outcome, given the model's assumptions, suggesting that telling women to eat more fish has greater benefits for public health than telling them to choose low mercury fish.

What's wrong with these scenarios? Plenty. First, they are all built around the same false "either/or" choice described on pages 3 and 4, above: Women must either eat more fish to gain benefits and accept mercury exposure, or avoid mercury and lose some benefits. In all four of FDA's scenarios, the beneficial effects of fish nutrition and the adverse effects of methylmercury partially offset each other. The "What If" scenarios do not include one in which women both increase their fish intake ***and*** switch to low-mercury fish. Had this "Scenario 5" been included, it would have projected far larger public health benefits than in any other scenario, because both changes—eating more fish, and eating fish with less mercury—have beneficial effects that would add to, not offset, each other.

How could FDA leave this obvious, widely-discussed and clearly preferable option out of its "What If?" modeling? The authors of the analysis either had an enormous blind spot, or a very strong bias toward promoting fish consumption without being concerned about simultaneously minimizing mercury exposure.

The other significant bias affects Scenarios 3 and 4. FDA's definition of "low mercury" fish includes canned light tuna. (See discussion in Section 3, below.) In the scenarios that involve women's eating only low-mercury fish, therefore, the women are still eating this canned tuna product. Canned light tuna is the most popular American fish choice, and it accounts for over 11 percent of the market. It is also the largest single source of mercury exposure in the US diet (see our Table 1, discussed later.) Since the model allows women who choose low-mercury fish to keep eating canned light tuna, their mercury exposure is not as low as it might be, and not as much different from exposure in the scenarios that do not involve choosing low-mercury fish as it might be. By defining low-mercury fish this way, FDA's model makes impacts of choosing low-mercury fish look much smaller than they would be if canned light tuna were not on the low-mercury list.

C. The Analysis Is Weakened by Numerous, Serious Scientific Errors

The overall scientific quality of the FDA analysis is quite low, far below a level that the public has a right to expect from the agency, or that is acceptable for a report with such significant policy implications. The scientific errors and flaws in the report are so many, and often appear to be so significant, that we believe the analysis is not an acceptable basis for policy decisions.

We cite many specific problems with the report's science in our Appendix. Some of the generic problems include:

- Many arbitrary choices made to suit the model. Many of them are questionable and a few seem untenable, in light of existing scientific knowledge.
- The report shows lack of understanding of basic principles of epidemiology, and how data from epidemiological studies can validly be interpreted, which leads to improper and often incorrect inferences about cited research results.
- Data selection is often based on criteria other than quality or reliability of the data; data are chosen to fit the model, even when they are not the most appropriate data.
- The analysts made innumerable data transformations, where data on one parameter are converted into data on another parameter required by the model. At each such conversion step, more imprecision and uncertainty are added to the results.
- Specific findings of certain studies have been misinterpreted, changing what the authors of the research papers reported. Most of these errors have bent research to fit the perceptions of the FDA report authors, rather than just stating what the original investigators reported.
- The report misses the forest for the trees; for example, it fails to note that recent studies strongly suggest that there is no threshold for methylmercury's adverse effects within the range of typical American exposure (See Section (4) for details.)

Although detailed scientific comments appear in our Technical Appendix, specifics are needed here, to illustrate the nature and possible impacts of the FDA report's scientific weaknesses. We will briefly examine the report's comparison of the beneficial effects of fish nutrition and the adverse effects of methylmercury on neurocognitive development, as an example of these generic scientific problems.

The ultimate objective of this part of FDA's analysis was to compare potential positive and negative effects and calculate the "net effect." For that reason, benefits and adverse effects needed to be expressed in some common metric. FDA chose verbal development as an outcome it felt could be quantitatively related to both fish nutrients and toxic effects of methylmercury, to support the desired comparison.

Next, FDA chose an index of verbal development from the large number of outcomes affected by methylmercury in different studies. The index chosen was age at first talking. FDA could find only two studies that offered data on that outcome, and both have major flaws and reliability issues in their data.

The first data set came from a study in Iraq of children whose mothers were poisoned by methylmercury in bread. Since one of the primary criteria FDA says it used to choose the studies it relied on was freedom from confounding, the fact that the women in this study did not get their mercury exposure from fish—and thus, possible beneficial effects of fish nutrients did not confound the results—was seen as an advantage. However, the study has several important disadvantages. The mercury doses involved were far higher than those ordinarily delivered by fish, creating a need to extrapolate effects from high doses to far lower doses. The study also evaluated only 81 children, a very small sample size. Neither the birth dates of the children nor the age at which they first talked were precisely known; instead, both were estimated within 3 to 6 months. In other words, the critical measure of outcome—the age of attaining a developmental milestone—is imprecise by 25 percent or more in this data set. This creates a very serious data quality issue.

FDA addressed the sample-size problem of the Iraq data by combining them with results on age of first talking from a larger study in the Seychelles. However, the mercury effect in the Seychelles was largely masked by beneficial effects of maternal fish consumption (see discussion of Davidson et al.'s 2008 paper, in Section (4) of these comments). FDA therefore adjusted for its selection of the flawed Iraqi data by ignoring one of its primary scientific criteria, lack of confounding, which affected its "adjusting" data set.

By combining these two data sets, FDA developed a dose-response relationship for the effects of methylmercury on age at first talking. Next, they needed data from which to develop a dose-response relationship for the beneficial effects of fish nutrients on age at first talking. Unfortunately, no studies provide such data.

Readers may be forgiven for being confused at this point. Wasn't the whole idea to find data on beneficial effects of fish nutrients and adverse effects of methylmercury *on the same outcome*, so that a net effect could be calculated? Since no studies have quantified

beneficial effects on age at first talking, why not choose a different outcome, one where both positive and negative effects have been measured? (Several studies have measured beneficial and adverse effects on the same developmental measures in the same children; see Section (4) of our comments, below, for descriptions of several of the studies.) But FDA chose instead to compare different outcomes.

FDA chose a single study of benefits of fish consumption on verbal development, by Daniels et al. (2004). The study used two standardized questionnaires to measure verbal development of children in the UK at the ages of 15 and 18 months. Age at first talking was not recorded. FDA defends its choice of this study for the comparison with mercury effects on first talking by reasoning that the children studied are "about the same ages as most children are when they start talking." I.e., FDA simply *assumed* that the effects are comparable, citing no scientific evidence to support this leap of faith.

Unfortunately, the UK study also has serious methodological problems and related data reliability issues. FDA considers the study as free of confounding, because the results showed no adverse effects of mercury exposure on verbal development. But the exposure index used in this case--the mercury content of umbilical cord tissue—has been shown to be less precise than other indices, such as blood or hair mercury, in other studies. When the exposure measure is imprecise, the likelihood than an association will be observed is reduced. There very likely *was* an effect of mercury in this population, even though the study did not detect it, in part because of confounding by fish benefits.

More problematic, though, were the verbal development outcome measures. Children in most of the published studies on methylmercury effects on cognitive development were evaluated by trained professionals in a controlled environment: Each child is tested in the same way, and inter-evaluator variability is measured and controlled for. The UK study mailed out questionnaires to the children's mothers, so it used 7,000+ evaluators whose myriad differences could not be controlled for. Mothers' subjective perceptions of their own children decreased the objectivity of data, and the mothers also knew how much fish they had eaten, so the study design was not "blind." How much these issues might have affected the reliability of the data is not known, but even if such data reliability issues are discounted, the Daniels data are qualitatively different from the results of most studies on mercury's effects, and thus difficult to compare.

FDA addressed the comparison problem by converting both outcome measures to IQ—an analytically useful step, but one that introduces additional uncertainties, because assumed equivalencies are only approximate. The more such transformations and assumptions are incorporated, the greater the uncertainty associated with quantitative results of the model.

FDA's conversion of age at first talking and the UK questionnaire results into IQ points for comparison also raises this obvious question: Most of the outcome measures of most of the studies of mercury effects on cognitive development could also be converted to IQ points. If, in the end, outcomes had to be expressed as IQ to be compared, why did FDA choose just two flawed studies for its model? Why not get and use the data from several other studies, including large, well designed ones with less ambiguity about the results?

FDA explains why each study was included or excluded, but the reasons given seem quite arbitrary. If the objective had been to get the best possible data on adverse effects of methylmercury on cognitive development for the risk-benefit model, it seems likely that most of the issues described could have been overcome.

The bottom line of this example is that FDA's analysis of the "net effect" of fish intake on fetal cognitive development is based on data from just three studies—two on the risk side, one on the benefits side. The analysts chose not to use data from more than a dozen other studies on the risk side, for largely arbitrary reasons. Each of the three studies FDA did rely on has important methodological flaws that call into question the reliability of its data. Different outcome measures were used for the benefits of fish consumption and the adverse effects of methylmercury on verbal development; converting them into IQ units for comparison introduces additional uncertainty and imprecision. The cumulative effect of the many selections, conversions, assumptions, uncertainties and other limitations built into the analytical process, in our judgment, is too large to accept the model's results as reliable scientifically.

Further evidence that the results of FDA's analysis are probably scientifically unreliable can be gathered by examining the results themselves:

- FDA's model predicts a very small adverse effect on IQ of mercury exposure. FDA compares its predicted effect with those estimated by two other analyses, including one by Cohen et al. at Harvard in 2005. Since FDA's estimate and that by Cohen et al. are similar in magnitude, FDA expresses confidence in its model.
- FDA's model predicts a comparatively large benefit from fish consumption, about four times *larger* than the mercury deficit. The same study by Cohen et al. looked at benefits as well as risks. Cohen et al.'s estimate of benefits was based on a thorough analysis of a wide range of published studies, and their estimated beneficial effect was far *smaller*—about one-third as large as the mercury deficit. Had FDA done the same thing with its benefits estimate that it did with its risk estimate—compared it with similar results of other investigators—it would have had to note that in this case, Cohen et al.'s estimate is more than an order of magnitude smaller than FDA's. That suggests strongly that FDA's benefits estimate—based on a single study with serious methodological problems, as we have noted—is unreliable.
- But FDA did not compare its benefits estimate with Cohen et al.'s (or anyone else's). The report merely presents the result as a fact, with virtually no discussion, and then immediately moves into discussion of "net effects" results.
- FDA's estimate of "baseline" net effects shows that the worst outcome predicted by its model is a loss of 0.41 IQ points, and that just 0.1 percent of the population would be negatively affected, with an average loss of 0.04 IQ points. Such small effects are unlikely to be detectable by even a large, well-designed epidemiological study.
- And yet, more than a dozen well-designed epidemiological studies have observed serious adverse effects of prenatal methylmercury exposure. Typically, effects have been performance deficits of several percentage points, across 10 to 50 percent of the studied population, i.e. at least 100 times greater than FDA's model predicts. Some

studies estimate both benefits and deficits, while others merely report substantial net adverse impacts of mercury exposure on fetal neurodevelopment.

- When the results of a model are so far out of line with extensive empirical evidence, it almost always means the model is wrong.
- We believe that is true in this case. FDA's model is wrong—primarily because its benefits estimate is not scientifically credible. The unreliable benefits estimate also invalidates the calculated "net effects"—a calculation we believe is conceptually flawed in any case, as explained above.

Please see the Technical Appendix for a more detailed critique, with our page-by-page comments on the FDA draft. The overall impression we are left with after studying this report is that, while it contains a great deal of ambitious analytical effort, it is also flawed by repeated instances of sloppiness, fuzzy thinking, thin rationalizations, and a sometimes breathtaking lack of scientific insight. Choice after choice has apparently has been driven primarily by the need to make the analysis fit a pre-determined "net effects" model. The accumulated weight of scientific flaws in this document, combined with a pervasive lack of adequate scientific caveats about the uncertainty of the results, degrades its credibility, and in our judgment, makes it an unsuitable basis for future policy decisions.

D. The Report Often Lacks Transparency

While this flaw is relatively minor compared to those just enumerated, we were frustrated in trying to evaluate the FDA report by occasional problems with lack of transparency. At several points, FDA offers important numerical values, but fails to explain clearly how they were derived. Several examples are discussed in the Technical Appendix.

The most serious transparency issue, in our judgment, is that the report's authors have failed to acknowledge or come to terms with the *cumulative* consequences of dozens of arbitrary assumptions, forced data choices and other artifacts associated with the model. While many specific assumptions are discussed where they are made, their likely impact on the results of the modeling exercise is often downplayed (see details in Appendix). As far as we can tell, no serious effort was made to assess the overall impact on the results of the uncertainties and biases introduced by the whole entire series of analytical decisions.

In general, the report lacks many necessary scientific caveats, even at points where they would ordinarily be required in standard scientific discourse. Single values are chosen to represent variables that span a broad range, without qualification. Model outputs that are subject to enormous uncertainty are presented as if they were undisputed facts.

Consequently, we feel that the undeniably large scientific limitations of this analysis have been substantially understated, leaving the impression that the results are more scientific and more credible than they in fact are.

(3) Elements of a More Appropriate Approach for Addressing Exposure to Methylmercury From Fish Consumption

In our judgment, the flaws, errors and biases pointed out in Section 2 render the FDA's quantitative benefit-risk assessment essentially worthless as a basis for policy, and we strongly urge that any plans to use it that way be abandoned. We think the analysis could be more useful as a guide to research needs, if it were reinterpreted with an emphasis on critical gaps and uncertainties that defeated the modeling effort. But it is not a credible scientific starting point for risk management.

However, as we stated in Section 2A, sound risk management strategies for promoting fish consumption while minimizing methylmercury risk already have been defined. They rely primarily on risk communication, teaching consumers about benefits and risks, and guiding them as appropriate to choose lower-mercury seafood varieties.

Communicating with consumers about methylmercury risks is one of our major roles in life; it is our professional concern, and it is something we know a great deal about. In this Section, we will outline the elements of an approach for thinking about mercury in fish, as a basis for communicating about that subject with the general public.

A. Mercury Levels In Fish

As FDA's report shows in detail, different fish have very different mercury content. The average methylmercury levels in 51 different fish and shellfish categories in Table AA-3 of the draft report span a range of more than 100-fold, from 0.012 ppm to 1.45 ppm.

An individual consumer's methylmercury exposure depends much more on the type(s) of fish consumed than on the amounts of fish consumed. Among people who consume fish at all regularly (say, one meal a month or more), the range of typical fish intakes is about 15- to 20-fold (one six-ounce fish serving per month would be about 6 grams per day; the 99th percentile consumer in FDA's model eats 88 to 136 grams per day). The comparative narrowness of this range vis-à-vis the 120-fold range in mercury levels suggests that fish variety is a far more important driver of mercury exposure than number of fish servings.

Viewed another way, people who consume enormous amounts of very low-mercury fish are unlikely to get an excessive dose of methylmercury, but those who consume even moderate amounts of high-mercury fish can easily exceed the Reference Dose by a wide margin. Clearly, mercury levels in different fish have greater impacts on exposure than do amounts of fish consumption.

From that perspective, discriminating among the types of fish and their different mercury content may well be the most critical element of risk communication.

Risk communication about mercury in fish faces two significant challenges: Effectively targeting information to specific groups and getting them to pay attention; and explaining differences in mercury levels and their risk implications in clear, understandable ways.

We focus here on the second challenge, because the expert community needs to clarify its own thinking in order to communicate clearly with the public on this topic.

For the average consumer, who probably eats fish once a week or less, differences in the mercury content of different fish do not matter a great deal. But for population subsets at significant risk—those described on page 8 of these comments—such differences matter a great deal. Communication efforts thus need to be designed and carried out with those specific audiences in mind. While how that might be accomplished is an interesting and complex topic, we will focus here on the content issue: How to think about and describe differences in mercury levels in different fish and shellfish.

We present here our own analysis, based on data from Table AA-3 of the FDA report. The data in Table AA-3 include the mercury levels in different fish and shellfish from the FDA database and market share data for 51 fish and shellfish varieties from the National Marine Fisheries Service (NMFS 2007). We estimate the contributions of different fish and shellfish items to total mercury in the US annual seafood supply, and thus to potential public exposure to methylmercury.

B. Contributions of Different Seafood Items to Americans' Mercury Exposure

Tables 1 and 2 (appended) show contributions of 51 different commercially important varieties of fish and shellfish to mercury in the US seafood supply. (Some varieties are "lumped" categories that include several similar but different fish or shellfish species.) According to FDA's draft report, these 51 categories represent about 99 percent of the total US supply of fish and shellfish for 2006 (NMFS 2007). There is no reason to think that including the other 1 percent would substantially alter the results of our analysis.

The mercury contributions shown in the table are relative inputs to the overall seafood supply, not precise exposure measures. Our analysis does not consider differences in the edible fractions of different fish and shellfish, for example. However, since the relative magnitudes of contributions of the different seafood items to total mercury inputs differ by more than 1,000-fold, these differences remain valid—and instructive—despite their acknowledged modest imprecision.

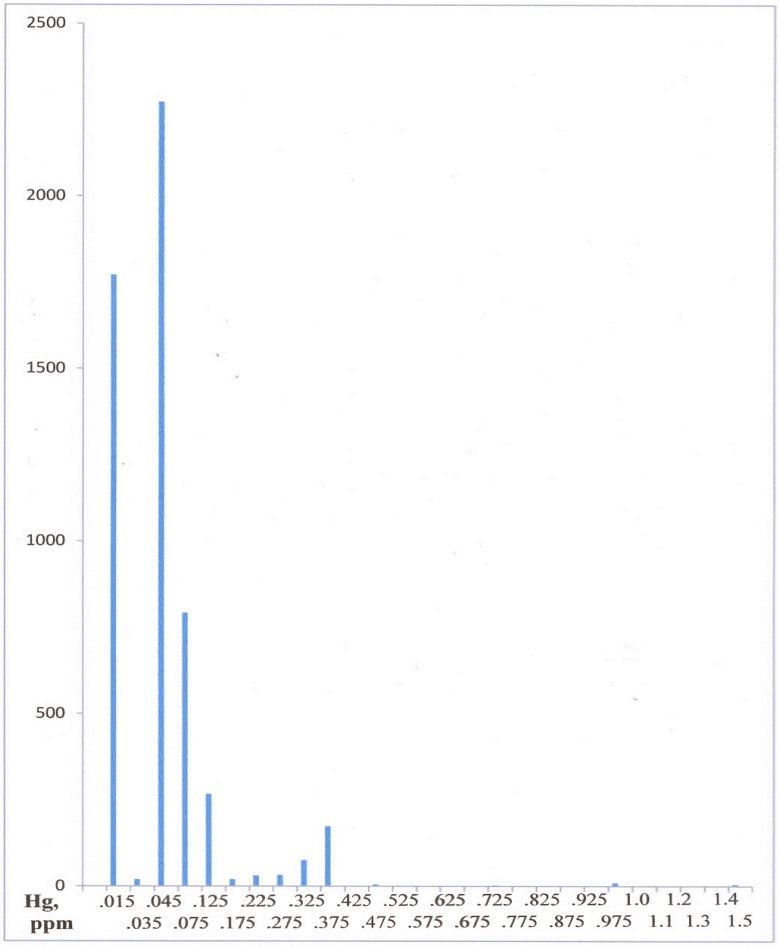
Table 2 shows that about one-quarter of the total mercury in the US seafood supply is found in comparatively low-intensity sources, such as shrimp, salmon, pollock, catfish, flatfish, and scallops. These seafood varieties have low or very low mercury levels, but are eaten in such large volumes (See **Figure 2**) that they still account for a substantial fraction of total mercury.

[Note to colorblind readers: We used colored fonts in the tables to help readers quickly discern differences in mercury content. We apologize if these colors are not visible to some readers, and will provide an all-black version of the tables on request.]

Collectively, the 10 **very low mercury** items (**green font**), including salmon and shrimp, two of the most heavily-consumed seafood items in the American diet, have a weighted

average mercury concentration of 0.018 ppm. These 10 items account for 42.9 percent of the seafood market, but contain only 9.1 percent of the total mercury.

FIGURE 2. DISTRIBUTION OF MERCURY LEVELS IN THE U.S. SUPPLY OF FISH AND SHELLFISH: THOUSAND METRIC TONS/YEAR AT EACH Hg LEVEL



The horizontal scale has been expanded at the low end and compressed at the high end. The figure shows that most fish and shellfish consumed in the US contain low mercury levels (less than 0.10 ppm). About 11 percent of seafood consumed here contains higher mercury levels, including barely visible (on this scale) amounts of shark and swordfish (0.975 ppm) and tilefish (1.45 ppm).

Eleven other items in the table have **below-average mercury** content (**blue font**), with a weighted average of 0.056 ppm. This group, which includes pollock, catfish, flatfish and crabs, makes up 24.1 percent of the total seafood supply, and contributes 16.0 percent of the total mercury. Together, the two lower-mercury categories account for 67 percent of the seafood market and contain 25.1 percent of the mercury.

Items in these two lowest-mercury categories are unlikely to lead to excessive mercury exposure for any individual consumers, no matter how much one may eat of them. This fact—most consumers already eat mostly low-mercury fish most of the time—means that risk communication can be targeted primarily toward people who prefer higher-mercury fish, a small minority whose behavior communication efforts should seek to modify.

Ten other items shown in Table 2, shown in **black font**, have **above-average mercury** levels (up to twice the overall average), with a weighted average for the group of 0.129 ppm. This group, which includes canned light tuna, cod, haddock and snapper, accounts for 22.5 percent of the seafood market and contains 34.3 percent of the total mercury. For an individual who eats much greater than average amounts of these items, their mercury content may be a concern, but it should not be an issue for most consumers.

However, one item in this **above-average** category calls for additional comment. Canned "light" tuna is the most popular finfish product and the second most heavily-consumed seafood item in the US diet. As our tables show, it contributes almost 16 percent of the mercury in the US seafood supply, slightly more than canned albacore tuna (which has three times its mercury content), and nearly twice as much as the next highest non-tuna fish category. The 2004 EPA/FDA advisory erroneously describes canned light tuna as a "low mercury fish." As Table 1 illustrates, canned light tuna contains 37 percent more mercury, on average, than does the U.S. seafood supply as a whole (0.118 ppm vs. 0.086 ppm). The mercury levels in canned light tuna also have been found to vary widely, as noted in FDA's report, with some lots of some brands exceeding 0.50 ppm (Malsch and Muffett 2006, Consumer Reports 2006).

At an FDA Food Advisory Committee meeting in December, 2003, during a discussion of the then proposed joint EPA/FDA advisory on mercury in fish, an FAC member asked the FDA staff how they drew the line between "low-mercury" fish and other fish. FDA's Clark Carrington responded, candidly, that FDA had wanted to include canned light tuna in the "low-mercury" category to avoid disruption of the market for this highly popular, economically important food item. Clearly, that choice, driven by economic and political concerns rather than scientific evidence, was an error. No item with a mercury level 37 percent higher than the average for all fish and shellfish can sensibly be classed as "low-mercury." It is time for FDA to acknowledge that error, reclassify canned light tuna as an above-average source of exposure and the largest single source of methylmercury intake for Americans (which it is), and redefine "low-mercury," probably as <0.086 ppm.

The chief sources of concern about potentially excessive exposure to mercury are the 20 higher-mercury fish and shellfish varieties shown in Table 1 and Table 2. We have sorted them into three categories: **moderately high mercury**, those with from two to four times the average level (**orange font**); **high mercury**, with four to eight times the average (**red font**); and **very high mercury**, with over eight times the average level (**violet font**).

The 10 **moderately-high-mercury** varieties in Table 2 have an average mercury content of 0.289 ppm and collectively account for 2.8 percent of the seafood market, but contain 9.6 percent of the total mercury. American lobster by itself accounts for 4.5 percent, and sea bass adds another 1.8 percent.

The six **high-mercury** fish and shellfish items in Table 2 have an average mercury content of 0.375 ppm. This group includes canned albacore tuna, fresh/frozen tuna and grouper, among other items. Collectively, this category accounts for 5.6 percent of the

seafood supply, but contains 24.6 percent of the total mercury. Canned albacore tuna accounts for 15.8 percent of the total, and fresh tuna for another 5.7 percent.

The four **very-high-mercury** fish in Table 2, swordfish, shark, king mackerel and Gulf tilefish, have an average mercury content of 0.964 ppm. Collectively they account for just 0.6 percent of the total market, but contain 6.5 percent of the total mercury. Swordfish alone accounts for 5 percent. While their relatively low market volume means these fish contribute only moderately to mercury exposure for the population as a whole, they are intense exposure sources that can result in excessive methylmercury doses for anyone who consumes them more often than occasionally.

Overall, as Table 2 shows, the 20 highest-mercury varieties collectively comprise just 8.9 percent of the seafood market, but contain 40.6 percent of the mercury in the fish supply. If the **above-average** category is included with the three higher groups, 30 seafood items that account for 31.5 percent of the market contain 75 percent of the mercury.

The three tuna categories, canned light, canned albacore and fresh/frozen, combined, account for 37.4 percent of Americans' dietary mercury exposure, or half the mercury contained in all 30 higher-mercury varieties. Tuna contributes nearly six times as much mercury as the entire **very high mercury** category, i.e., the four varieties singled out in the federal advisory, and more than four times as much mercury as the entire **very low mercury** category.

At the other end of the spectrum, 67 percent of the fish and shellfish market contains below-average mercury levels. The 11 **below average mercury** items are 24.1 percent of the market and include four of the 10 top-selling varieties, catfish, flatfish, pollock and anchovies. Four more of the top-10 selling items (shrimp, salmon, tilapia and clams) are in the **very low mercury** category, which makes up 42.9 percent of the market. Overall, two-thirds of seafood meals are low in mercury, and motivated, informed consumers can easily find widely available and popular low-mercury choices.

Table 3 presents mercury "intensity indices" for the six different categories of fish by mercury content, shown in Table 2. The mercury intensity index is a ratio, the percent of total mercury contributed by a category divided by the percent of the total market supply of fish and shellfish the category accounts for.

The Mercury Intensity Indices indicate the relative mercury dose consumers get from a standard serving of an average item in each category. As Table 3 illustrates, the intensity indices of the six different fish categories vary by more than 50-fold. A serving of a fish from the **very high mercury** group (swordfish or shark) delivers more than 50 times the mercury dose of the same sized serving of a choice from the **very low mercury** group (shrimp or salmon). An average serving from the **moderately high mercury** group (sea bass, lobster or halibut) delivers 16 times the mercury dose of an average of a serving of **very low mercury** fish or shellfish, while a choice from the **high mercury** group (orange roughy, albacore tuna or grouper) provides about 7 times the mercury dose of a choice from the **below average** mercury group (catfish, flounder or crab). A serving of canned

light tuna from the **above average** category contains ten times as much mercury as a serving of shrimp, from the **very low mercury** category.

TABLE 3. MERCURY INTENSITY INDEX OF DIFFERENT FISH CATEGORIES SHOWN IN TABLE 2

Category	Color	Hg range, ppm	Percent of Supply	Percent of Hg	Intensity Index
Very Low Hg	Green	0.01-0.043	42.9	9.1	0.21
Below Average Hg	Blue	0.044-0.086	24.1	16.0	0.66
Above Average Hg	Black	0.087-0.172	22.5	34.3	1.52
Moderately High Hg	Orange	0.173-0.344	2.8	9.6	3.43
High Hg	Red	0.345-0.688	5.6	24.6	4.57
Very High Hg	Violet	>0.688	0.6	6.5	10.83

MPP believes these distinctions matter, and are the primary determinants of mercury risk from fish and seafood. A consumer's mercury exposure depends very strongly on which fish he or she chooses to eat, much more so than on how often he or she eats fish. In our judgment, the differences between above average, moderately high, high and very high mercury levels, as well as the differences between very low and below-average mercury levels, can critically affect exposures for individuals. We believe FDA and other expert advisors need to draw more such distinctions—not merely separate fish into broad "low-mercury" and "other fish" categories, singling out the four highest-mercury fish (i.e., as in the current advisory and the database on the FDA web site).

We discuss what we believe are advantages of this six-tiered classification of mercury levels in different fish and shellfish in more detail in the Technical Appendix.

A proper risk assessment should focus on higher-mercury seafood varieties, and model mercury exposure among consumers who frequently eat the items listed in the three high mercury categories Table 2. While an average consumer eating average amounts of fish with an average mercury content is quite likely at very little risk, there are consumers at risk of excessive mercury exposure from fish consumption. A better job needs to be done of assessing the risks of excessive exposure associated with above-average consumption of fish varieties with above-average mercury content. While FDA's model tries to assess

those risks, it is seriously constrained by inadequate fish consumption data, as we discuss in our Technical Appendix. Getting better consumption data so that the analysis of risk among high-end consumers can be sharpened should be a high priority.

C. Implications of MPP's Analysis for Risk Communication

From the risk management perspective, risk communication messages need to focus on teaching consumers how to discriminate among fish and shellfish varieties by their very different mercury contents. For average and below-average fish consumers, i.e., those who eat fish once a week or less, the longstanding basic advice to "eat a variety of fish" should probably be fine-tuned, to include stronger suggestions to avoid eating high- and very-high-mercury fish any more often than seldom.

However, for people who eat more fish than average, and especially for consumers whose fish intake falls above, say, the 95th percentile of consumption, government advice needs to be far clearer about the wide differences in the mercury levels in different fish. Simply saying "choose a variety" is inadequate: A variety including swordfish, shark, tuna steak, sea bass and grouper would be a diverse but very high-mercury diet. Higher-volume fish consumers need advice on lower-mercury fish and shellfish, i.e., those that can be eaten often without risk of excessive mercury intake, and on higher-mercury fish and shellfish, i.e., those that should be enjoyed infrequently, to limit mercury exposure.

High-end fish consumers are a small minority of the total population; by definition, only 5 in 100 people fall above the 95th percentile in fish consumption. But some such high-end consumers like, and repeatedly eat, high-mercury fish, such as tuna and swordfish. The Mercury Policy Project has compiled and analyzed case-histories of 24 patients who were diagnosed by their physicians with methylmercury poisoning, caused by their heavy consumption of higher-mercury fish (MPP 2008). When we spoke with several of those patients, they expressed a recurring theme: "Why weren't we told? Why didn't anyone inform us that these fish we loved to eat were high in mercury?"

Whether FDA adopts our six-level classification of mercury content or another system of its own devising, it is absolutely critical that future risk communication messages avoid suggestions that "fish is fish," and instead draw clear distinctions among mercury levels in different fish.

D. Beyond Risk Communication: Revising and Enforcing Action Levels

Risk communication, i.e., giving consumers information they need to manage their own mercury exposure, will remain the primary tool for managing this risk. Given the benefits of seafood consumption, restricting the sale of even very-high-mercury varieties probably is inadvisable, and would be politically difficult to implement even if desired.

Nevertheless, FDA should consider updating, and making much more vigorous efforts to enforce, its Action Level for methylmercury in seafood. We believe the US should adopt

a two-tiered mercury action level, using 1 ppm only for very-high-mercury fish (the four varieties in violet font in Table 2), and setting the limit at 0.5 ppm for all other varieties. The two-tiered system has been adopted by the Codex Alimentarius Commission as the consensus international standard, and is in effect in most of Europe and many other parts of the world.

As Table 1 shows, aside from the four very-high-mercury fish varieties, only one other fish variety of the 51 types listed—orange roughy—has an average mercury level greater than 0.5 ppm. Adopting a second, 0.5 ppm Action Level for most fish would give FDA more flexibility to ensure that practical efforts are exerted to keep the mercury levels in commercial fish within acceptable guidelines.

Any Action Level, however, is of little use if it is not enforced. FDA has for many years chosen not to enforce the 1 ppm Action Level. Consumers Union has tested swordfish for mercury content on several occasions, and routinely found that at least half the samples it purchased exceeded 1 ppm. FDA's database shows an average mercury content of 0.976 ppm in swordfish, with a large number of samples above 1 ppm, and an average level of 1.45 ppm in Gulf of Mexico tilefish, most samples of which violate the Action Level.

Failure to enforce the Action Level sends an unintended, counterproductive message, i.e., that very high mercury levels in fish "don't matter." For consumers who choose fish with such high levels often, that is decidedly not true. Recent tests of a relatively small number of swordfish samples from European countries, by The European Environmental Bureau, an NGO, found no samples with more than 1 ppm of mercury, suggesting that the limit is being fairly effectively enforced in the European Union (MPP 2009).

FDA should commit resources to enforcing its own limit, and make it clear to both the fishing industry and consumers that the high mercury levels in some fish are justifiably a matter of regulatory concern.

(4) Critical Recent Evidence on Positive and Negative Effects of Fish Consumption During Pregnancy

Based on FDA's descriptions and interpretations of the scientific literature in the draft risk/benefit report, MPP believes FDA has not adequately grasped the significance of some recent research. The report also seems focused primarily on the issue of whether given studies can be used in FDA's model, rather than on what their findings show or imply about public health impacts of fish consumption. In this section we will review critical recent studies that, in our judgment, are redefining the paradigm for assessing prenatal effects of fish consumption.

Thirty years ago, an epidemiological study of lead exposure and cognitive performance among New England school children transformed scientific understanding of the public health impacts of lead pollution. Prior to 1979 it had been assumed that very high doses of lead, such as came from ingesting paint chips, could cause serious brain damage, but

that ordinary exposures—what the average child absorbed from lead in air, water, foods, soil and dust—had no discernible adverse effects.

The pivotal study, by Needleman et al. (1979) used improved methodologies compared to prior studies and showed that the school performance of children with average, "normal" lead exposure was adversely affected. As their lead exposure increased, performance on 11 indices of learning behavior declined, with no apparent threshold within the range of typical exposure.

Needleman et al.'s pioneering work was soon confirmed by other investigators in several countries, and the mounting evidence of public health harm from low-level lead exposure prompted vigorous, largely successful efforts to eliminate the metal from gasoline, foods and water supplies. Today, the average US child's blood lead level is less than one-fourth of what it was 30 years ago, and while lead poisoning has not been entirely eliminated, its toll on public health has been drastically reduced.

MPP believes the scientific community is on the verge of a similar paradigm shift with respect to the prenatal effects of methylmercury. Several recent studies have reported adverse effects of very low levels of mercury exposure, within the range of low-average American exposure, on cognitive development. Most of these papers have been published very recently, several within the past year. FDA's draft report cites these studies, in its bibliography or in tables, but largely omits discussion of their findings, and uses none of their data in its analysis, in part because they appeared so recently.

We believe FDA's report has given insufficient weight to this body of evidence, and that FDA needs to re-interpret several aspects of the studies it does cite, in light of the newly-emerging data. Most significantly, we believe this critical recent evidence should be the central concern of risk assessments in support of future policy actions on methylmercury exposure from fish consumption.

A. New Research Approaches Yield Critical New Insights

The common problem addressed by the studies reviewed here can be stated as follows:

Women are advised to consume fish during pregnancy, because of nutritional benefits for the baby's developing brain, particularly those associated with omega-3 fatty acids. Consuming fish also exposes the child prenatally to methylmercury, at doses that vary with the types and amounts of fish the mother chooses. The beneficial effects improve cognitive performance, while methylmercury impairs it, and both opposing effects are associated with fish consumption. Their simultaneous occurrence creates two problems: For the child, methylmercury may reduce the cognitive benefit derived from maternal fish consumption; and for researchers, the two effects may confound each other, making it more difficult to detect and quantify either benefits or harm.

We will review here seven recent studies, six of which have explored the simultaneous occurrence of beneficial nutritional effects and adverse effects of methylmercury on the

developing brain. The seven studies and their key findings are summarized in Table 4. In five of these studies, the researchers used sophisticated statistical analytical methods to separate beneficial and adverse effects. By taking both kinds of outcomes into account as confounding variables in the statistical models, these studies observed previously hidden effects and/or more accurately estimated their size. The relative magnitude of risks versus benefits is a central concern of FDA's analysis, so it is issue we address here.

1. Cohen et al. (2005a)

We begin by examining the well-known study of benefits and risks of fish consumption, and of potential public health impacts of changes in fish consumption behavior, carried out by the Harvard Center for Risk Analysis in 2005.

The study had two major components. First, expert teams conducted literature reviews and performed meta-analyses of major studies, to develop dose-response relationships for the main health effects of interest. With respect to cognitive development, our focus here, the study team did a meta-analysis of recent literature on omega-3 fatty acids and brain development, and a similar analysis of three prospective studies of methylmercury and cognitive development in populations with high-fish diets. They expressed the two dose-response relationships in terms of changes in IQ score—a positive change per dose of omega-3s, a negative change per dose of methylmercury (Cohen et al. 2005b, 2005c).

The second component of the study involved constructing hypothetical scenarios, based on assumptions about how American fish-eating behavior might change; projecting the associated changes in nutrient and mercury intake across the population; then applying the dose-response relationships generated in the first phase to estimate potential positive and negative impacts of the dietary changes on public health. They developed five such scenarios, described briefly as follows:

Scenario 1 assumed that women of childbearing age would follow the 2004 EPA/FDA advisory on mercury and fish consumption. That is, women would eat fish while pregnant but would avoid high-mercury varieties and choose low-mercury fish. No changes in fish consumption for other populations were assumed in this scenario.

Scenario 2 also focused only on women of childbearing age, but assumed they would misunderstand the EPA/FDA advisory, and reduce overall fish consumption in order to avoid mercury.

Scenario 3 assumed that not just women of childbearing age, but everyone in the US population, would be frightened by mercury advisories and cut back fish consumption.

Scenario 4 assumed that efforts to persuade Americans to eat more fish would succeed, increasing everyone's fish consumption by 50 percent, except for women of childbearing age, who did not change their consumption.

Scenario 5 assumed that everyone, including women of childbearing age, would eat 50 percent more fish. Scenarios 4 and 5 assumed increased consumption of fish of all types, without discrimination by mercury content.

The positive effects of omega-3s and the negative effects of methylmercury on prenatal cognitive development, as projected in these scenarios, are bimodal: I.e., when omega-3 intake increases, IQ increases; when omega-3 intake decreases, IQ decreases. Mercury has the opposite effects: When mercury exposure increases, IQ decreases, and when the women's mercury exposure is reduced, the babies' IQ is increased.

The positive and negative effects on IQ in the four relevant scenarios are displayed in Table 4. (Scenario 4 involved no change in women's fish consumption, thus no changes in effects on IQ.) The results are expressed in terms of aggregate IQ points for all babies born in the US in a year.

Scenario 1 had far the best outcome. Women continued to eat fish, chose low-mercury fish, and essentially eliminated their mercury exposure. The projected impact included a modest benefit from omega-3 consumption, and an enormous benefit (i.e., elimination of a large adverse effect) from the reduced exposure to mercury.

Scenarios 2 and 3, those with reduced fish consumption, projected substantial net benefit to aggregate IQ, the combined result of a loss of some cognitive benefit because of lower omega-3 intake, more than offset by greater benefit from reduced mercury exposure.

Scenario 5 had the worst outcome. Increased fish consumption by mothers-to-be led to the largest benefit from increased omega-3 intake in any scenario, but this was more than offset by a much larger negative impact on IQ from increased mercury exposure.

Although the scenarios are hypothetical (and the assumptions underlying them can be and have been criticized, including by us), the most noteworthy aspect of the HCRA study's results with respect to IQ effects, in our judgment, is the relative magnitudes of positive and negative effects. The dose-response relationships, developed by meta-analyses of the best evidence on prenatal effects of omega-3s and methylmercury, respectively, available as of late 2004, clearly suggest that of the two dietary components, mercury has by far the more powerful effect on the developing nervous system. In Scenario 1, the benefit from avoiding methylmercury is almost 10 times as great as the benefit from increased intake of omega-3s. In the other three scenarios, the mercury effect is about three times as great as the omega-3 effect.

Even in Scenario 1, the optimal outcome, the aggregate IQ effect is not terribly large; a change of 410,000 IQ points represents about 0.1 point per baby born in the US annually, on average. However, as we noted earlier in these comments, risks and benefits are not distributed equally, and the average IQ effect is probably not the proper focus.

The benefits of omega-3s vary with the type of fish consumed, but in the absence of data to support a better assessment of distribution, might reasonably be taken as an average,

across the population. But the adverse effects of mercury would affect most intensely the children whose mothers regularly ate higher-mercury fish, a small fraction of all women. However, for women in that subset, the effects of changes in mercury exposure—whether lost IQ points due to increased mercury intake, or improvements in IQ scores because of switching to low-mercury fish—the effects would be far greater than the average of 0.1 IQ point per child.

2. Oken et al. (2005)

A team of investigators associated with a large ob-gyn practice in the Boston area did this study, on women enrolled in Project Viva. Project Viva is a large, prospective study that measured a wide variety of dietary and environmental factors for women who enrolled in the cohort when they became pregnant, and is examining the development of babies born to those mothers, looking for associations with factors that may have affected the women during gestation.

In the 2005 study, Oken et al. examined a cohort of children born to their subjects, testing them for cognitive development at the age of six months, then looked for associations of developmental progress with the mother's fish consumption and mercury exposure when she was pregnant. Key results are shown in Table 4.

The outcome measure used was a standard battery of tests for visual recognition memory, (VRM) used to assess cognitive development in infants. The mother's mercury exposure, based on hair samples taken during pregnancy, was used to classify babies into low- and high- mercury groups. The mother's fish consumption, as self-reported on a questionnaire she completed during prenatal visits, was used to quantify intake of beneficial nutrients; women were classified as average or above-average fish consumers. Multiple regression analysis was used to measure associations between fish consumption, hair mercury level, and positive and negative effects on cognitive outcomes.

This study used sophisticated statistical analyses to treat beneficial nutrient effects and adverse mercury effects as confounding variables that could each tend to mask the other effect. By doing so, they were able to adjust their mercury results for nutrient effects, and vice versa. With that methodological advance, they documented beneficial and adverse effects of the mothers' fish consumption during pregnancy.

Children born to women in the high fish-consumption group had better VRM scores. But infants whose mothers were in the high-mercury-exposure group had lower VRM scores. The negative effects were slightly larger, and each effect was stronger and more readily detected when the confounding effect of the other variable was taken into account.

The most notable aspect of this study, other than the advances in statistical methods that allowed them to observe the associations, was the nature of the study population. Women in this Project Viva cohort were quite average in terms of fish consumption and mercury exposure. Their mean fish consumption was 1.2 meals per week, only slightly above the US average. High mercury exposure was defined as above the 90^{th} percentile in maternal

hair mercury; the 90th percentile in this case was 1.2 ppm, very close to the 90th percentile of typical hair mercury values for American women.

This study was one of the first, if not *the* first, to report adverse effects of mercury on prenatal cognitive development in a population whose fish intake and mercury exposure were representative of typical Americans. Since it was published, five additional papers have appeared that largely replicate and confirm these findings, four of them in 2008.

3. Oken et al. 2008

A second report by the same Project Viva team presented findings of cognitive testing performed on children from the same cohort of mothers at the age of three years. As Table 4 shows, the results confirmed the earlier findings at age six months.

Children were evaluated using the Peabody Picture Vocabulary Test, which measures verbal development, and the Wide Ranging Assessment of Visual Motor Abilities, a test that involves matching and copying figures and evaluates fine motor coordination. Key results are shown in Table 4. Children born to mothers in the high-mercury group had significantly lower scores on both tests. Children whose mothers ate more fish scored significantly higher on the visual-motor test; their score on the verbal test was slightly higher, but the difference was not statistically significant.

These results strengthen the conclusion that fish consumption during pregnancy has both beneficial and adverse effects on children's cognitive development. In this case, positive and negative effects appear to be of roughly the same magnitude.

Once again, the fish consumption and mercury exposure of the mothers were well within the typical range. The women's average fish intake was 1.4 meals per week; the "high" consumers ate fish twice a week or more. (The average differed from the earlier study's because the 2008 paper examined a larger sample chosen from the overall study cohort.) High mercury exposure, above the 90th percentile in maternal hair mercury, was also 1.2 ppm in this case. The mercury level in blood was not measured, but the high-exposure mothers' blood mercury level was probably also around the 90th percentile.

According to the 1999-2004 NHANES survey, the 90th percentile blood mercury level for women in the Northeastern US was 5.2 µg/l (Mahaffey et al. 2009, Supplement, Table 2). This study therefore suggests that adverse effects of mercury on cognitive development can occur at an average dose below the Reference Dose and the corresponding Reference Level of 5.8 µg/l mercury in blood.

4. Lederman et al. (2008)

This study examined women who were exposed to air pollutants from the September 11, 2001 disaster at the World Trade Center (WTC) in New York City while pregnant, and evaluated their children's cognitive development. The mothers' mercury exposure was measured and examined for associations with proximity to the WTC fires and with fish in

the diet. Assessments of cognitive development were performed at the ages of 12, 24, 36 and 48 months.

No association was found between living or working near the WTC and maternal blood mercury or umbilical cord blood mercury levels. However, mercury levels were strongly associated with fish consumption. Both beneficial and adverse effects of fish intake on cognitive development were observed. Like the Oken et al. studies, this one considered mercury effects and nutrient effects as potential confounders of each other, adjusted the model statistically to take those opposing effects into account, and was therefore able to observe stronger associations for each variable.

The cognitive tests used were the Bayley Scales of Infant Development, 2nd Edition (BSID-II) at ages 12, 24 and 36 months, and the Wechsler Preschool and Primary Scale of Intelligence, Revised (WPPSI-R) at age 48 months. The BSID-II tests include two measures, the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). The WPPSI-R tests provide Verbal, Performance and Full IQ scores.

The key results, shown in Table 4, found significant positive and negative effects on the PDI component of the BSID-II at age 36 months, and on IQ scores at 48 months. Effects were stronger as the children grew older. Umbilical cord blood mercury was associated with significant decreases in the 36-month PDI score and with lower scores on all three components of the WPPSI-R IQ. Beneficial effects of fish intake were observed on the PDI score at 36 months and on verbal and full IQ at 48 months. In this study, beneficial effects were somewhat larger than adverse effects.

As in the Boston study, the women in this New York cohort were quite "average." The mean maternal blood mercury level was 2.29 µg/l , and in cord blood it was 5.05 µg/l. The geometric mean blood mercury level was 0.91 µg/l, compared to 0.92 µg/l for the 1999-2002 NHANES sample. In the New York study, 5.66 percent of the women had blood mercury above the US EPA reference level of 5.8 µg/l; in the NHANES sample, 5.95 percent were above that level. Data were not collected on the frequency or amounts of seafood consumption; instead, women were asked how many types of seafood they had eaten while pregnant.

Overall, this study reinforces the finding that both beneficial effects of fish nutrients and adverse effects from methylmercury occur in children whose mothers' exposure during pregnancy was essentially average for American women. The vast majority of women in this study were exposed at doses below the Reference Dose.

5. Davidson et al. (2008)

This paper and the next one (Strain et al. 2008) are reports from the large, prospective study of mercury effects in the Republic of Seychelles, where the diet is high in fish. In most previous reports from that study, the researchers have failed to observe statistically significant associations between mercury exposure and cognitive outcomes. The authors considered it likely that beneficial effects of fish nutrients might have masked adverse

effects of mercury, and vice-versa. They designed the current study, like the three just described, to control for these confounding effects in the analysis, to determine whether previously unobserved associations might emerge.

The Davidson et al. paper reports the assessment of mercury effects. Strain et al.'s paper (discussed below) assesses the positive effects of fish nutrients.

As shown in Table 4, this time, after making adjustments for the confounding effects of fish nutrition, the investigators did find an adverse effect of mercury exposure on child cognitive development. The outcome measure used here was the BSID-II, administered at 9 and 30 months of age. As in Lederman et al.'s study, mercury effects were more clear-cut in older children. The result, shown in Table 4, was a small but statistically significant decrease in the BSID-II PDI component at age 30 months. No significant effects on either the PDI or the MDI score at 9 months, nor on the MDI at 30 months, were observed.

The Seychellois population eats a great deal of fish; women in this cohort reported eating nine meals with seafood per week. Their intake was 537 grams/week, three to four times higher than the US average. The average maternal hair mercury level was 5.9 ppm, much higher than is typical here.

Nevertheless, this paper moves the Seychelles study closer toward agreement with other investigations that have reported adverse effects of methylmercury on prenatal cognitive development, and it reaffirms the methodological importance of taking into account the confounding influence of opposite effects of fish nutrients and mercury on developmental outcomes.

6. Strain et al. (2008)

This companion paper to the study by Davidson et al., just described, reports the analysis of nutrient variables and their possible association with cognitive outcomes, in the same Seychellois mothers and children just described, using the same cognitive test results.

Instead of assessing nutritional status using subject-reported fish consumption, this study measured levels of long-chain polyunsaturated fatty acids (LCPUFA) in maternal blood at several points during pregnancy.

As Table 4 shows, the study found no association between blood PUFA levels and either component of the BSID-II test, at age 30 months. There was a small but significant effect of blood omega-3 levels on the PDI at 9 months, which was stronger after adjustment for the confounding effect of mercury. But the effect did not persist when the children were tested at the age of 30 months.

Overall, these two recent papers from the Seychelles found stronger evidence of adverse effects from mercury than of beneficial effects of fish nutrients, and both effects were quite small compared to those seen in other studies. An interesting observation in Strain et al.'s paper is that the measured blood LCPUFA levels did not correlate at all with the

mothers' reported fish consumption. This suggests that self-reported fish intake may not be an accurate measure of potential nutritional benefits of fish intake during pregnancy, an issue explored in more detail in a separate paper (Bonham et al. 2008).

7. Jedrychowski et al. (2006)

This study, done in Krakow, Poland, was concerned only with potential adverse effects of prenatal methylmercury exposure; it did not attempt to assess the beneficial effects of fish consumption. Nevertheless, it is included in this review because of its concordance with the findings of other studies here regarding mercury effects at very low exposures.

Infants were evaluated for cognitive development at the age of one year, using BSID-II. The infants' scores were sorted into "normal" and "delayed" categories of neurocognitive performance, and the mercury exposure of children (umbilical cord blood mercury level) and mothers (maternal blood mercury) in the two groups were compared. Confounding variables were tested for influence with multiple regression analysis. The mothers' fish consumption was determined by food frequency questionnaires administered three times during pregnancy; fish intake was classified as smoked, fried, roasted or grilled, but not by variety or mercury content, and quantities consumed were not recorded.

Key results are shown in Table 4. The infants with delayed neurocognitive performance had significantly higher mercury exposure (mean maternal blood mercury, 0.75 µg/l; cord blood mercury, 1.05 µg/l), compared to infants with normal neurocognitive performance (0.52 µg/l and 0.85 µg/l, respectively). Differences between the groups were marked on both components of the BSID-II: The high-mercury infants scored 16.6 points lower on the PDI, and 10 points lower on the MDI. These negative effects are substantially larger than those observed in other studies reviewed here.

No dietary factors were associated with differences in cognitive development, indicating that maternal fish consumption—at least as measured by the questionnaires used in this study—did not differ significantly between mothers of normal- and delayed-performance infants. Differences in mercury exposure therefore appeared to depend on types of fish consumed, not amounts. The absence of association of maternal fish intake and cognitive outcomes prevented this study from examining possible beneficial neurocognitive effects. Such effects might in theory have been present but obscured by larger effects of mercury, but the analyses required to discern that were not performed in this case.

The geometric mean maternal blood mercury level in the women in this study was only 0.55 µg/l, slightly more than half of the geometric mean in Lederman et al.'s study of New York women. The range of blood mercury in these Polish women was 0.10 to 3.40 µg/l, and 90 percent had less than 2.0 µg/l, below the typical range for American women. Like the previous studies cited here, this one suggests that methylmercury has adverse effects on the developing brain at dose levels in the range of typical American exposure, with no apparent threshold.

The same research team published a second study (Jedrychowski et al. 2007), in which they evaluated children of the same cohort of women for cognitive development at ages 24 and 36 months. The effects that were observed at age 12 months were not seen in the two- and three-year-old children.

In this study, mothers' fish consumption was quantified, and was strongly associated with mercury exposure. Fish intake during pregnancy of the mothers whose children had high cord-blood mercury (>0.90 µg/l) was 31 percent higher during the first two trimesters and 55 percent higher during the third trimester than the fish consumption of mothers of low-mercury babies. While this higher fish intake led to higher mercury exposure, it clearly also exposed the high-mercury babies to larger doses of beneficial nutrients, confounding possible developmental effects of mercury. Although the analysis did control for several other confounding factors, potential confounding by fish intake was not assessed.

B. Discussion

Collectively, the studies reviewed here provide strong new evidence that the adverse effects of methylmercury on cognitive development occur at low mercury doses, well within the range of typical exposure among American women of childbearing age. The Boston women studied by Oken et al. had a 90th percentile blood mercury level of about 5 µg/l; Lederman et al.'s New York cohort had an average blood mercury level of 2.3 µg/l; and the Polish women studied by Jedrychowski et al. had an average blood mercury level of just 0.75 µg/l. Collectively, these studies indicate no threshold for adverse effects of mercury on the fetal brain within the range of normal, everyday exposure associated with fish consumption.

Most of these studies show that fish consumption during pregnancy also has nutritional benefits for cognitive development. The model developed by Cohen et al. for comparing benefits and risks, using meta-analysis to develop dose-response relationships for omega-3 fatty acids and methylmercury, suggests that the negative impact of mercury is larger than the positive impact of omega-3s. Most of the studies reviewed here suggest that the benefits and risks are of about the same magnitude, with variability from study to study. The issue of relative magnitude of benefits and risks to prenatal cognitive development remains to be resolved by future research.

Whatever their relative magnitude, nutritional benefits and adverse effects associated with fish consumption during pregnancy are differently distributed. Benefits appear to occur with consumption of most fish, while mercury effects are concentrated among the women who eat higher-mercury fish. As we have shown in Table 3, the mercury dose a woman gets from a serving of fish can vary by more than 50-fold, depending on which category of fish (stratified by mercury content) she chooses from.

The question of why the largest negative impact on cognitive outcomes was reported in a study with the lowest blood mercury levels is worth examining. In studies of nutritional benefits of fish consumption on cardiovascular health, the largest effect has often been associated with eating "some fish," versus "no fish." That is, the incremental benefit of

an increase in fish consumption tends to be less than the initial benefit of consuming any fish at all. Perhaps something similar holds true for toxic effects of mercury; i.e., the largest impact may come from initial mercury exposure, compared to almost none, and increases above that initial dose may have less severe incremental impacts.
The Polish women studied by Jedrychowski et al. had mercury exposure well below the average in most studies. Even groups with "low" mercury exposure in other studies seem to have considerably higher exposure than the women in the Polish study. The fact that "normal" populations themselves have only slightly lower mercury exposure than "high-exposure" groups in most studies may have made it harder to detect effects of very low doses in those studies. This possibility can be explored by future research.

We believe, based on the evidence cited here, that methylmercury exposure in women of childbearing age is a greater public health concern than previously recognized. We think a revised scientific consensus will soon emerge or is already emerging: That the typical, relatively low mercury exposure an average American woman gets from eating fish and seafood has discernible adverse effects on the developing brain. There appears to be no level of exposure to methylmercury that is free of significant risk.

If so, it is all the more important to highlight the advice offered by the authors of most of these studies: Women should eat fish while pregnant, but choose low-mercury fish. In its future policy actions, FDA should re-emphasize this message and expand its efforts to get the message out to all women in the target group.

We cannot state strongly enough that the importance of reducing this risk is not lessened by the benefits of fish consumption. There is no need to accept this risk as a trade-off for improved cognitive development or reduced cardiovascular risk. As Cohen et al.'s study made clear, there is a simple, enormously successful "win/win" approach: Teach women to follow the current EPA/FDA advice and eat low-mercury fish.

(5) Possible Adverse Effects of Methylmercury in Populations Other Than Women of Childbearing Age

Conventional scientific wisdom has long held that the developing brain is the system most sensitive to toxic effects of methylmercury, and that the critical populations at risk are therefore women of childbearing age and young children, up to age six or so. It has been widely believed that the methylmercury doses associated with ordinary levels of consumption of fish from unpolluted waters are too low to have adverse effects in other population groups. Consequently, there has been far less research on the potential for such effects in populations other than mothers and children.

While the attention paid to women and children is entirely appropriate, significant health risks of methylmercury, worthy of attention in strategies for managing mercury risks, also occur in other populations. These other at-risk populations include adults of both genders and children with atypical levels or patterns of fish consumption, and individuals who are hypersensitive to toxic effects of methylmercury.

Atypical fish consumers include those who eat fish very often (perhaps four or more times a week), and those who have a strong preference for, and repeatedly eat, varieties of fish and shellfish that fall in the three higher-mercury categories in Table 2. Among the latter group, consumption frequency of only once or twice per week may lead to an excessive mercury dose, depending on fish varieties chosen and portion sizes.

It is well known that individual people respond differently to pharmacological and toxic agents, for a variety of intrinsic reasons. In theory, human variability in response to toxic substances is believed to span at least a 10-fold range. In practice, actual variability has not been well characterized for most agents, and variability in sensitivity to toxic effects of methylmercury has not been empirically quantified. However, it is certain that some people experience toxic effects at doses far below those that affect an average individual, while others may experience no toxic effects at doses far higher than those that produce symptoms in the average person.

Late last year, MPP prepared an analysis of 24 published reports of individuals who were diagnosed by physicians as having methylmercury poisoning caused by consumption of high-mercury fish (MPP 2008). Most of the cases ate fish five to ten times per week, and ate primarily or exclusively higher-mercury fish. Among the 21 cases who ate fish caught commercially (the other three were sport anglers), 86 percent ate tuna, and 38 percent ate swordfish, for example.

Blood mercury levels in the 24 patients ranged from 7 to 228 µg/l. Among the cases with moderate to severe symptoms, one group had blood levels of 58 to 125 µg/l, but a second group—one-third of the total cases—had blood levels of 12 to 38 µg/l, an indication that they were probably unusually sensitive to toxic effects.

Such extreme exposure is certainly rare—and cases with symptomatic methylmercury poisoning, even rarer. MPP has estimated, using three different methods, that less than one-tenth of one percent of the population may have extreme elevated mercury exposure from their fish consumption. Nevertheless, the risk of extreme mercury exposure seems both real and significant for a definable sub-population of high-end fish consumers. This public health problem should be amenable to carefully targeted risk communication, and FDA should address that need.

While cases involving overt symptoms of methylmercury poisoning are rare and most likely involve hypersensitive individuals, there is an additional concern: Methylmercury can impair cognitive and neurobehavioral functions with subtle, subclinical effects. Two studies published in 2003, neither in the US, demonstrated that, when appropriate tests are used, similar to those used to evaluate children in the studies in the Faeroes and the Seychelles, similar functional deficits can be observed in adults with elevated exposure from consuming high-mercury-fish diets.

Yokoo et al. (2003) examined members of Amazonian tribes living in an area where the rivers and fish supplies were polluted by mercury from gold mining. They assessed 129

adults using five different test batteries for neurocognitive and fine-motor functions. They classified subjects' mercury exposure based on hair levels. The mean hair mercury level was 4.2 ppm, the range 0.56-13.6 ppm; this range overlaps the range seen in the study in the Seychelles, as well as in some high-end fish consumers in the US. Results of the tests for cognitive and fine-motor functions showed clear dose-related impairments of function as mercury exposure increased. The specific outcomes affected include fine-motor speed and dexterity, response inhibition, and visuo-spatial attention and concentration.

Carta et al. (2003) examined a group of 22 Italian men who habitually ate tuna fish, and compared them with 22 controls who ate no large predatory fish. The tuna-eaters had a median blood methylmercury level of 41.5 µg/l (range, 13-85), while the controls had a median of 2.6 µg/l (range, 0.8-4.0). Neurocognitive effects were assessed both through a questionnaire that asked about a variety of neurotoxic symptoms, and with a battery of tests for cognitive and fine-motor functions. The test methods are described in detail in a companion paper by Lucchini et al. (2003).

Results showed that the tuna-eaters reported no overt symptoms of neurotoxic effects on the questionnaire; based on that, they were indistinguishable from controls. But the tests revealed subtle but significant impairments of cognitive functions (color word vigilance, digital symbol recognition) and fine-motor coordination (finger tapping). While results on just those three tests were statistically significant, the tuna-eaters in fact had average scores lower than controls on every one of the neurobehavioral tests.

While these two relatively small studies fall short of being compelling evidence, they do suggest rather strongly that, with appropriate assessment methodologies, neurocognitive effects of methylmercury can be observed in adults with elevated exposure from a high-mercury fish diet. Further studies with comparably sensitive designs, including some in the US, are clearly desirable on this question.

Until better data are available, MPP believes it would be prudent public health policy to consider adults and older children with significantly elevated blood mercury levels from eating higher-mercury fish to be subpopulations at risk for neurocognitive effects, and to develop appropriate risk-management measures, involving risk communication designed to educate those populations to choose low-mercury fish. FDA's risk-benefit report says the 99.9th percentile blood mercury level in US women of different ages is 22.7 to 24.6 µg/l, while fewer men have levels that high. MPP used three methods in our report to estimate the size of populations with extreme exposures; our results are consistent with FDA's, which are based on NHANES data. Given the range of individual sensitivity, we consider it appropriate to classify anyone with a blood mercury level above 20 µg/l as potentially at risk for subtle neurobehavioral effects.

If we assume that 85 percent of the US population (roughly 275 million people) are fish consumers, and if we define extreme mercury exposure as having a blood mercury level above the 99.9th percentile (i.e., 1 in 1,000 people), there would be 275,000 such people in the United States.

Subtle health impairments among 275,000 (or so) Americans may not be the largest or most fearsome public health issue that FDA needs to respond to, but this risk is almost entirely preventable. This subset of the population is not trivial in absolute terms, and it is the sector where the risk of mercury in fish falls most heavily. It is unconscionable, in our opinion, for FDA not to advise this identifiable at-risk group to choose low-mercury fish. Yes, promote fish consumption for its benefits, but do not abandon the mission to explain clearly and forcefully where the risk lies, and how it can be minimized.

(6) Summary and Recommendations

The FDA's draft analysis of risks and benefits of fish and seafood consumption violates a basic principle of risk analysis, by attempting both a scientific task (risk assessment) and a value-laden risk management task (balancing risks and benefits) in the same analysis. This fundamental weakness introduces massive errors and biases into the risk assessment.

The most obvious biases involve choosing data, converting data and making countless arbitrary assumptions to suit "the model;" each of these choices adds uncertainties to the model's results. FDA's analysis also seems more interested in documenting benefits from fish consumption, and demonstrating that the benefits are greater than the risks, than it is in carrying out a credible risk assessment of methylmercury's adverse effects.

Some of the many and serious scientific errors in FDA's analysis have been discussed here; more details are presented in the Technical Appendix. The cumulative impact of all the errors, biases and uncertainties in the model is to render its results invalid as either credible science or an appropriate basis for policy decisions.

In our judgment, the FDA report is insufficiently candid about the weaknesses in the data it relied on, and the arbitrary, debatable nature of most of its key assumptions. This lack of scientific caveats understates the enormous uncertainties about and the questionable validity of the results, projecting a false confidence that the analysis is reliable, when in fact it is anything but. Details, again, are in the Technical Appendix.

We have argued here that there is no need for a massive quantitative analysis of risks and benefits of seafood consumption—especially one as severely flawed as this one—because an obvious, sensible policy approach that promotes benefits and minimizes risks has long been available: Educate consumers to eat more low-mercury fish. We believe that FDA's effort to promote this analysis as a basis for policies may seriously retard progress toward that win/win solution, already embodied in the 2004 EPA/FDA advisory.

With an eye on improving risk communication to foster progress toward promoting fish benefits while minimizing mercury exposure, MPP presented here an analysis of mercury levels in different fish and shellfish, and contributions of 51 different varieties of seafood to the total amount of mercury in the US seafood supply. Our analysis shows that lowest-mercury choices make up 43 percent of the total seafood consumed, but contain just 9 percent of the total mercury. This group includes several of the most heavily consumed

fish and shellfish, including shrimp, salmon, tilapia, scallops, oysters, clams and sardines. If motivated to do so, consumers can easily choose very-low-mercury varieties.

We also show that 20 varieties of fish and shellfish with higher mercury levels account for just 9 percent of the seafood consumed but contain 41 percent of the mercury in the US supply. The three varieties of tuna (canned light, canned albacore and fresh/frozen) combined account for 37.4 percent of total mercury, and more than six times as much mercury as the four highest-mercury varieties (swordfish, shark, king mackerel and Gulf tilefish) combined.

We urge FDA to abandon this flawed draft assessment and do a proper risk assessment, focused on high-end fish consumers who prefer higher-mercury fish. Existing surveys have included too few such consumers to shed empirical light on exposure distribution within this critical population subset, on whom much more of the risk from mercury in the fish and shellfish supply falls than accrues to average fish consumers.

We have reviewed seven recent studies that collectively suggest that a paradigm shift is occurring among epidemiologists studying prenatal effects of methylmercury. Recent evidence suggests that exposure to methylmercury at doses associated with typical US levels of fish consumption can discernibly impair neurocognitive development, with no threshold in the range of ordinary mercury exposure from fish. The fact that maternal fish consumption during pregnancy also benefits cognitive development in no way lessens the urgency of teaching women of childbearing age to choose low-mercury fish.

We also review a small body of credible evidence that toxic effects of methylmercury occur in populations other than women of childbearing age, i.e. in adults and children who consume much more fish than average and repeatedly eat high-mercury fish. Such individuals are undoubtedly rare; for example, we assumed that this risk might affect only those fish consumers with blood mercury levels above the 99.9th percentile. If that is the case, there are 275,000 such Americans. While this is a small subpopulation compared to women of childbearing age, it is the sector of the public that bears the greatest risk from mercury exposure. We believe it is absolutely essential that a risk-management strategy be developed to address this second at-risk population.

We therefore ***recommend*** that FDA take the following actions:

- Consider the draft risk/benefit assessment to be an object lesson in the difficulty of doing such an assessment, with results that are not scientifically credible.
- Abandon any plans to use this assessment as a basis for policy decisions.
- Begin again and focus on collecting data that can support a sounder risk assessment, one that focuses on the consumption of higher-mercury fish. The first step probably should be to commission a survey to get much better data about consumption of fish and shellfish varieties with elevated (i.e., > 0.1 ppm) mercury levels.
- Promote the nutritional benefits of fish consumption *and* the importance of reducing mercury exposure by consistently and unequivocally advising consumers to choose low mercury fish.

- Expand efforts to disseminate the current EPA/FDA advisory on mercury in fish, which has not yet reached most Americans effectively.
- Increase emphasis on keeping women's exposure within the Reference Dose.
- Develop a new, additional advisory for people who eat a great deal of fish, making clear the mercury levels in different fish and shellfish, and consumers' need to pick low-mercury varieties.
- Provide more extensive and detailed information to consumers that sorts fish into categories by mercury content, as we have done in Table 2.
- Actively support state and private-sector initiatives to place information about the mercury content of different fish and shellfish on display at points of sale.
- Revise the current EPA/FDA advisory and all related information to remove canned light tuna, a fish with above-average mercury content, from the list of "low-mercury" fish and shellfish choices.
- Consider revising the FDA Action Level for mercury in fish, to adopt the two-tiered system used in many other countries, permitting up to 1 ppm in a limited number of large, predatory species, and limiting mercury in other fish to 0.5 ppm.
- Enforce the Action Level. The current policy of allowing fish that contain more than 1 ppm to be sold without penalty sends a message that mercury in fish is not a public health concern. Visible enforcement is needed to reverse that misimpression.
- Consider making a joint request, with the EPA, for a new NAS/NRC review of recent scientific evidence on health effects of methylmercury, with emphasis on evidence that ordinary levels of exposure, associated with average fish consumption, can have significant adverse impacts on prenatal cognitive development.
- Consider convening a stakeholder forum (under FDA's auspices, or through outside facilitators such as the Keystone Center) with participation from all sectors—mercury epidemiologists, fish nutritionists, academics, the fishing industry, federal and state government regulators, consumer and environmental NGOs—to see if a consensus can be reached for all sectors to promote eating more low-mercury fish.

Thank you for considering these comments.

Respectfully submitted,

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TABLE 1. MERCURY CONTRIBUTIONS OF 51 FISH AND SHELLFISH ITEMS TO TOTAL MERCURY
IN U.S. SEAFOOD SUPPLY, RANKED IN DESCENDING ORDER BY Hg AMOUNT
USING DATA FROM FDA REPORT, TABLE AA-3

Fish/Shellfish Variety	Mean Mercury (ppm)	Market Share (percent)	Market Mercury Input	Percent of Total Hg Inputs	Cumul. Percent
Tuna, Canned Light	**0.118**	11.41	1.3464	15.863	15.863
Tuna, Canned Albacore	**0.353**	3.81	1.3449	15.845	31.708
Haddock, Hake and Monkfish	**0.170**	4.86	0.8262	9.734	41.442
Tuna, Fresh/Frozen	**0.384**	1.22	0.4807	5.663	47.105
Swordfish	**0.976**	0.44	0.4294	5.059	52.164
Catfish	**0.068**	5.71	0.3951	4.655	56.819
Cod	**0.115**	3.36	0.3864	4.552	61.371
Lobster, American	**0.310**	1.22	0.3782	4.456	65.827
Pollock	**0.049**	7.32	0.3587	4.226	70.053
Shrimp	**0.012**	22.21	0.2665	3.140	73.193
Salmon	**0.028**	6.83	0.1912	2.253	75.446
Bass, Saltwater	**0.301**	0.51	0.1535	1.809	77.255
Anchovies, Herring & Shad	**0.050**	3.06	0.1530	1.803	79.058
Squid	**0.070**	1.92	0.1344	1.583	80.641
Grouper, All varieties	**0.460**	0.27	0.1242	1.463	82.104
Flatfish (Flounder, Sole & Plaice)	**0.050**	2.42	0.1210	1.426	83.530
Snapper, Porgy and Sheepshead	**0.137**	0.86	0.1178	1.388	84.918
Orange Roughy	**0.550**	0.20	0.1100	1.296	86.214
Crabs, All varieties	**0.050**	2.12	0.1060	1.249	87.463
Halibut	**0.220**	0.48	0.1056	1.244	88.707
Tilapia	**0.020**	4.83	0.0966	1.138	89.845
Lobster, Spiny	**0.121**	0.71	0.0859	1.012	90.857
Shark, All varieties	**0.988**	0.07	0.0692	0.815	91.672
Skate	**0.137**	0.46	0.0630	0.742	92.414
Bass, Freshwater	**0.318**	0.19	0.0604	0.712	93.126
Mackerel, Pacific (Chub)	**0.088**	0.61	0.0537	0.634	93.760
Sablefish	**0.273**	0.19	0.0519	0.611	94.371
Oysters and Mussels	**0.023**	2.22	0.0511	0.602	94.973
Mackerel, Atlantic	**0.049**	1.04	0.0510	0.601	95.574
Clams	**0.023**	2.04	0.0469	0.553	96.127
King Mackerel	**0.730**	0.05	0.0365	0.430	96.557
Scallops	**0.023**	1.46	0.0336	0.396	96.953
Sardines	**0.016**	1.73	0.0277	0.326	97.279
Trout, Saltwater	**0.269**	0.10	0.0269	0.317	97.596
Freshwater Perch	**0.162**	0.14	0.0227	0.267	97.863
Freshwater Trout	**0.037**	0.60	0.0222	0.262	98.125
Bluefish	**0.340**	0.06	0.0204	0.240	98.365
Ocean Perch and Mullet	**0.040**	0.47	0.0188	0.221	98.586
Mackerel, Spanish	**0.368**	0.05	0.0184	0.217	98.803
Crayfish	**0.033**	0.47	0.0155	0.183	98.986

Croaker, Atlantic	**0.073**	0.21	0.0153	0.180	99.166
Tilefish, Gulf	**1.450**	0.01	0.0145	0.171	99.337
Whitefish	**0.075**	0.19	0.0143	0.168	99.505
Marlin	**0.489**	0.02	0.0098	0.115	99.620
Smelt	**0.092**	0.09	0.0083	0.098	99.718
Carp and Buffalofish	**0.203**	0.04	0.0081	0.095	99.813
Lingcod and Scorpionfish	**0.286**	0.02	0.0057	0.067	99.880
Pike	**0.056**	0.10	0.0056	0.066	99.946
Butterfish	**0.058**	0.04	0.0023	0.027	99.973
Croaker, Pacific	**0.303**	0.00	0.0012	0.014	99.987
Tilefish, Atlantic	**0.111**	0.01	0.0011	0.013	100.000
Totals/[weighted average]	**[0.086]**	**98.45**	**8.4878**	100.000	

KEY TO COLOR-CODING OF Hg LEVELS:

Less than half the weighted average Hg: 0.022

Half of average to average mercury level: 0.058

Average to twice average mercury level: 0.115

Two to four times average mercury level: 0.250

Four to eight times average mercury level: 0.465

More than eight times average mercury level: 0.976

TABLE 2. MERCURY CONTRIBUTIONS OF DIFFERENT FISH AND SHELLFISH, GROUPED INTO CATEGORIES BY INCREASING MERCURY CONTENT

USING DATA FROM FDA REPORT, TABLE AA-3

Fish/Shellfish Variety	Mean Mercury (ppm)	Market Share (percent)	Market Mercury Input	Percent of Total Hg Inputs	Cumul. Percent
Very Low Mercury (<0.01-0.043 ppm)					
Shrimp	0.012	22.21	0.2665	3.140	
Salmon	0.028	6.83	0.1912	2.253	
Tilapia	0.020	4.83	0.0966	1.138	
Oysters and Mussels	0.023	2.22	0.0511	0.602	
Clams	0.023	2.04	0.0469	0.553	
Scallops	0.023	1.46	0.0336	0.396	
Sardines	0.016	1.73	0.0277	0.326	
Freshwater Trout	0.037	0.60	0.0222	0.262	
Ocean Perch and Mullet	0.040	0.47	0.0188	0.221	
Crayfish	0.033	0.47	0.0155	0.183	
Group Totals/[weighted average]	[0.018]	**42.860**	**0.7701**	**9.074**	**9.074**
Below-Average Mercury (0.044-0.086 ppm)					
Catfish	0.068	5.71	0.3951	4.655	
Pollock	0.049	7.32	0.3587	4.226	
Anchovies, Herring & Shad	0.050	3.06	0.1530	1.803	
Squid	0.070	1.92	0.1344	1.583	
Flatfish (Flounder, Sole & Plaice)	0.050	2.42	0.1210	1.426	
Crabs, All varieties	0.050	2.12	0.1060	1.249	
Mackerel, Atlantic	0.049	1.04	0.0510	0.601	
Croaker, Atlantic	0.073	0.21	0.0153	0.180	
Whitefish	0.075	0.19	0.0143	0.168	
Pike	0.056	0.10	0.0056	0.066	
Butterfish	0.058	0.04	0.0023	0.027	
Group Totals/[weighted average]	[0.056]	**24.130**	**1.3567**	**15.984**	**25.058**
Above-Average Mercury (0.087-0.172 ppm)					
Tuna, Canned Light	**0.118**	11.41	1.3464	15.863	
Haddock, Hake and Monkfish	**0.170**	4.86	0.8262	9.734	
Cod	**0.115**	3.36	0.3864	4.552	
Snapper, Porgy and Sheepshead	**0.137**	0.86	0.1178	1.388	
Lobster, Spiny	**0.121**	0.71	0.0859	1.012	
Skate	**0.137**	0.46	0.0630	0.742	
Mackerel, Pacific (Chub)	**0.088**	0.61	0.0537	0.634	
Freshwater Perch	**0.162**	0.14	0.0227	0.267	
Smelt	**0.092**	0.09	0.0083	0.098	
Tilefish, Atlantic	**0.111**	0.01	0.0011	0.013	
Group Totals/[weighted average]	**[0.129]**	**22.510**	**2.9115**	**34.303**	**59.361**

TABLE 2, Continued

Moderately High Mercury (0.173-0.344 ppm)					
Lobster, American	**0.310**	1.22	0.3782	4.456	
Bass, Saltwater	**0.301**	0.51	0.1535	1.809	
Halibut	**0.220**	0.48	0.1056	1.244	
Bass, Freshwater	**0.318**	0.19	0.0604	0.712	
Sablefish	**0.273**	0.19	0.0519	0.611	
Trout, Saltwater	**0.269**	0.10	0.0269	0.317	
Bluefish	**0.340**	0.06	0.0204	0.240	
Carp and Buffalofish	**0.203**	0.04	0.0081	0.095	
Lingcod and Scorpionfish	**0.286**	0.02	0.0057	0.067	
Croaker, Pacific	**0.303**	0.00	0.0012	0.014	
Group Totals/[weighted average]	**[0.289]**	**2.814**	**0.8119**	**9.565**	**68.926**
High Mercury (0.345-0.688 ppm)					
Tuna, Canned Albacore	**0.353**	3.81	1.3449	15.845	
Tuna, Fresh/Frozen	**0.384**	1.22	0.4807	5.663	
Grouper, All varieties	**0.460**	0.27	0.1242	1.463	
Orange Roughy	**0.550**	0.20	0.1100	1.296	
Mackerel, Spanish	**0.368**	0.05	0.0184	0.217	
Marlin	**0.489**	0.02	0.0098	0.115	
Group Totals/[weighted average]	**[0.375]**	**5.570**	**2.0880**	**24.599**	**93.525**
Very High Mercury (>0.688 ppm)					
Swordfish	**0.976**	0.44	0.4294	5.059	
Shark, All varieties	**0.988**	0.07	0.0692	0.815	
King Mackerel	**0.730**	0.05	0.0365	0.430	
Tilefish, Gulf	**1.450**	0.01	0.0145	0.171	
Group Totals/[weighted average]	**[0.964]**	**0.570**	**0.5496**	**6.475**	**100.000**

TABLE 3. MERCURY INTENSITY INDEX OF DIFFERENT FISH CATEGORIES SHOWN IN TABLE 2

Category	Color	Hg range, ppm	Percent of Supply	Percent of Hg	Intensity Index
Very Low Hg	Green	0.01-0.043	42.9	9.1	0.21
Below Average Hg	Blue	0.044-0.086	24.1	16.0	0.66
Above Average Hg	Black	0.087-0.172	22.5	34.3	1.52
Moderately High Hg	Orange	0.173-0.344	2.8	9.6	3.43
High Hg	Red	0.345-0.688	5.6	24.6	4.57
Very High Hg	Violet	>0.688	0.6	6.5	10.83

TABLE 4. SUMMARY OF CRITICAL RECENT STUDIES ON COGNITIVE EFFECTS OF FISH CONSUMPTION

					Magnitude of Effects		
		Studied	Index of		Nutritional	Mercury	
Authors & Date	Where	Group	Exposure	Outcome measures	Benefit	Adverse	Net
Cohen et. al (2005)	Hypo-	n.a.	n.a.				
Scenario 1	thetical			Aggregate IQ points	+39,000	(-380,000)	+410,000
Scenario 2	(See			for all babies born	-48,000	(-140,000)	+92,000
Scenario 3	paper)			annually in the US	-48,000	(-140,000)	+92,000
Scenario 5					+140,000	-410,000	-270,000
Oken et al. (2005)	Boston	135 mother-infant pairs	Maternal hair Hg; 1.2 ppm @ 90th percentile	Visual recognition memory & novelty preference in infants at age 6 months	VRM score + 4.0 per fish meal	VRM score -7.5 per 1 ppm Hg	n.a.
Oken et al. (2008)	Boston	341 mother-child pairs	Maternal hair Hg; 1.2 ppm @ 90th percentile	Verbal (PPVT) and visual-motor (WRAMVA) tests at age 3 years	PPVT: +2.2 (NS) WRAMVA: +6.4	PPVT: -4.5 WRAVMA: -4.6	n.a n.a
Lederman et al. (2008)	New York	329 mother-child pairs	Mother's blood & umbilical cord Hg, means 2.29 & 5.05 µg/l	BSID-II PDI scores at age 36 months WPPSI-R Full IQ at age 48 months	PDI: +8.7 IQ: +5.6	PDI: -4.2 IQ: -3.8	n.a. n.a.
Davidson et al. (2008)	Seychelles	229 mother-child pairs	Maternal hair Hg, Mean 5.7 ppm	BSID-II scores at age 30 months	n.a.	PDI score -2.7	n.a.
Strain et al. (2008)	Seychelles	229 mother-child pairs	Omega-3s in maternal blood	BSID-II scores at ages 9 and 30 months	PDI score, improved @ 9 mo, not @ 30 mo	n.a.	n.a.
Jedrychowski et al. (2006)	Krakow, Poland	233 mother-	Maternal blood Hg, 0.75 µg/l	BSID-II score in infants	n.a.	PDI score -16.6	n.a.

infant pairs	Cord blood Hg, 1.05 µg/l	at age 1 year	MDI score -10.0

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TECHNICAL APPENDIX

Section-by-Section
And Page-by-Page
Comments on the
FDA Draft Report

TECHNICAL APPENDIX

To the Comments
Submitted by the Mercury Policy Project/Tides Center

On the draft FDA Report of
Quantitative Risk and Benefit Assessment
of Consumption of Commercial Fish

Introduction

These comments are organized by section and page number of the FDA draft. Our focus here is on technical and scientific issues, often in some detail, while the main body of our comments addressed several broader themes.

Those themes are echoed here, but not discussed in detail. After commenting on an aspect of the draft here, we briefly tie this technical discussion to one or more broader themes in our main Comments, but we will do so concisely, e.g., "Suggests bias in favor of feeding the model, discussed in our main Comments."

We also have not appended a list of cited references in this appendix. All papers cited are either listed in FDA's bibliography or in that of our main Comments; we will cite papers by authors and date and assume that readers have access to the full references.

At the outset, we should explain that our principal concern with the risk assessment side (adverse effects of methylmercury) of the FDA's analysis is that we believe it is unable to accurately model exposure, and therefore risk, at the very high end of consumption, more specifically for consumers who frequently eat high-mercury fish. We also believe that the dose-response relationships developed are based on data from two studies with important data-quality issues, data that may not be representative of evidence gathered in a number of more recent studies. Our chief concern about FDA's dose-response relationship for the neurodevelopmental benefits of fish consumption is that it is based on data from a single study, one also with substantial data-quality problems, while considerable other evidence suggests that those data are not representative of most other studies on this subject.

We are concerned that the authors of the FDA report seemed unaware of, or unconcerned about, these important issues of data quality, data reliability and study representativeness. These issues are addressed only partially and inadequately in FDA's discussion of its risk estimates, and barely addressed at all in their discussion of benefits estimates, suggesting insensitivity to or ignorance of critical scientific issues at the heart of the analysis.

As with our main comments, we have chosen (with one exception) to focus on sections addressing benefits of fish consumption and risks of methylmercury in prenatal cognitive development. We suspect there are similar flaws in the analysis of cardiovascular effects of fish consumption, but we leave it to others to point those out.

FDA's Executive Summary

This very brief overview frames the analysis around a false dichotomy, that consumers must choose whether to eat fish or not eat fish, a wrongheaded concept that permeates the report. (See "Flawed Concepts, page 3 of main Comments.)

The Summary describes this report as presenting "science," but also states that the major purpose of the effort is to "balance risks and benefits." Balancing risks and benefits is a risk-management task, one that clearly requires weighing values. By not acknowledging openly that the exercise is inherently laden with value judgments, the authors increased the risk that hidden value judgments would find their way covertly into the report. (Many have indeed done so, as we will point out.) Such covert value judgments tend to bias and undermine the scientific integrity of any risk (or benefits) assessment.

In fact, in the fourth paragraph of the Summary, the authors state that this analysis is not a risk assessment, but rather an attempt to balance risks against benefits. This indicates to us that doing a rigorous risk assessment was a secondary objective of the analysis, at best, and illustrates the value-weighted biases discussed on pages 7-8 of our main Comments.

The Summary explains that verbal development was chosen as the health endpoint for measuring positive and negative effects on cognitive development, with a rationale that such effects could be compared, to calculate "net effects." (See discussion of the flaws in the concept of "net effects," on page 4 of our main Comments.) While certain aspects of verbal development were in fact used as measures of these positive and negative effects, they had to be converted to IQ points in order to be compared with each other. Since it is possible to convert many of the developmental outcomes of most of the published studies on methylmercury effects into IQ points, and this has been done by other authors, it was not necessary to select one type of outcome, such as verbal development, as the basis for the dose-response relationship. I.e., the rationale offered is scientifically invalid.

In short, FDA has chosen to do a very narrow analysis, based on two (flawed, as we shall show) studies of risk and one (flawed) study of benefits, to develop dose-response curves for its model. A broader approach that sought to use more data, and to use the best data, from the dozens of other well-designed studies on mercury risks (and some number, we are less familiar with the literature, on beneficial effects), would have been a far sounder scientific approach. The explanation FDA has offered for taking the narrower path does not make scientific sense. It leaves the choice looking highly arbitrary.

The fact is, FDA's model of mercury's adverse effects is based on work done a decade ago by agency scientists Clark Carrington and Michael Bolger. It appears that one reason for choosing to use the studies selected was that the work had already largely been done. On the benefits side, no such prior analysis by the FDA has been published. The decision to develop a dose-response model based on a single study may reflect a desire to limit the amount of work involved. An approach that required obtaining and integrating data from, say, several of the best studies, would have been much more work—but better science.

Overall, this discussion suggests that the FDA's analytical approach was neither deeply interested in the evidence of benefits and risks, nor concerned with thorough, rigorous, as opposed to superficial, analysis of the data. This impression does not inspire confidence in the model, its guiding purposes, or its results.

These defects indicate two of the broader problems discussed in our main Comments: A general lack of understanding of how to view and treat epidemiological data, with a lack of sensitivity to essential safeguards to avoid using data improperly or drawing incorrect inferences; and the analytical bias, where feeding the model takes precedence over most other scientific considerations.

The Summary notes that FDA did not have adequate evidence on which to distinguish among types of fish in terms of their beneficial nutrients, and because of that, all fish are treated generically on the benefits side of the analysis. This generic approach—treating "fish as fish"—occasionally spills over into the risk assessment as well, but the latter for the most part is aware of and seeks to address important differences in mercury levels in different fish.

This substantial asymmetry—treating mercury's adverse effects properly as skewed in distribution, while assuming benefits are spread evenly across the population—all but invalidates the risk-benefit comparisons. (See discussion of the flaws in the concept of "net effects, on page 4 of our Comments.) This flaw in the model should probably have stopped the analysis—since it makes little sense to compare an effect whose distribution can be modeled with one whose distribution cannot be properly modeled. (Distribution of fish intake is modeled, but not distribution of exposure to omega-3s, for instance.) The fact that the analysis proceeded despite this flaw indicates the pro-analysis bias discussed on page 6 of our main Comments.

On page 3 of the Summary, it is stated that the analysis shows that "consumption of fish species that are low in methylmercury has a significantly greater probability of resulting in a net benefit." Our comment: Why do we need an elaborate benefit-risk analysis to tell us that? (See page 6 of main Comments.)

The Summary briefly describes the central results of the modeling exercise, noting that benefits were "modest" and that (according to the model) a "net adverse effect" occurred in just one-tenth of 1 percent of the population. This quantitative result suggests an effect far smaller (by a factor of over 100) than those observed in the majority of well designed epidemiological studies on effects of methylmercury on cognitive development. In other words, the results of the model are sharply at odds with the bulk of published literature on the subject.

That incongruity would suggest to most analysts that there might be something wrong with their model. But the FDA authors do not even raise the possibility that the outputs of the model might be anything other than reasonable and reliable. This is lack of scientific humility—not just here, in a summary, where discussion is abbreviated, but later, in the

sections of the report where results are presented in detail. Even in sections where data gaps and limitations in the model are discussed, the main emphasis is on minimizing the impact of these problems on the model's results. Phrases like "if the model is correct," or "within the uncertainty bounds of the model's assumptions" can hardly be found in the report at all, and such caveats are most absent where they are most needed.

The lack of normal, expected scientific candor about limitations and possible inaccuracies of one's modeling work is startling, and indicates a severe problem with the report. It is a sign that the authors may not have been familiar enough with the way this kind of science is done to know that such caveats must be included. And it suggests strong biases of both types discussed on pages 6 to 9 of our main Comments: Bias to run the model, no matter what; and bias toward demonstrating benefits of fish consumption and showing that they outweigh the risks of methylmercury exposure. This latter bias could explain why results that suggest benefits far greater than indicated by other analyses have not been critically evaluated, but instead are presented as simple facts.

Section 1. Purpose

Again, emphasis is on balancing risks and benefits, not on conducting a sound, rigorous risk assessment, and/or a sound, rigorous benefits assessment. Emphasis on "net effects" indicates biases, and reliance on flawed concepts.

Pages 5-6

In explaining the choice of verbal development indices, FDA explains that one reason was "because we had data on it sufficient to develop dose-response functions" for both adverse and beneficial effects. Translation: FDA had done the risk side of this analysis, about 10 years ago. This seems like a "lamp-post" decision (see page 7 above in these Comments), as well as a way to limit the effort required. Neither of these is a scientific criterion for such a pivotal data-selection decision.

Page 6 (second paragraph) lists some "limitations of the assessment." Needless to say, this is a very superficial, partial list. In fact, there were dozens of choices made in the course of the analysis that each limit the accuracy or reliability of the outcome in some way. A full list of the limitations might require an Appendix devoted just to that topic.

Two possibilities could explain paying such superficial attention to the limitations of the analysis, here and elsewhere in the report. Perhaps the authors were unaware of many of the significant limitations and uncertainties in their model, or perhaps they chose not to disclose them. Either explanation would severely diminish the scientific credibility of the report. No matter how well-intentioned the analytical effort might have been, if it fails to recognize and disclose its limitations and weaknesses, it is not good science.

Page 6 also describes the "Companion Document," the literature review on beneficial effects of fish consumption on cognitive development. As stated in our main Comments, the inclusion of a major literature review on benefits, but none on methylmercury risks,

when as strong a case or a stronger one could be made that the latter is needed, shows a bias on the part of the report's authors to focus on benefits, and downplay risks.

Section II. Exposure to Methylmercury

This section describes the exposure components of FDA's model: How they represented fish consumption, methylmercury levels in fish, and the exposures of individuals and populations to methylmercury in their model.

This part of the model is largely built upon work done by Carrington and Bolger, during the past decade. Their basic approach is scientifically reasonable, is innovative in many respects, and has generated numerous insights on useful ways to look at several problems encountered in doing this sort of analysis. This does not mean it is above criticism.

We have two general criticisms of the Carrington and Bolger model. The first is that any model is only as good as the data that exist to be fed into it, and there are some serious limitations in the data needed to assess methylmercury exposure. To give the authors of Section II credit, most of those limitations are frankly discussed in the draft report; we will, however, have comments on several issues where we feel the limitations are more serious than the modelers have acknowledged.

Our other criticism of the Carrington and Bolger approach is that it is biased, in that a great deal of the work was done in the context of evaluating alternative "interventions," or FDA policy responses to methylmercury exposure from fish consumption. The earlier work by this team included several iterations of an assessment of whether urging women to limit the amount of fish they consumed to 12 ounces per week, or telling them to eat low-mercury fish, would result in better public health protection. Their analysis showed that limiting consumption was their preferred policy approach.

We disagree with that, and will explain why and how in detailed later comments. But the bias arises in that the modelers in this case have a strongly stated preference for policies based on overall quantity of fish consumed, rather than on types of fish consumed. This preference tends to filter into the analysis and exert biases—some subtle, some not so—at various points where the results bear on that policy question. We will point out several such instances in comments later, when we get to the Results of the "What If" scenarios and to Appendix AA, the detailed description of methodology.

Page 7 describes sources of data on mercury levels in fish. We consider FDA's data on mercury in different fish and shellfish varieties to be the best overall source of such data available, and have used the data often in our own analyses and publications (see Section (3) of the main Comments.) We note with interest that this report contains updated data on several species, particularly those with rather low mercury levels. While better data could always be sought on many specific aspects of this topic, we appreciate the effort FDA has made to generate, analyze, assemble and update these data, and the agency has made the data available on the CFSAN web site, a significant public service.

We also recognize the NHANES data on blood and hair mercury among Americans as the best available data-set on those questions. However, as the authors of this section of the report point out, there are some serious limitations to the NHANES data. FDA does not always consider these limitations a serious problem. On page 9, for example, FDA asserts that those limitations "do not significantly affect the utility of NHANES in a nationally representative assessment of risk relating primarily to commercial species." This reflects the analyst's bias to accept the data, with limitations, and run the model. However, one needs to resist the temptation to understate how known data limitations may affect the results.

We disagree with FDA's assertion in one important respect. We believe the NHANES sample is too small to adequately characterize people with extreme fish consumption patterns—those whose high overall fish intake (above the 99th percentile) and preference for high-mercury fish places them far above the 99th percentile in blood mercury levels. Although there are about 3.25 million Americans above the 99th percentile (of anything), there were only 52 women or children above the 99th percentile (in any parameter) in the NHANES five-year sample of 5,214, and far fewer than that in the two-year samples FDA used for parts of its exposure analysis.

In our judgment, these samples are too small to provide an adequate "window" into the fish-eating behavior of the admittedly small minority of Americans who, unfortunately, have the highest exposure to and greatest risk from mercury in fish. There are people in the US who love tuna, swordfish, sea bass or other high-mercury species, and eat those fish several times a week. Our own report on methylmercury poisoning in high-end fish consumers (MPP 2008) described 24 of them. Some fraction of women of childbearing age also may have such preferences for high-mercury fish, and in their case, far lower exposures could have public health impacts.

Such consumers do exist, but they are rare enough that a sample size of a few thousand Americans is unlikely to contain more than a handful, if that. Thus, none of the existing surveys on fish consumption gives us an adequate picture of how many such people there are, or what their fish choice patterns may be. We don't believe that such idiosyncratic individual consumption patterns can be reliably modeled from general data, such as the market shares of high-mercury fish. We return to this theme in subsequent comments.

We think the comparison of methylmercury exposures in the US with those in other parts of the world on pages 9-10 is gratuitous, and should be deleted. The fact that Americans at the 99th percentile in fish consumption might be "average" in some other cultures is not relevant; the issue is, what is the risk for those Americans? Making this comparison with no discussion of scientific considerations, such as overlaps in the distributions of intake across cultures, gives this passage an unseemly air of a "public relations" effort to make Americans' risks from methylmercury seem trivial. We see it as further evidence of the general bias in the report to downplay risks and promote benefits.

On page 11, FDA says that the "Top 10" items in US seafood consumption account for about 73 percent of the market, and that most of the top 10 items are low in mercury. We

agree with the latter point but question the former. Based on NFI data shown in the table below, the top 10 items account for 14.8 to 15 pounds of per capita consumption per year. Since total US per capita consumption is about 16.3 pounds per year over the three years shown below, these NFI data suggest that the top 10 account for 90 percent of overall consumption. We have calculated a weighted average methylmercury content for the top 10, using FDA's mercury data and the data below for 2007. That average is 0.057 ppm, affirming that most of the fish eaten by most Americans are low in mercury.

If canned tuna is excluded from the "top ten" below, the weighted average mercury level for the other nine items drops to 0.03 ppm. In other words, canned tuna doubles mercury exposure associated with 90 percent of the fish Americans eat (using NFI's data), and it accounts for more than half (57 percent) of the mercury in the top 10 items.

Top 10 Seafoods, 2005 -2007

US consumption in pounds per capita per year (NFI)

Rank	2005		2006		2007	
	Species	Lbs	Species	Lbs	Species	Lbs
1	Shrimp	4.10	Shrimp	4.40	Shrimp	4.10
2	Tuna, can	3.10	Tuna, can	2.90	Tuna, can	2.70
3	Salmon	2.43	Salmon	2.03	Salmon	2.36
4	Pollock	1.47	Pollock	1.64	Pollock	1.73
5	Catfish	1.03	Tilapia	1.0 0	Tilapia	1.14
6	Tilapia	0.85	Catfish	0.97	Catfish	0.88
7	Crab	0.64	Crab	0. 66	Crab	0.68
8	Cod	0.57	Cod	0. 51	Cod	0.47
9	Clams	0.44	Clams	0.44	Clams	0.45
10	Flatfish	0.37	Scallops	0.31	Flatfish	0.32
Total, Top 10		15.0		14 .9		14.8

On page 11, FDA speaks of fish with "mid-range" mercury levels, i.e., those that fall between what FDA deems "low" and "high" mercury levels. From this discussion, it appears that FDA considers "low" to be below 0.2 ppm, and "high" to include the four varieties with the highest levels, which range from 0.73 to 1.45 ppm. "Mid-range" thus includes any fish with between 0.2 and 0.6 ppm mercury.

With due respect for tradition, because FDA has been looking at mercury levels in fish this way for a many years, we believe this is an outdated approach, one that does not well

serve consumers seeking to manage their mercury exposure. Nor is it consistent with recent insights, such as the perspective gained from using the weighted average mercury level in all US fish and seafood as a reference point, an innovation advanced by FDA in this report (and one we appreciate).

We propose that FDA, and consumers, could make more intelligent decisions about fish and shellfish choices if the relative mercury content of different varieties were presented on a scale with more, and more meaningfully defined, intervals. In our Tables 1 and 2, attached to our main Comments, we have proposed the following definitions:

Mercury Levels in Fish and Shellfish

Very Low	< 0.043 ppm
Below Average	0.044 – 0.086 ppm
Above Average	0.087 – 0.172 ppm
Moderately High	0.172 – 0.344 ppm
High	0.345 – 0.688 ppm
Very High	>0.688 ppm

Our mercury scale explicitly uses the weighted average as a reference point, and each category break represents a doubling of mercury content. That is, the boundaries between categories are set at 0.5, 1, 2, 4 and 8 times the weighted average level. Not only does this make intuitive sense to consumers, it also more or less reflects natural break points in the distribution of the mercury levels in different fish.

Whether FDA adopts our proposed classification or not, it needs to improve how it talks about and thinks about mercury levels in fish. We offer these points for consideration:

- Many consumers need to and want to discriminate among fish choices by mercury content, but few have the time or the ability to comb through the mercury data on the CFSAN web site and make their own lists. FDA should list fish in several categories of mercury content that are meaningful for consumer choices.
- The weighted average level in the US supply of seafood is a very useful reference point, and should be used appropriately.
- Many consumers want to minimize their mercury exposure. Including a "very low mercury" category—the best choices for such consumers—is therefore important.
- The definition of "low mercury" fish cannot sensibly include fish that have well above average mercury levels. I.e., since the average is 0.086 ppm, 0.20 ppm cannot be sensibly used as a boundary between "low" and "mid-range." In fact, the current cutoff of 0.12 ppm for "low-mercury" seems much too high to us.
- We believe high-end fish consumers, in particular, need more distinctions drawn between fish with well above-average mercury levels, since the differences between twice, five and ten times the average may matter a great deal in individual cases. We thus have included four levels of "higher-mercury" fish.

The discussion on page 11 of the variability of mercury levels in canned light tuna, and the statement that some cans of light tuna have as much mercury as do cans of albacore tuna, are welcome. These facts support our view that canned light tuna should not be promoted as a "low-mercury" choice in government advisories. The possibility that some cans of light tuna may contain much higher than average mercury levels, combined with the acknowledgment elsewhere in the report that the toxicological impact of short-term peak exposures (as from a single meal of high-mercury fish, at a key developmental stage during pregnancy) cannot currently be assessed, suggests that pregnant women should not be encouraged to eat any form of tuna. It seems prudent to suggest that they choose from the many other fish and shellfish varieties that offer comparable nutritional benefits and are far lower (up to an order of magnitude lower) than light tuna in mercury content.

On pages 11-12, FDA asks whether concentrations of mercury in fish are increasing, and concludes that there is little evidence of an increase, at least for varieties from the open seas. Consumer Reports magazine has been testing canned tuna for mercury periodically since about 1970, and has consistently found essentially identical average levels over that period, completely consistent with FDA's experience.

Section III. Scientific Basis for Risk And Benefit Assessment

On page 12, FDA states that this section "reviews research from studies…germane to evaluating the risks associated with methylmercury jointly with the benefits of commercial fish consumption." Unfortunately, this promise goes largely unfulfilled. The literature review here is incomplete, superficial, biased and in some cases, inaccurate.

An actual scientific review of "germane" studies would have been a far more ambitious undertaking. As noted, FDA's bias toward estimating benefits led the agency to prepare a large separate review of studies on the benefits side, but no such effort was made on the methylmercury risk side. Instead, FDA refers readers to the decade-old review by the National Research Council, and encourages us to read the many individual studies that have been published since then.

The obvious greater interest in benefits assessment, the comparative short shrift given to the literature on methylmercury risks, and the corresponding relative lack of effort given to both reviewing and, one must suspect, understanding the epidemiological literature on the effects of methylmercury on cognitive development, shows in numerous ways.

One problem with the brief review of studies of prenatal methylmercury exposure and cognitive development presented here (it fills just eight pages, and much of that is in the form of a table with a lot of blank space) is that it fails to place studies in the context of what the literature shows as a whole. The review presents no overview of what is now agreed, what issues remain to be resolved. Each study seems to have been evaluated on its own, discrete from the rest of the evidence.

For example, several recent studies (reviewed in Section 4 of our main Comments) have strongly suggested that methylmercury can adversely affect cognitive development even

at normal, typical American levels of fish intake, not just in populations with high-fish diets or those who eat shark and pilot whale meat. FDA cites most of these studies, but never notes their collective import: I.e., it now appears that methylmercury's cognitive effects have no threshold within the range of ordinary exposure. This omission is either scientific myopia, or unwillingness to raise an issue with profound policy implications. Whatever the reason, the FDA's review of the evidence has almost completely missed a critically important, central theme of recent research.

Perhaps related to the lack of analysis of the epidemiological literature as a whole, this review fails to address most of the important methodological issues related to collecting and interpreting epidemiological data. The critical issue of how accurately such studies can quantify effects is hardly explored. The problem of confounding (the presence of variables in the population studied that could tend either to obscure real effects, or give the false impression of effects) is mentioned, and lack of confounding is stated as one of FDA's primary criteria for selecting studies to use in its model. But discussions of the various studies suggest that the FDA authors really do not understand what confounding is, where it is present, or what its presence says about the data. Numerous examples of this lack of understanding are presented later in this Appendix.

FDA's brief review also describes each study it mentions very concisely, summarizing and in many cases omitting crucial information about the studies. In at least one case, FDA has re-interpreted data presented by a study's authors and presented them here in a manner that is both scientifically incorrect and highly misleading (see details later).

In pages 16-20, FDA reviews evidence from studies in Minamata, the Faroe Islands, the Seychelles and New Zealand. This section shows a powerful lack of scientific insight, in that it summarizes three major epidemiological studies with somewhat differing results, but makes no effort to assess the collective weight of evidence, or to explain the seeming inconsistencies among the studies. These three studies illustrate confounding, one of the basic problems in epidemiology, and how to address it in research design. FDA says it is aware of confounding, but did not discuss it when the moment arose.

Briefly, the nutritional benefits of fish consumption for cognitive development can mask the adverse effects of methylmercury, and vice versa, confounding a study's ability either to detect or to quantify accurately either kind of effect. The New Zealand study largely avoided confounding by stratifying its subjects by their level of fish consumption, then comparing cognitive scores of children based on mercury exposure within the same fish intake category. The study in the Faeroes was designed differently, but the authors were able to reanalyze their data in the same manner; by doing that, they showed that in fact, there were benefits of fish consumption in the children they studied, and that when fish benefits were corrected for, adverse effects of mercury were even larger than had been initially reported. In the Seychelles study, substantial benefits from fish consumption all but obscured adverse effects of methylmercury. But in recent papers from that study, the investigators have managed to sort out the two opposing factors, and by correcting for fish intake, have now observed adverse effects of mercury (see discussion of papers by Davidson et al. 2008 and Strain et al. 2008, in our main Comments.)

Had FDA addressed these issues in its review of the evidence, rather than summarizing but not interpreting the studies, it might have concluded (as most experts in the field have), that the Faeroes and New Zealand studies offer the best, least confounded data on methylmercury's effects. The study in the Seychelles, by contrast, represents almost a textbook example of confounding, and its data on adverse effects of methylmercury on cognitive development, at least prior to 2008, are almost certainly inaccurate, because of the masking effect of fish consumption benefits.

Had FDA interpreted the research correctly, it probably would have concluded that the earlier reports from the Seychelles were not the best, or in fact, not even a defensible, scientific source of data for developing a quantitative dose-response relationship for methylmercury's prenatal effects. Yet FDA did choose those Seychelles data, as well as data from another study in Iraq (discussed later), for use in its model, and elected not to use data from the other, well designed, less confounded studies.

This section shows, in a nutshell, some critical problems with the risk assessment side of FDA's analysis. The authors seem insensitive to or unaware of the things that make good epidemiological data. Their lack of scientific acumen, biases or perhaps both led them to choose less reliable studies, studies they had used in a previous analysis. As we will show later, these same problems also profoundly affect the benefits assessment.

This section is marred, in our judgment, by repeated emphasis on how high the levels of exposure were in the cited studies, compared to exposure in the US. Again, this feels like a public-relations effort to diminish concern with US exposures, rather than a scientific assessment. The latter would note that high-end consumers in the US may approach or exceed exposure levels seen in the other studies, and/or that effects that can be observed at higher doses generally can predict smaller but likely still significant effects at lower doses, which may be difficult to observe but no less real. Once again, FDA's discussion of the evidence shows bias, and no scientific insight.

On page 17, the authors for the first time describe the study by Daniels et al. (2004); in this context, they report that the study found benefits of fish consumption but no adverse effect of mercury exposure. But they fail to ask why the study might have failed to see adverse effects. Two very likely explanations could be posited: The mercury exposure index used, levels in umbilical cord tissue, is relatively imprecise; and confounding by benefits of fish nutrition was undoubtedly present.

Ironically, the FDA authors later cite the lack of a reported mercury effect as evidence that the Daniels et al. study is free of confounding—i.e., that it meets their criteria for use in the model. This conclusion is incorrect; the lack of an observed mercury effect is more likely to be evidence that confounding was present than that it was not. Misinterpretation of this study illustrates two of our "theme" problems: Lack of scientific understanding, in this case a fundamental lack of comprehension of the critical issue of confounding; and bias, in that the authors uncritically embrace data from a study finding significant benefits

from fish consumption and no risks form methylmercury, without pausing to assess what might explain the results or how valid they might be.

On pages 17-18, the report summarizes the 2005 study by Oken et al., discussed in Section 4 of our main comments. FDA's authors have "recalculated" one of the two central results of the study. As shown in our Table 4, Oken et al. reported an increase of 4.0 points (against a norm of 100) on the VRM score for each fish meal the mothers ate, and a decrease of 7.5 points on the VRM score for each ppm of mercury in maternal hair. FDA has re-stated the mercury effect as a decrease of 1.28 points per fish serving, with the rationale that this facilitates direct comparison of benefits and deficits.

This FDA "data conversion" is based on a statement by Oken et al. that maternal hair mercury level was associated with fish consumption, and increased by 0.47 ppm for each serving of fish. That unsurprising finding cannot, however, be used the way FDA used it, to calculate a "mercury deficit per fish serving." The correlation that led to the ratio of 0.47 ppm per fish serving is based on all the fish eaten by all the women in the study, i.e., it is a weighted average. The only way the mercury effect could be expressed per serving of fish would be if all the women always ate fish with average mercury content. If that had been the case, however, there would have been no high- and low-mercury exposure groups; all the women's mercury exposure would have been the same.

FDA's expression of "mercury deficit per serving of fish" is therefore not scientifically valid. It is also highly misleading, in that it makes the mercury deficit seem to be much smaller than the fish benefit, when it was no such thing. The correct way to present the data is the way Oken et al. presented them, using the exposure indices that they used in the study. Fish consumption was measured in meals per week, and mercury exposure was measured as ppm in maternal hair. Of 135 women in the study, nine ate fish more than twice a week, and 14 had mercury levels above 1.2 ppm. The high-mercury group thus is at or above the 90^{th} percentile, and the high fish consumers are above the 93^{rd} percentile. It is reasonable to compare these two groups. Children born to women who ate fish twice a week would have a beneficial effect of 8 points on the VRM. Children born to women with hair mercury of 1.2 ppm would have a deficit of 9 points on the VRM score. From this more valid, appropriate comparison, it appears that the beneficial and adverse effects are about the same size, or the mercury effect (at the 93^{rd} percentile) is slightly larger.

FDA also takes a minor finding from Oken et al.'s paper and overstates its importance. The authors found that VRM scores were 12 points higher in women who ate fish more than twice a week and had lower hair mercury levels. In women with high hair mercury, the benefit of eating fish more than twice a week was just 2 VRM points. FDA uses the data here to conclude that mercury exposure can reduce the benefits of fish consumption, which is true. However, the report fails to note two critical aspects of the data: First, only nine women ate fish more than twice a week; the 12-point and two-point boosts represent effects in just 7 and 2 children, respectively, not statistically robust samples. Second, the overall average VRM score was 61 in the low-mercury group, and 53 in the high-mercury group. The difference between high fish eating, low mercury and low fish eating, high mercury groups' VRM scores was 19 points. If one is going to use such a very small data

set to make a point, then the obvious conclusion is that mothers-to-be should eat plenty of low-mercury fish—the precise conclusion Oken et al. reached.

The FDA report's misinterpretations of this study show, again, the report authors' lack of scientific understanding and a bias toward minimizing results that suggest that mercury risks are as large as or larger than fish nutrition benefits.

One additional important point that FDA did not seem to grasp: The benefits and adverse effects in children around the 90th percentiles of exposures in Oken et al.'s study occurred in different children. Women's mercury exposure depended on which kinds of fish they ate, not just on how often they ate fish. It would be scientifically inappropriate, and also highly misleading, to combine the + 8 and – 9 scores on the VRM just mentioned into a "net effect" of -1 point. Each individual child had a positive or negative "net" effect, but combining the two in a risk-benefit assessment does what confounding does in an epidemiological data set. It tends to make effects that are very real and probably significant for the affected individuals "disappear."

Stated another way, we cannot say that Group A was harmed less because Group B had an equivalently large benefit. Nor should we assert that the benefits to some don't matter because harm is occurring to others. The independent distributions of each effect are what matter. The "net effect" concept is inherently bad science that, if relied upon by decision makers, could lead to bad public policy.

The FDA report also mentions but does not discuss Oken et al.'s 2008 paper, examining children from the same cohort at the age of 3 years, which confirmed results observed at age six months. (See our description in Section 4 of our main Comments.)

Although the title of this section in FDA's report refers to studies where fish intake and methylmercury exposure were "comparable" to those in the US, the Oken et al. papers are the only ones mentioned that fit that description. Four other recent studies, those by Lederman et al. (2008), Davidson et al. (2008) Strain et al. (2008), and Jedrychowski et al. (2006, 2007), all described in our main Comments, bear on exactly this question, but FDA essentially ignores them.

On one hand, it is understandable that FDA might not have been able to include several of the most recently published studies in its analysis. On the other hand, we believe these recent studies are critically important evidence—absolutely pivotal for understanding the emerging consensus on methylmercury effects at low exposure levels. We simply cannot understand why FDA had to publish this risk-benefit assessment now. With so much new and (to anyone in the field) obviously critical evidence having been published within the past year or two, why not spend the extra few months, study the new evidence intensely, and see if it requires re-thinking any aspects of the risk-benefit model? Instead, FDA has put out a flawed draft document that fails abysmally to address pivotally important recent evidence. This does the agency no credit.

FDA tries to beef up this otherwise scientifically thin section by again discussing the Faeroes and New Zealand studies, on page 18. But once again, FDA fails to address the critical issues of data quality and reliability, and the superior design of those studies. The report merely suggests that these studies "could be interpreted to be consistent with" the results of Oken et al. (which FDA has just finished misrepresenting). Again, studies are cited but the authors apparently don't understand what they mean.

Table IIIA-1 on pages 18-22 summarizes studies cited in the text. Like the text, this table includes incorrect and misleading information. The erroneous conversion of the mercury effect in Oken et al.'s 2005 study to "deficit per fish serving" is repeated. The opposing and confounding effects of fish intake and mercury in Oken et al.'s 2008 study are also misconstrued; it is stated in the Table that mercury caused a "reduction in benefits," but in fact the nutritional effects and adverse effects were independent of each other and had quite different distributions in the studied population. How much effect mercury had on the beneficial effects or vice versa for individual children cannot be determined from the published data.

The Daniels et al. (2004) study in the UK is included in this table, for reasons that are far from clear. It is inaccurately described as having used "neurodevelopmental tests" to evaluate the children. In fact, the children's mothers filled out questionnaires rating their own children. This subjective data is quite different from objective test data. The FDA authors seem either unaware of that methodological weak link in the UK study, unable to grasp its significance, or uninterested in discussing it.

Table IIIA-1 mentions the two Polish papers discussed in our main Comments, although the text here does not. The description in the table is both uninformative and scientifically myopic. Neither the magnitude of the effects observed in the first study (large) nor the blood mercury levels involved (low, about half the typical levels in the US) are given in the table. The presence of confounding by fish consumption in the second paper, which probably explains why adverse effects were not observed in that analysis, is not noted. Instead, the impression is left that since the adverse effects observed in the first study apparently vanished in the second study, the earlier effects were probably not real. This shallow treatment of an important recent study once again shows no scientific insight, and a bias to discount risks wherever possible.

On the whole, this section again reveals the FDA authors' deep lack of understanding of what the overall body of epidemiological evidence shows, what it means, and how it can and cannot be interpreted. We believe it also reflects the authors' bias, i.e., their lack of stronger interest in the emerging evidence that has solved certain mysteries about prenatal methylmercury exposure's adverse health effects and raised interesting new questions.

Table IIIA-2, on pages 23-24, purports to be about studies of beneficial effects, but the Lederman et al. (2008) study is listed here. That paper belongs with and should have been discussed with the Oken et al. papers. In fact it is not discussed at all in the text, and the Table describes the study so briefly that it fails to inform. The study measured mercury exposure from fish consumption (not mentioned here by FDA). While it does note that

both beneficial and adverse effects were observed, the Table does not indicate exposure levels; the women in this study were almost exactly "average" for women in the US in terms of blood and hair mercury levels. And yet there were adverse effects from this low level of mercury exposure, as well as benefits of fish consumption. Again, the authors appear to have missed the significance of this important study, or not been interested in exploring its implications.

We find it significant that every one of these 2008 papers, and the 2006 and 2007 Polish papers, concluded that pregnant women should eat fish, but should choose low-mercury fish. This theme resonates through the recent literature, but cannot be found anywhere in FDA's summary interpretation of that literature.

Pages 22-25 discuss effects of post-natal effects of fish consumption in children. Again, it shows blindness to critical methodological issues in epidemiological studies. The Daniels et al. study is discussed at some length, once again without paying any attention to data quality and reliability issues. The Seychelles and Faeroes studies are cited as evidence that higher mercury exposure is associated with better cognitive performance (because of the association of mercury with fish nutrients), and it is stated that no adverse effects of mercury were found in either study, at levels of fish consumption by young children that are far higher than those in the US.

We find this discussion misleading. The lack of observed adverse effects of mercury may well have been due to the confounding effects of beneficial fish nutrients. It is not enough for FDA to explain the improved cognitive outcomes as due to fish nutrients, without also mentioning the very strong likelihood that adverse effects of mercury were obscured by the countervailing nutritional effects. We also note that FDA found several reasons not to use the Faeroes data, generally regarded as the best available data on the adverse effects of prenatal mercury exposure on cognitive development, in its risk assessment. But here, FDA devotes a lengthy discussion to an aspect of the study that suggests that, at least for postnatal development, fish consumption appears to have larger benefits than risks.

FDA also has failed to note that most of the fish consumed in the Faeroes is cod, which is comparatively low in mercury. If their mercury exposure came from their fish alone, the Faroese cohort would be very similar to Americans. It is their consumption of pilot whale meat that makes mercury exposure in the Faeroes unusually high.

Section III-B is about cardiovascular effects; we have no comments.

Section IV: The FDA's quantitative risk-benefit model

Page 33 describes the conceptual framework for the model, states FDA's commitment to the "net effect" approach. We have made clear why we think this concept is neither good science nor a sound basis for policy. We will try not to repeat ourselves.

The agency's decision to use verbal comprehension as its index of methylmercury's and fish nutrients' effects on cognitive development is reiterated here. Again, we have already

noted that by choosing to build its model around just this effect, FDA committed itself to use just a narrow slice of the available data, largely without regard for methodological issues such as quality, reliability or representativeness of the data. While FDA did use a few other analyses that took broader approaches and considered multiple other outcome measures, it essentially used them only for comparison, making subjective judgments as to whether their model was reasonable or not. A much broader analysis, using the best recent data on a wider range of outcome measures, would have produced a much sounder basis for developing the dose-response relationship. Perhaps such an effort was beyond FDA's competence, or beyond available resources. Whatever the reasons, the impacts of this critical, narrow choice of outcomes and studies reverberate through virtually every part of FDA's modeling effort.

Again, we will try not to repeat ourselves, but we will point out later numerous ways in which these analytical choices constrained and added uncertainty to the modeling results.

The "What If" Scenarios: A Critical Omission, A Critical Inclusion

On page 34, the authors describe what the model was used to examine. First, they looked at "baseline" exposure, i.e., the distribution of mercury exposure associated with US fish consumption across the population, factoring in amounts of different fish consumed, and fish with all different mercury levels. This part of the analysis is straightforward, though we believe it has a major "blind spot" with regard to high-end consumers who repeatedly eat high-mercury fish; we will address that in more detail below.

The model was then used to examine possible health impacts of changes in US patterns of fish consumption, much as Cohen et al. (2005) did. FDA redid its analysis, assuming women of childbearing age eliminated their consumption of higher-mercury fish, and ate only "low-mercury" fish. Four other scenarios were also examined; they are described in Box IV-2. Briefly, the scenarios all applied to women of childbearing age, and involved the following changes: **(1)** Assumes women are limited to 12 ounces of fish a week, i.e., those who now eat more than that would reduce their consumption, and all eat the same fish varieties as before; **(2)** Assumes that women below the 95th percentile all increase their fish intake to 12 ounces per week, that high-end consumers reduce their intake to 12 ounces, as in (1), and that women eat the same varieties of fish as before; **(3)** Assumes a limit of 12 ounces per week, as in (1), but that everyone eats low-mercury fish; and **(4)** Assumes no changes in amounts consumed, but every woman eats low-mercury fish.

There are two major problems with the way FDA has framed these scenarios. The first is that the agency's definition of "low-mercury fish" includes canned light tuna. So, in the scenarios that involve eating just "low-mercury" fish, women would continue to eat the largest single source of mercury in the American diet. According to market data in FDA's Table AA-3, canned light tuna constitutes 11.4 percent of the US seafood market—more than all other higher-mercury fish varieties combined—and as our Table 1 shows, canned light tuna contributes 15.9 percent of all the mercury in the US seafood supply. So, what FDA means when it says the women in Scenarios (2) and (3) eat only "low mercury fish" is not what most people would probably take the expression to mean.

This assumption—not revealed unless one gets to Footnote 20 on page 118—seriously biases results of FDA's "what if" scenarios. Because women eating "low mercury fish" in those scenarios are still consuming the largest and most frequently consumed source of mercury in their diet, their mercury exposure is not so drastically different from that of women in the scenarios who do not switch to eating "low-mercury fish." In other words, by including canned light tuna as "low-mercury," FDA substantially reduces the impact of choosing low-mercury fish in the results of these scenarios.

The other serious problem we have with FDA's four "what-if" scenarios is what they leave out. None of the four scenarios represents the "win/win" solution, in which women eat more fish ***and*** eat only low-mercury fish. Such a scenario would combine scenarios (3) and (4); that is, all women would eat at least 12 ounces of fish, some could eat more than 12 ounces if they wished, and all the fish they consumed would be low-mercury.

The fact that FDA left out this possibility is simply stunning. It suggests that the agency had no curiosity about how their model would project results of the best-case scenario, or that FDA did not want to discuss what clearly appears to be the best approach.

Omission of this scenario—we will call it "What If Scenario 5"—also seriously distorts the results of the analysis. Stated simply, the scenarios that involve reduction of high fish consumption (limiting women to 12 ounces per week) result in loss of benefits with only minor reductions in mercury exposure, for a net negative public health impact. Scenarios that involve choosing "low-mercury" fish result in only modest gains due to the reduction in mercury exposure—in large part because mercury exposure is not reduced as much as it would be if canned light tuna had been assumed not to be eaten in those two scenarios. The two scenarios in which all women eat more fish (Scenarios 2 and 4) result in modest net gains in IQ because of the increase in fish consumption, partially offset by increased mercury exposure. The impression one gets by comparing these outcomes is, first, that all the effects are small, and second, that advising women to eat more fish has more positive impacts on public health than advising them to choose low-mercury fish.

Those results are debatable for many reasons, and they are also perniciously biased. The scenario that was left out, our Scenario 5, would show that the public health impacts of doing both things simultaneously—telling women to eat more fish, ***and*** telling them to eat only low-mercury fish—would have vastly greater benefits than any other scenario. Only in this scenario are the two changes working in tandem—more fish intake and less mercury exposure. In the other four scenarios, reduction in mercury exposure requires reduction in fish benefits, or increased benefits are accompanied by increased mercury exposure. By leaving the "win/win" scenario out of its analysis, FDA has created a false "either/or" choice—women either eat more fish, or they avoid mercury.

We really cannot understand why FDA left out "Scenario 5," which is intuitively an obvious combination of changes to look at, and one that has been widely discussed and recommended in recent research papers. The omission approaches irrationality. While it is difficult to choose just one of the massive flaws in this analysis as its most egregious

error, the single flaw that most damages the credibility of its results, if forced to choose, we would probably pick this one.

FDA should re-run its "What If" scenarios, with two major changes. It should re-define low-mercury fish as those with less than the average level of 0.086 ppm. And it should add "Scenario 5," in which women increase their fish consumption to 12 ounces a week or more, ***and*** eat only low-mercury fish. Making those corrections will not remedy the many other defects in the model, noted throughout this Appendix. But it would in effect "unload the dice." We would be very interested in seeing what the model projects with just those two revised assumptions incorporated.

Cardiovascular Outcomes Benefit-Risk Modeling

On page 38, we encountered a statement that brought us up short. While we have elected not to comment on most aspects of the model that involve cardiovascular effects, because that is not our strongest suit, we nevertheless were struck by this statement:

> "We did not model an adverse methylmercury contribution to the net effect for fatal coronary heart disease and fatal stroke. For these endpoints the potential for adverse effects from methylmercury exposure are [sic] not well enough understood and, furthermore, we did not have data on the concentration of methylmercury in the fish consumed. Thus we can only estimate whether the overall net effect from commercial fish is likely to be adverse, neutral or beneficial."

This statement makes almost no scientific sense. Adverse effects of methylmercury on cardiovascular health could be modeled the same way the adverse effects on cognitive development were, by generating a dose-response curve from existing studies, and using the exposure model to simulate Americans' exposure to mercury from fish consumption. Not knowing the mercury levels "in the fish consumed" (by the subjects in the published studies, one assumes FDA means) is irrelevant; such data were generally unavailable in studies on neurobehavioral effects, too. It is the mercury levels in people's bodies—their blood, hair or other tissues—that are used to generate dose-response curves. The mercury levels in fish that matter for the risk assessment are those in the American diet, already built into the model. The fact that mercury's potential adverse cardiovascular effects are "less well understood" means primarily that more uncertainty might be attached to dose-response curves for these effects—but major uncertainties did not stop other aspects of the modeling effort.

Beyond its scientific (and grammatical) illiteracy, this statement once again shows the bias of the report's authors: They were really interested in modeling the benefits of fish consumption, and when modeling risks seemed too difficult, they just skipped it. Not only does this frank admission reflect on the authors' state of mind, it largely undercuts the entire purpose of the report. To translate that turgid final sentence of the quotation: "Due to technical difficulties, we could not complete one of the four critical modules of our model, and therefore failed to accomplish our primary stated objective."

FDA may have known in advance that they would not be able to quantitatively model the adverse effects of mercury on cardiovascular health; after all, the HCRA study by Cohen et al., cited so often by FDA, was unable to do so. If so, then why start the analysis at all? Or, if they determined that they could not do this major component of the analysis only after the process was under way, why not stop at that point? Instead, they have created a three-legged dog and are trying to pass it off as a greyhound.

Page 38 also notes that modeling the contributions of differing nutrient profiles of fish of different varieties was "beyond the scope" of the analysis. Elsewhere, the authors say that this task was also too difficult. Instead, all fish are treated generically as far as beneficial effects are concerned. The effect of that choice is a model in which the risk is distributed unevenly throughout the population, but the distribution of the benefits is unknown, and thus is assumed to be uniform (even though it isn't). This asymmetry, as we have noted, further diminishes the likelihood that the model could shed meaningful light on so-called "net effects." Yet once again, faced with a scientifically difficult task for which they had no solution. the authors pressed onward, ignoring and denying the impact of omission of difficult but essential components of the model.

Pages 37-38 describe FDA's exposure assessment. This follows a familiar path, well-trod by the agency for many years now. Fish consumption data from the CSFII and NHANES surveys were used to generate a distribution of intake of various fish varieties that make up the US market (or 98.4 percent of it). Information on mercury levels in each variety of fish, including variability of mercury levels in samples of the same fish variety, were then incorporated. The model was run and generated a distribution of mercury intake estimates across the population of women of childbearing age.

Selection of Studies for Dose-Response Models: Critical Errors and Biases

On page 39, FDA lays out its criteria for choosing the studies it elected to rely on for its dose-response relationships. This choice is described as "a key challenge." That is a huge understatement. As we have said (and we are trying not to repeat ourselves, but it is hard, given the way the FDA report endlessly reiterates itself), this choice entails using some data, and not using other data. Which data one chooses to use—or not to use—can have numerous impacts on the outcome of the analysis. Data selection for this process should be based on rigorous scientific criteria—such as the strength of the study design, lack of methodological problems that call into question the reliability of the data, the statistical power of the study, the representativeness of the data (how closely they fit in with all the other data in the literature), and the relevance of the effects to the problem one is trying to understand, for example.

FDA's criteria for choosing studies do not include most of the standard scientific criteria. They seem at times to have been developed post-hoc, to describe studies that already had been chosen as the basis for the analysis. As FDA acknowledges in Appendix A, on the risk side, the analysis was initially done a decade ago by two FDA scientists, and rather than begin again from scratch, they chose to use that previous work as their basis for this

model. There is no examination in the report of whether the criteria used by Carrington and Bolger to select the data they used in their 2000 paper are still appropriate criteria for the current modeling effort.

In any case, the criteria FDA has stated do not begin to cover data quality and reliability issues. And the studies FDA chose to incorporate in its model fail to meet some of their stated criteria. Once again, the authors of the report seem to have no idea how sloppy and unscientific their approach appears to be.

The criteria for data to model methylmercury's adverse effects include (1) Freedom from confounding by beneficial effects of fish nutrients; (2) Indicative of the effect magnitude, i.e., the data should show an outcome that could be a reasonable surrogate for aggregate neurodevelopmental effects of methylmercury; and (3) FDA had access to the raw data on individual subjects. The first two of these criteria address data representativeness and reliability issues; the third is related to needs of the model.

The first study FDA chose for this part of the analysis was a 1987 report on the effects of a methylmercury poisoning incident in Iraq. FDA felt it met the first criterion, freedom from confounding, because the methylmercury exposure came from bread contaminated with a fungicide, not fish consumption. In fact, there might have been differences in fish consumption among the study subjects, which might have had an effect on the outcomes, but in all likelihood those effects would have been overwhelmed by the massive doses of methylmercury consumed by the women. So, the Iraqi study passes the first test. It also passes the third test—FDA already had the individual subject data, which it had used in the analysis published in 2000.

On the second criterion, though, this study is more problematic. The very high doses of methylmercury involved are far greater than any likely to occur from fish consumption. Using these data requires extrapolating from effects at very high doses to possible effects at much lower doses. Such extrapolations are common in risk assessments, but always introduce uncertainty.

This study had another disadvantage, in that the studied group was small—81 children, quite a small cohort as epidemiological studies go. The neurodevelopmental outcomes it measured included age at first talking and first walking. FDA asserts that the former is as good as other indicators of verbal development, the outcome it chose to use in its model. We believe that epidemiologists who have studied methylmercury's effects could have a long and interesting debate over that assertion.

Beyond these issues, the Iraq study had several serious problems with data quality and reliability. The FDA authors acknowledge these problems, then try to rationalize them away; after all, the studies were chosen, the analysis already done. The crux of the issue is that Iraqis do not celebrate, or even record, birthdays. The exact ages of the children were therefore unknown; the investigators asked the mothers when during the year their babies were born (spring, summer, fall or winter) and hoped their memories were good.

Given the imprecision of the children's ages, the researchers recorded their age at first walking or first talking only in six-month intervals.

That means that the Iraq data on the outcome of most interest—age at first talking—are very imprecise. Given that most children begin talking between the age of one and two years, a possible error of 3 to 6 months in each data point amounts to an imprecision of about 25 percent. This imprecision results in large uncertainties about the slope of the dose-response curve, which is what this study contributes to FDA's model. However, the imprecision did not prevent effects from being observed; the methylmercury damage was severe, with delays of years rather than months in reaching developmental milestones for many of the children.

FDA briefly considers the implications of the imprecision in these data, and dismisses it as not a concern, a conclusion we strongly disagree with. But, to try to deal with some of the other problems of the Iraq study—the small sample size, and the very high doses—FDA combines the Iraq data with those on the same outcome, age at first talking, from the Seychelles study. The Seychelles data do represent a much larger number of subjects, with lower exposures. But the Seychelles data have another major data quality problem: Mercury exposure in the Seychelles came from fish consumption, in a very high-fish diet. Thus, the effects mercury may have had on cognitive development in Seychelles children were largely masked by the offsetting benefits of fish nutrients.

In short, the Seychelles data are massively confounded by fish consumption—so this data set fails to meet FDA's first selection criterion. FDA dismisses this problem, on page 64, in a marvelous example of circular logic. It does not matter that the Seychelles data were confounded, the authors argue, because the effect of mercury in the Seychelles was small and had little effect on the overall slope of the dose-response curve; the Iraqi data had the dominant influence. Translations: (A) The Seychelles data had little effect, because they showed little effect, because they were confounded by fish consumption. So how does the confounding not matter? And, (B) The Seychelles data had little effect, thus the effort to use them to adjust the admittedly suspect Iraq data failed to make any difference, leaving FDA dependent on the Iraq data with all their acknowledged weaknesses.

The criteria for selecting studies to model the dose-response curve for fish benefits, also stated on page 39, are: (1) No confounding of the fish effect by methylmercury; (2) The effect is expressed as a function of fish intake, rather than of individual nutrients in fish (this criterion eliminates clinical studies that involved measured doses of omega-3s from fish oil, for instance); (3) Comparability; the studies should measure essentially the same outcome that was used on the risk side, so that "net effects" could be calculated; and (4) FDA should have access to the individual subject data.

The first of these criteria deals with methodological issues and data reliability, while the other three address primarily the needs of the model. (I.e., the choice of "representative" outcomes has already been made on the risk side, so the issue here is compatibility with that pre-determined outcome.)

FDA found only a single study that it says met all these criteria—the Daniels et al. 2004 paper, already critiqued here (see pages 59 and 62 in this Appendix.) To briefly repeat the salient points: First, FDA claims Daniels et al.'s study is free of confounding, because no effect of mercury was observed; in fact that is evidence that confounding was present, not that it was absent, although FDA clearly does not understand it that way. The study thus fails to meet FDA's first criterion.

Second, although FDA claimed that outcome comparability was a primary reason for choosing this study, the study did not measure age at first talking; it used very different methodologies to estimate children's verbal development. In the end, to compare these data with the Iraqi/Seychelles data, FDA converted both to IQ equivalents. Since most of the developmental outcomes measured in essentially all methylmercury studies can be (and have been, by Cohen et al.) converted into IQ equivalents, there was no scientific reason to choose this outcome, and the Iraqi and Seychelles data sets, to model the dose-response relationship. The model could have used any number of other data sets on any number of outcomes from other (better-designed) studies instead of or in addition to the data FDA selected. Likewise, the choice of the Daniels study was not required by a need to compare outcomes, since the outcomes in many benefits studies could also have been converted to IQ equivalents. One is left with the impression that FDA's choice of this study as the sole basis for its cognitive benefits estimate was essentially arbitrary.

Finally, while FDA seems to have chosen this study because it meets the needs of the model, the authors of the report pay no attention at all to the data quality and reliability issues we have raised here. In fact, they do not present any critical perspective on the study at all, they simply describe it, assert that it meets the criteria, and move on. This treatment is in stark contrast to the discussion of the studies used to estimate the dose-response curve for methylmercury's prenatal cognitive effects, which occupies several pages. The authors clearly understand that methodological issues matter, as far as risk estimates are concerned, even though we feel they inadequately addressed most of the major methodological weaknesses in the studies they relied on. But when it comes to studies on benefits, the authors seem not to understand that methodological issues even need to be considered. Again, this stark asymmetry reflects the FDA authors' bias: The focus was on demonstrating benefits, not on discussing the quality of the evidence.

Having explained—unconvincingly and with impressive lack of insight into the critical scientific issues involved—why it chose the studies it chose for its model, FDA later explains why it did not try to use data from other studies. Table IV-3, beginning on page 68, lists all the studies considered, and reasons why they were not used. Frankly, most of the reasons for not using studies sound like flimsy excuses. The most frequent reason is "data on individual subjects not available." In fact, most researchers will share their data for such an analysis, if asked. We understand that FDA contacted the senior author of one major study to ask about acquiring their data, and was told how it could be arranged, then did not contact the researcher again. We suspect that what "data not available" actually means is, "We did not go out looking for more data, because we already had an analysis, done ten years ago, with data from the Iraqi and Seychelles study, and we decided we did not need more or better data."

A second frequent excuse offered in Table IV-3 for not using other data sets is that they measured "different outcomes" from those FDA was interested in. Since, as noted, most outcomes could be converted to IQ equivalents, this also is an unconvincing reason. In one case in particular, the Oken et al. 2005 study, the outcome measured was a standard test of verbal development in children before they reach the age of speech. For FDA to choose verbal development as its outcome measure, then to reject these data on grounds of a "different outcome measure," makes no scientific sense at all.

FDA did compare their model results for mercury's effects on cognitive development with two similar analyses, one by Axelrad et al., who converted the results of the three major epidemiological studies (Seychelles, New Zealand, Faeroes) to IQ equivalents, and the analysis by Cohen et. al, which did the same. The FDA authors report that the results of their model and the other two analyses were quite similar in terms of IQ effects, which suggested that their model produced reasonable results on this parameter.

However, FDA has a double standard about citing such other analyses. FDA's model in general predicts larger beneficial effects of fish consumption than it does adverse effects of methylmercury, on cognitive development. In FDA's scenarios, beneficial effects are about four times greater than adverse effects. As we noted when we discussed the Cohen et al. study in Section 4 of our main Comments, HCRA found an opposite result: They projected adverse effects of methylmercury on cognitive development that were about three times larger than the beneficial effects of fish intake. FDA's model thus predicts benefits at least an order of magnitude greater than Cohen et al.'s did. Such a difference from other analyses in one of the model's central results needs explaining.

While FDA readily cites Cohen et al. to support the reasonableness of their estimates of mercury's adverse effects, the authors completely ignore what the same study could have told them about their estimates of benefits of fish consumption: I.e., that FDA's results are drastically out of line with another major attempt to estimate the same effects. This selective blindness to evidence that might call the model's benefit results into question is typical of the bias throughout the report, i.e., failure to be appropriately scientific or self-critical about the benefits side of the assessment.

Overall, we believe that the benefits assessment is by far the weaker, and more severely scientifically flawed, portion of the analysis. That is a strong statement, because we feel the flaws and limitations of the risk assessment side are also numerous and serious. But the results on the benefits side, based on a single seriously flawed study, and different by an order of magnitude from the quite respectable analysis by Cohen et al., simply are not scientifically credible. And when the benefits half of the equation is not credible, the "net effects" calculations are equally unreliable.

Exposure Modeling Overview

Table IV-1, beginning on Page 42, lists sources of data used in the exposure assessment, major data gaps and problems, and the assumptions FDA made to address them. FDA is

to be commended for this detailed discussion of data quality issues—unfortunately, its inclusion here also highlights its absence from most other sections of the report. While it is understandable that FDA would continue the analysis despite problems with the data, we wish as much attention had been devoted to what the model does ***not*** represent well, as was devoted to explaining what it does do.

In our main Comments, we have addressed the concern that the CSFII data, gathered 20 years ago, may not adequately represent current US fish consumption patterns. FDA is aware of that, and has adjusted the CSFII data by using fish consumption data from the NHANES survey. The CSFII survey covered just three days; NHANES covers 30 days, which increases reliability of the data somewhat. We believe extrapolating from either of these short-term surveys to estimate consumption patterns for a year still introduces large uncertainties into the consumption estimates. FDA asserts that the extrapolation seems "reasonable" to them, and does not dwell on the uncertainties.

Our primary concern is that we feel the data—and thus, the model—have serious "blind spots" when it comes to people with relatively extreme fish consumption patterns. The greatest risk of excessive mercury exposure occurs in people with the highest fish intake who also prefer to eat higher-mercury fish. For women of childbearing age, we define high-end consumption fairly conservatively, as above the 95th percentile (women who eat more than 12 ounces of fish per week.) Within that group, only a fraction are likely to choose high-mercury fish repeatedly, but those are the women who bear most of the risk of adverse cognitive effects in their children.

For the rest of the population, we would define high-end consumption as above the 99th percentile (i.e., people who eat fish 4 to 6 times a week or more). Here, too, the concern is the minority that repeatedly choose high-mercury varieties like tuna, swordfish, sea bass or grouper.

The key question seems to us to be, how many such extreme consumers—high-end fish eaters with a strong preference for large, predatory, mercury-accumulating species—are "out there?" There are about 4 million pregnant women at any given time in the US; 5 percent of them would be 200,000. If we extend concern to women of childbearing age who are not currently pregnant—as we probably should—the number rises to about 3 million. One percent of the US population as a whole is about 3.25 million. Out of these large numbers, the crucial question is, how many repeatedly eat high-mercury fish?

As FDA has pointed out in its report, the top 20 fish and shellfish choices account for at least 90 percent of the market, and most of them are low in mercury. The other 10 percent of the market consists of 31 fish varieties, listed in our Tables 1 and 2 and FDA's Table AA-3. Our Table 2, which sorts fish varieties into categories by mercury levels, lists 21 varieties with below-average mercury levels, and 30 with above-average levels. Most higher-mercury fish have small market shares; that, and the 30 varieties to choose from, suggests that most consumers are unlikely to eat many of the higher-mercury fish very often. Based on these general observations and simple probability calculations, very high mercury exposure from eating fish might seem likely to be rare.

However, two important exceptions to these general assumptions are critical to doing an accurate mercury exposure assessment. First, we know—from widespread but anecdotal evidence—that some consumers simply love one or two types of fish and eat that fish on most of their fish-eating occasions. I.e., consumer fish preferences are not random and do not, therefore, strictly follow laws of probability. Idiosyncratic individual tastes can have significant consequences.

And, second tuna is a very important exception to the general observations that the most highly-consumed fish are low in mercury, and most high-mercury fish have small market shares. Canned light tuna accounts for 11.41 percent of the market, canned albacore tuna another 3.81 percent, and fresh and frozen tuna an additional 1.22 percent. Combined, the three forms of tuna constitute 16.44 percent of the market—which means that almost one out of every six fish meals is tuna. Tuna is also far and away the most heavily consumed fish with elevated mercury levels: as we noted in our main Comments, 37.4 percent of the mercury in the US seafood supply comes from tuna. While the canned albacore variety has about three times as much mercury on average as canned light tuna does, both types are potentially important sources of exposure. Someone who eats canned light tuna four times a week, and many women who eat it more than twice a week, would exceed the reference dose for methylmercury.

We think there is a critical need for an exposure assessment that looks only at high-end fish consumers, as defined here: Women of childbearing age above the 95th percentile, and for everyone else, those above the 99th percentile. The assessment should attempt to model repeat consumption of high-mercury fish among these high-end populations.

Now, FDA may respond that their model already does this. We grant that it attempts to do it, but we believe the attempt was not very effective, because of limitations in the fish-consumption data.

As we noted earlier, there are about 3 million people above the 99th percentile for fish consumption in the US, but very few of them were included in the CSFII or NHANES surveys. CSFII provides data on 3,525 people, representing a cross-section of the US population. The main NHANES sample consists of 5,214 women and children, although FDA used just a subset of those surveyed individuals.

The CSFII sample included just 35 people above the 99th percentile in fish consumption, which we believe is too small a sample to provide adequate data on repeat choices. The maximum number of fish meals reported by any individual in the three-day survey period was four meals, so the maximum number of data points (fish choices) by these high-end consumers was 140. Except for tuna, most fish they ate were low-mercury varieties. We therefore think the number of data points on higher-mercury fish choices is far too small to generate meaningful information about repeated consumption of these fish.

FDA used two years of NHANES data on women who ate fish more than 4 times in the 30 day survey to generate repeat consumption ratios. We admire their inventiveness, but

think the model still falls short of providing convincing answers to central questions in a mercury exposure assessment for high-end fish consumers. If we assume an average six-ounce serving, four fish meals per month amounts to about 23 grams per day, which is at about the 80th percentile for fish consumption, so sample size was less of an issue.

Nevertheless, since 90 percent of fish and shellfish other than tuna chosen by repeat consumers are low-mercury, and there are 30 or so varieties of higher-mercury fish to choose from the other 10 percent of the time, the number of data points on repeat eating of most of those fish varieties is still likely to be small, and thus subject to considerable uncertainty. In addition, the NHANES survey includes only women of childbearing age and young children, offering no data on repeat consumption patterns among men, older women and older children. The NHANES sample is also nationally representative; thus it includes very few individuals from ethnic and tribal minorities with high-fish diets. And yet, such "outlier" groups are of particular interest for a mercury exposure assessment.

Ultimately, we feel the best way to answer questions about how many people repeatedly eat relatively high-mercury fish like swordfish, tuna steak, grouper, or orange roughy is to gather new empirical data. A survey that identified several thousand people who eat fish more than, let's say, four times per week, and asked them what fish they have eaten and how often during the past month, should provide the kind of data needed to answer this question fairly definitively. Unless or until such survey data are obtained, Carrington and Bolger's model may be the best available, but unfortunately, we believe it is subject to too much uncertainty to lay the issue to rest.

Converting Dietary Intake to Other Indices of Exposure

On pages 48-49, FDA explains how they converted their estimates of dietary exposure to methylmercury (from their estimates of fish consumption and fish varieties consumed) into estimates of hair mercury levels. They needed to do that because their dose-response relationship, derived from the Iraq and Seychelles data, expressed effects on cognitive development as a function of maternal hair mercury levels.

This data transformation required two steps: Converting dietary mercury intake in µg/day into a blood level in µg/l; and converting blood mercury in µg/l into hair mercury in µg/g. FDA used the dietary mercury/blood mercury relationship from a 1984 British study, and the weighted average hair mercury/blood mercury ratio from the NHANES survey.

In each case, FDA used a single point value for the conversion factor. But in each case, the number chosen represents an average of distributed values. In fact, individuals vary quite widely in terms of the blood mercury level they attain from a given dietary intake, or the hair level they develop from a given average blood level. The appropriate scientific way to express these relationships would be as a mean value with a standard deviation.

When such values are incorporated into a model, one needs to decide how many standard deviations to include. If only the average value is used—as FDA did here—the model can represent only the average individual. In reality, some members of a population will have

substantially higher blood and hair mercury levels than the average, at any given level of dietary mercury intake (and some will also have much lower levels). Empirical data exist to estimate the range of variability in these relationships; EPA incorporated consideration of this variability when it set the Reference Dose, in 1997.

By choosing to use only average values for these conversions, FDA has built yet another strong bias into the model: It cannot "see" the fraction of the population that would have much higher than average hair mercury levels at a given level of intake. It therefore does not "see" people at much higher than average risk, because of normal human variability in how our bodies metabolize mercury. It assumes everyone is alike. This is scientifically untenable, and leads the model to substantially underestimate adverse effects.

The diet/blood conversion is subject to considerable uncertainties. It was based on a study of 20 male volunteers who ate fish with known mercury content over a 90-day period and had their blood mercury levels monitored. The sample size was too small to represent the range of normal variability, and included just adult men; the data don't necessarily apply to women or children. This means the conversion factor used for the dietary intake/blood mercury relationship is imprecise, at best, particularly for women. If it is off by, say, 25 percent, then so are all the projected effects of methylmercury on cognitive development generated by the model. The same British authors (Sherlock et al.) published a second study that examined the blood/hair mercury relationship. FDA might well have compared the results of that study with the ratio they derived from the NHANES survey, to get an indication of whether the British results are consistent with empirical US data. But FDA does not mention the second Sherlock et al. study.

Again, FDA does not discuss the uncertainties that affect the conversion factor used for diet-to-blood. They simply present the number, cite the paper they got it from, and move on, as if this were a straightforward decision that need not be examined.

In fact, these two conversion factors are among the critical determinants of the outcomes of the model, and as on other components, the way FDA has built them into the model is scientifically highly questionable, and possibly inappropriate. FDA does discuss these assumptions and their implications for the analysis, later in the draft report (see page 76 of these comments, below). That discussion minimizes effects of these assumptions and suggests that the resulting uncertainties are insignificant. Again, we strongly disagree: A bias in the model that blinds it to the high end of the exposure distribution curve, making it underestimate the risk distribution, is very significant indeed.

Later in the report, FDA uses these diet/blood/hair conversions in scientifically incorrect and inappropriate ways. For example, Table V-7, on page 92, presents FDA's projected benefits of fish consumption, based on the Daniels et al. data, converted to IQ points. The table tracks the increase in benefits as fish consumption increases from almost none to the 99.9^{th} percentile. To show "net effects," FDA has incorporated data on the hair mercury levels associated with each level of fish intake. The hair mercury levels are based on the assumption that all the fish consumed contained the average mercury level, 0.086 ppm.

This analysis repeats the same conceptual error discussed above, on pages 60 and 61 of this appendix, when we addressed FDA's misinterpretation of the study by Oken et al. In real life, women do not all consume fish with "average" mercury levels; some get higher mercury doses, others get lower mercury doses. The adverse effects of mercury exposure on cognitive development are not uniformly distributed. Pretending that they are, and calculating average "net effects" for women with different levels of fish consumption in this manner, misrepresents the actual distribution of risk, and conceals the potential for a significant adverse public health impact in a small fraction of the population. It amounts to sweeping a risk that should be FDA's focus under the rug.

On page 50, FDA describes another data adjustment, a correction to adjust blood mercury data to eliminate inorganic mercury. This relatively minor adjustment may be justified, but FDA's description of how they did it is unclear. It seems likely that FDA again used a single average value to represent a parameter with a distribution of values. If so, this adds another bias in the model to represent only "average" individuals, and be blind to normal human variability that increases risk for some fraction of the population.

FDA's Discussion of Its Model's Limitations

Table IV-2 on pages 51 to 62 summarizes limitations in knowledge that affect the FDA model, assumptions made to cover knowledge gaps, and the implications of those choices for the results of the model. While we commend the authors of this section of the report for including such an analysis, we feel it is scientifically inadequate and biased in many important ways. FDA's discussion is keyed to numbered points in a figure describing the model, which for some reason begin with Point 8.

Overall, Table IV-2 describes a great many crucial choices and assumptions that, taken as a whole, have enormous impacts on the reliability of the model, and the uncertainty (or in many cases, lack of uncertainty that should have been recognized and built in) of model results. A reasonable observer, noting the many critical assumptions and data gaps, might understandably conclude that this model cannot possibly produce credible results. FDA, of course, does not reach that conclusion. Unfortunately, their comments in this table often tend to ignore, minimize or dismiss substantial problems with the model.

The model starts with a distribution of fish consumption, Point 8 in the reference model diagram. FDA has modeled consumption from the 10^{th} to the 99.9^{th} percentiles of intake. It takes each individual member of the CFSII sample, and models their annual intake of fish of different types. From the fish types consumed, FDA calculates an average annual mercury content for each person's fish, and uses that average to model that individual's mercury exposure from each fish serving.

Again, in real life, people's daily or weekly mercury intake fluctuates up and down over a considerable range. The decision to use average values, rather than a distribution of doses actually likely to be encountered, biases the model to underestimate risk. If the model had incorporated fluctuations, it could have estimated, let us say, the difference between the highest and lowest deciles of weekly mercury exposure across the population. As it is, the

model estimates the differences in annual average mercury exposure; because individual averages converge toward the mean over the long term, the difference between highest and lowest annual exposures is much smaller than it would be for weekly doses.

FDA contends that long-term average exposure, not short-term peak exposures, is what drives risk. This assumption is scientifically debatable; as FDA acknowledges in Table IV-2, the effects of short-term peak exposures versus longer-term average doses cannot be effectively modeled with current knowledge. As a practical matter, then, if the model had been used to generate estimates of high-end short-term exposures, we would not be sure how to interpret them. Nevertheless, we believe the model should be used to do just that. Knowing the full range of short-term (weekly) methylmercury doses would suggest how important this gap in basic knowledge really is.

Point 9 in the model addresses the conversion of dietary intake values to blood mercury estimates. FDA's discussion in Table IV-2 is inadequate. It does not discuss the issues related to sample size, or the lack of data on anyone except adult men, in the study FDA used as its basis for this conversion factor. The authors simply assert that they believe the factor to be "reasonably accurate," a subjective, undefined term. They defend the use of a single average value instead of a distribution of values by observing that the confidence intervals in the cited data were "relatively narrow." This undoubtedly reflects the small and homogeneous nature of the group of subjects studied, but FDA seems unconcerned. They conclude that "this is likely to be a minor source of uncertainty." We don't believe there is a persuasive scientific basis for that conclusion.

Point 11 addresses the blood/hair mercury conversion factor. This was based on actual blood and hair values in the NHANES sample. In Table IV-2, FDA acknowledges that the NHANES data show a very wide distribution of individual values—magnifying the effects of using a single average value in the model (i.e., the way the model then fails to represent the true range of mercury doses). FDA reasons, however, that some of the wide variation in the blood/hair ratio is irrelevant (caused by measurement inaccuracy at the low end, and hair contamination at the high end). They therefore ignored the data at the high and low ends of the distribution, and assumed that the relationship between blood and hair mercury levels was constant over the rest of the range (i.e., that a single ratio value was sufficient for the model). They support this by asserting that the Sherlock et al. study (described in Point 9) showed such an approximately linear relationship. (But had FDA looked more critically at the Sherlock et al. study, they might have questioned the reliability of that reported linearity.) Also, even if the linear relationship from Sherlock et al.'s study is accepted as valid, it describes the dietary/blood mercury relationship in a very high dose range, far higher than that in the NHANES sample. Extrapolation of the slope of that curve from high doses to much lower doses creates additional uncertainty.

FDA concludes, at the end of its discussion of this issue in Table IV-2, that its use of a single value for the blood/hair ratio "is not a significant source of uncertainty." In this case, we disagree vigorously with that conclusion.

The combined effect of Points 9 and 11 in the model is that using point values instead of distributions for conversion factors that translate dietary exposure into hair mercury, and thus into all subsequent calculations of effects of mercury exposure, eliminates the "tails of the curve" from the results. Since the high end of the curve is where the significant risk lies, these choices do severely compromise the model's results. Perhaps "uncertainty" is the wrong term. These choices do not so much introduce uncertainty into the results as they do blindness, a blindness to the most critical outcomes the model might otherwise have examined. It is unfathomable to us that FDA would make such choices in the first place, then explain them away as of no consequence.

Points 12 and 13 in the model diagram refer to analytical choices in modeling the benefits of fish consumption for cardiovascular health. Except for expressing our disappointment Over the absence from the model of a module that estimates effects of methylmercury on these outcomes—a striking omission that defeats the purpose of estimating "net public health effects of fish consumption"—we have no comments on these issues.

Point 14 addresses data and assumptions used to estimate benefits of fish consumption for cognitive development. Here, FDA addresses the concern that their choice of verbal development as the index of effects might not be representative of all the evidence on methylmercury effects on the developing brain. They acknowledge their choice is "a significant source of uncertainty," but immediately dismiss that concern by asserting that the results of the Daniels et al. study are "consistent" with those of other studies.

While this assertion appears in the table, there is no discussion in the text, anywhere in the report, that compares Daniels et al.'s data with those of other studies, or cites those other studies FDA thinks are comparable. In fact, since the premise is that the Daniels et al. study is the only one that met FDA's criteria, the report pays virtually no attention to other literature on the subject.

While FDA addresses whether the effect they selected is representative of all effects on cognitive development, they do not address the more critical possible impacts of relying on a single study: What if the data are unreliable? In Table IV-2, FDA again justifies the choice of the Daniels et al. study as based on "comparability," not a scientifically valid reason, as we have explained. It refers to the data from the study as "tests," when actually they were questionnaires filled out by the mothers. It asserts that the study was free of confounding by mercury exposure, a contention we have also exposed as scientifically incorrect. It notes that FDA had access to the individual subject data, and asserts that this was the only study of cognitive benefits that met all four of the selection criteria.

FDA also presents a lengthy discussion of the assumptions it made and the ways it used the Daniels et al. data in the model to calculate beneficial effects. This discussion is fine, but it never touches on the basic issue of whether the Daniels et al. data are credible.

In short, FDA's discussion of the Daniels et al. study in Table IV-2 repeats the errors of scientific interpretation and failures to evaluate the study critically that pervade the text sections that discuss this study. The difference is that here, in the Table, FDA claims it

addresses the key limitations in data, assumptions FDA made, and their implications for the results of the model. With respect to the Daniels et al. study, none of that essential scientific discussion is actually presented.

Point 15 discusses the dose-response model for adverse effects of methylmercury on cognitive development, and the two studies FDA relied on for that part of the analysis. They defend their choice of age at talking as an indicator that represents other effects on cognitive development, and say they needed an index that could be compared with the verbal development outcomes measured by Daniels et al. Again, since these effects all were converted to IQ points for comparison, this rationale makes no scientific sense. We are wiling to accept that age of talking is one reasonable indicator, but why not look at a wider range of methylmercury effects, and try to integrate them into an overall index of impact on IQ, as Axelrad et al. did?

Table IV-2's discussion of Point 15 also discusses problems with the Iraqi data, and the use of the Seychelles data to "adjust" the dose-response curve derived from the Iraqi data. FDA says here that "The uncertainty [in the dose-response relationship] is the primary source of uncertainty in the simulation model estimates."

We disagree with that statement. In our judgment, the effort made to define this dose-response relationship as accurately as possible comes closer to a scientifically rigorous approach than what is evident in any other aspect of the analysis. This dose-response curve may still contain substantial uncertainties, as FDA admits. But much larger errors are likely to be present in the model's estimate of cognitive benefits, and we believe the errors introduced by ignoring the distribution of exposure values, as we have discussed, are potentially greater than likely errors from the dose-response data.

Unfortunately, FDA's discussion of the limitations of the Iraqi data in Table IV-2 shows the same scientific myopia seen in other parts of the report. The issue of confounding by fish consumption (in Iraq) is discussed; here, FDA concludes that, since their combined data from Iraq and the Seychelles showed that the Seychelles data had little impact on the slope of the curve from the Iraq data, little confounding was present. We agree that such confounding was unlikely, but FDA fails to consider that the Seychelles data, as heavily confounded as they were by fish consumption, showed little overall effect of mercury exposure, and that was the primary reason why they had little effect on the curve.

In this discussion, FDA also raises the issue that the Iraqi children's ages were unknown, which makes estimates of age at talking very imprecise. FDA asserts, basically, that this does not matter much, because the impre4cision was only 3 to 6 months, and the error was thus "small relative to the size of the effects," which involved developmental delays of over a year. We believe this is wishful thinking; an error of 25 to 50 percent in data on the critical outcome variable leaves the Iraqi data subject to enormous uncertainty. But FDA was committed to using those data, so they do their best here to minimize the data reliability concern.

Point 16 in Table IV-2 discusses the methods and assumptions used to combine benefits of fish consumption and adverse effects of methylmercury to calculate "net effects." We are less concerned with the methodological issues here than with the concept of "net effects." As we have explained, this construct is basically scientifically meaningless. Far more useful insights into the relative importance of benefits and risks could be gained by modeling the distribution of each independently and comparing the separate distributions.

Confounding of Mercury Effects by Fish Consumption

On page 66, FDA discusses dose-response relationship for cognitive effects of prenatal methylmercury exposure that it used in its model (derived from the Iraqi data), and those for similar relationships developed by other analysts, which FDA compares with its own analysis. The authors here address the problem of confounding. Their bottom line is that they assume confounding was not present, or that if present it had minimal effects on the dose-response curves. This discussion illustrates a serious lack of understanding by FDA of the evidence from major epidemiological studies.

FDA concludes that significant confounding by fish was not present in the Faeroes study because the primary source of mercury exposure there was pilot whale meat. In fact, the Faroese also have a relatively high-fish diet, as is typical for Island nations, and there was significant confounding in their estimates of mercury effects. The researchers there have re-analyzed their data, using additional statistical procedures to adjust for confounding by fish intake, and have thereby shown that the adverse effects of methylmercury are larger than was initially reported.

FDA then addresses the Seychelles study, and concludes that since Axelrad et al.'s analysis calculated an adverse IQ slope from those data, confounding was not present. FDA simply ignores the largely erroneous impression, which FDA cited earlier in this report, that the Seychelles study found no adverse effects of prenatal methylmercury exposure on cognitive development. In fact, the Seychelles study did observe several such effects, but none reached statistical significance. Years of scientific discussions attempted to understand why the Seychelles study largely failed to observe effects that were clear-cut in the Faeroes and New Zealand studies. The consensus is that adverse effects of mercury were largely masked by offsetting benefits associated with the high-fish diet in the Seychelles. As we discussed in our main Comments, two recent papers from the Seychelles research team have applied improved statistical methods and have been able to separate these confounding effects, revealing the previously unobserved (statistically significant) adverse effects of methylmercury.

FDA's superficial analysis of these studies, its scientifically unsupportable conclusion that confounding by fish consumption did not significantly affect their results, and its use of that conclusion to justify its assumption that fish confounding does not affect the dose-response relationships in its own model, provide yet another example of FDA's extreme scientific myopia on the subject of confounding in epidemiological data

Similarly, FDA repeats, on pages 66-67, its assertion that the Daniels et al. study used to estimate cognitive benefits is free of confounding by methylmercury effects, because no such effects were observed. As noted, since fish benefits tend to mask methylmercury effects, this lack of observed effects is probably evidence of confounding, not evidence of its absence. In this case, if mercury effects were present, they would lead FDA's model to underestimate the apparent benefits of fish consumption.

Pages 68-73, Table IV-3, lists the major studies of methylmercury's effects, says which ones were used and which were not used in FDA's analysis, and gives FDA's reasons for including or excluding data from each study. As noted previously, the explanations for not using most of the excluded studies are unconvincing and/or scientifically incorrect.

Section V: Results of the Model

Table V-1 on page 82 presents results of the model for the distribution of fish intake, showing estimates for women of childbearing age (15 to 45), older women, men ages 15 to 45, and older men. The results shown cover the 10th through 99th percentiles. We have no particular problem with these results, but suggest that a 99.9th percentile estimate also would have been useful. Although "extreme," the 99.9th percentile represents 325,000 Americans, as we have explained.

The 99th percentile estimates range from 618 to 711 grams per week in women, and 923 to 952 grams per week in men, the equivalent of about four to five servings per week, if serving sizes average 150 to 180 grams. There are, however, many consumers who eat fish more than once a day; Hightower and Moore (2003) reported on a cohort of 123 San Francisco residents, many of whom ate fish 10 to 15 times per week. By truncating the model's results at the 99th percentile for fish consumption, FDA has excluded one of the most interesting subsets of the population from the published results.

Table V-2 shows results for dietary methylmercury intake for women of childbearing age. As in Table V-1, the distribution is truncated at the 99th percentile, i.e., it does not address the subpopulation with the highest exposure, those above the 99th percentile.

The results in Table V-2 also understate possible high-end mercury exposure because of the inadequacy of data on repeat consumption of high mercury fish, discussed earlier in this appendix (see pages 72-74).

Table V-2 shows that the women at the 99th percentile would ingest 10.3 micrograms of methylmercury per day, and at the 95th percentile, the dose is 4.9 µg/day. The Reference Dose for a 60-kg woman is 6 µg/day, so the FDA's model projects that perhaps 3 to 4 percent of women exceed the reference dose. The NHANES data show about 6 percent of women with blood mercury levels above 5.8 µg/l, the level that corresponds to long-term intake at the Reference Dose. In other words, FDA's model appears to have significantly understated frequency of methylmercury exposure above the Reference Dose, compared to the extensive empirical data. Although this comparison strongly suggests that the FDA

model errs on the side of understating exposure and related risks, the FDA authors do not comment on that possibility; they simply present the results as facts, and move on.

Table V-3 on pages 83-84 presents model results for estimated blood and hair mercury levels calculated by the model from dietary intake estimates. As we have stated earlier, the fact that the model uses a single average value to make these conversions means the results do not show the effects of human variability on these key exposure measures, and therefore substantially understate exposure at the high end of the range.

Table V-3 shows a 95th percentile blood mercury level of 4.3 µg/l; the 95th percentile blood mercury level in the NHANES national sample was 5.4 µg/l, suggesting again that FDA's model underestimates exposure and risk, compared with empirical data. Also, the NHANES survey found wide regional differences in methylmercury exposure; the 95th percentile blood value for women in the Northeast was 8.2 µg/l, while in the Midwest, it was 2.7 µg/l. FDA's model's reliance on national average values for so many variables once again results in a failure to fail to "see" differences that matter in the distribution of risk in different segments of the population.

On pages 84-86, FDA explains the methodology it used to convert its measures of the positive and negative cognitive effects into IQ equivalents. This discussion does not pay much attention to the imprecision thus introduced: Since any conversion of this type is approximate, the resulting numerical values for IQ contain more uncertainty than was present in the original data on age of walking, or scores on the questionnaires used by Daniels et al.

In Table V-4, FDA also presents the results in one of the original metrics, age of talking. Their model suggests that women's methylmercury exposure at the 99.9th percentile (for some reason, FDA at this point starts extending the model to the 99.9th percentile, rather than truncating it at the 99th), would delay the onset of talking by 4.4 days. This effect is minuscule—so small it would be unobservable in even a large epidemiological study.

We do not find this result credible. We believe the reason it is so small is not that the toxic effects of mercury on cognitive development are insignificant. Instead, we think FDA's model contains so many biased, scientifically inappropriate assumptions that the cumulative effect is to blind the model to risk associated with the high end of variable exposure distributions, which has been effectively excluded from the model.

We also note that FDA's projected adverse effect of a developmental delay of 4.4 days (a delay of 1 percent for a child who begins talking at age 15 months), affecting one-tenth of 1 percent of the population, is far out of line with results of epidemiological studies. For instance, Oken et al. (2005) reported an adverse effect of methylmercury of 9 points on a 100-point test score for verbal development, at the 90th percentile of exposure. That is, at least 10 percent of the children were affected, with a deficit of 9 percent or more on this developmental index, an effect about 900 times larger than FDA's model predicts. Other studies have shown similarly large and widespread adverse effects.

When a model's results are so radically inconsistent with empirical data from multiple studies, it almost always means the model's results are wrong. FDA does not appear to have seriously considered that possibility.

In Table V-5, FDA presents the results of its model's mercury effects converted to IQ points. The results show an adverse effect of 1.4 IQ points at the 99.9th percentile. These results are subject to the same comments applied above to the projected effects on age of talking, i.e., the model is biased to overlook larger effects, and the epidemiological data as a whole suggest that substantially larger effects occur in much larger fractions of the population than 0.1 percent. The IQ results are affected by the additional uncertainties attendant on converting the original metrics to IQ points.

In Table V-6, FDA summarizes the results of Axelrad et al.'s and Cohen et al.'s similar analyses of effects of methylmercury on IQ. Those analyses suggest an effect of the loss of 0.87 IQ point at the 99.9th percentile, slightly smaller than but in the same ballpark as the FDA's model results. While this similarity is somewhat reassuring, we nevertheless believe the FDA model has substantially underestimated exposure and the distribution of exposures in multiple ways that have inevitably reduced the projected effects of mercury on IQ.

Table V-7 shows FDA's model results for the beneficial effects of fish consumption on cognitive development. This Table does not indicate percentiles for fish intake, but they appear to extend to the 99.9th percentile. At that level, the model estimates a gain of 3.9 IQ points. I.e., the model projects a benefit from 99.9th percentile fish intake about three times as large as the adverse effect of 99.9th percentile methylmercury exposure.

As we have explained above, we do not consider these results credible, both because of data reliability issues in the single study FDA used for its benefits dose-response function and because FDA's estimate far larger than Cohen et al.'s 2005 analysis estimated for the same relationship.

The next section of FDA's presentation of its model results addresses the "net effects" calculated by combining the benefits estimates and the mercury estimates. Because we do not consider the benefits estimates used in these comparisons scientifically valid, we do not accept the "net effects" results as credible, either. This leaves aside our deep concerns about the lack of scientific soundness of the "net effects" concept to begin with, stated at many other points in these comments.

On page 95, FDA presents an interesting discussion of issues involved in comparing the beneficial effects of fish consumption with the adverse effects of methylmercury. Their first Table of "net effects" results assumes that everyone eats fish with average mercury content, all the time. Since this assumption is completely at odds with reality, the results shown in Table V-8 are simply not credible. But for its later scenarios involving changes in fish-consumption behavior, FDA ran the model using its estimates of consumption of different types of fish with different mercury levels.

In discussing this "baseline" analysis and the subsequent scenarios branching off from it, FDA acknowledges that, when the model considers different mercury levels in different types of fish, benefits cannot be directly compared with adverse effects. Specifically, they say, "Because…fish vary substantially in the amount of methylmercury they contain, we could not equate any particular level of exposure to methylmercury to a corresponding amount of fish per day, or vice versa." Translation: FDA recognized that its expressions of effects of mercury "per serving of fish," elsewhere in the report, are scientifically not defensible. But they included them in the report anyway.

FDA's solution to the problem at this point was to express results in these tables in terms of the percent of the population likely to experience an effect of a particular magnitude, without associating it with a particular percentile of exposure. This approach (which is not explained very clearly) makes the results at this point somewhat less transparent, but that is the least of the problems with them.

The next section of FDA's report presents the results of its "What If" scenarios. The same basic criticism made above applies to all those scenarios: I.e., comparisons in which one of the estimates (benefits) is scientifically unsound are also scientifically unsound. Also, please see our earlier discussion of serious biases and flaws in the "What If" scenarios, on pages 64-66 of this appendix. We need not repeat those points here.

The remainder of FDA's results presentation describes the model's outcomes for the cardiovascular benefits of fish consumption. We have elected not to comment on these aspects of the model.

This concludes our comments on the body of the FDA report.

Appendix A: Technical Description of Methodology

The Appendix to FDA's report goes over essentially the same ground covered in the main body of the report. We will not repeat our comments on issues that we have already gone into at length. However, there a few issues arise anew here in the Appendix, on which we now focus our attention.

Appendix A includes two very interesting and useful tables, Tables AA-2 and AA-3, which present FDA's database on mercury levels and combine that with data on market shares for 51 different categories of fish and shellfish, from NMFS reports.

As we have explained in our main Comments, we used the data in Table AA-3 for our own Tables 1 and 2, which show the relative mercury contributions of those 51 types of fish and shellfish to the total amount of mercury in the US seafood supply, and then sort the 51 varieties into six categories, by increasing mercury content.

We had previously done a very similar analysis, using an earlier iteration of FDA's data on mercury levels in different fish, and annual seafood supply data for 2006 from NMFS.

In re-doing the analysis for these comments, we noted a few discrepancies that we would like to call to FDA's attention.

FDA states in Appendix A that the 51 categories of fish and shellfish listed in their (and our) tables represent about 99 percent of the US seafood market. (Actually, we added up the percentages in Table AA-3 and the total is 98.4 percent, which is still an impressive number.) Many of the 51 categories lump together several species or even several types of fish, so the tables include far more than 51 actual varieties.

When we did our earlier analysis, we were unable to include a several fish and shellfish varieties that appeared in the NMFS supply data, but not in the FDA mercury database. There were also a few items in the FDA database for which the nomenclature used by FDA did not precisely match the categories in the NMFS data. We appreciate that FDA has made an effort to resolve these nomenclature problems for their current analysis, and increased the congruence of the data sets.

However, we are still concerned about a few discrepancies between the NMFS data we relied on for our previous analysis and the data in FDA's tables. NMFS data showed that pollock accounted for 36 percent of the total US catch for 2006. FDA shows pollock as having a market share of 7.52 percent. Granting that the US catch data do not account for imports (such as canned tuna) with substantial market share, we still cannot resolve this large difference. Perhaps much of the pollock harvest is used for non-food purposes, such as animal feeds? We hope FDA can clarify this issue.

The 2006 NMFS report also shows that the amounts of swordfish caught in 2005 and 2006 were around 3,000 metric tons per year, or about 0.05 percent of the market. FDA shows swordfish accounting for 0.44 percent of the market, almost an order of magnitude more than our NMFS data suggested. We considered the possibility of a decimal point error in FDA's data for swordfish. If FDA's number is correct, this high-mercury fish is consumed much more widely and in larger amounts than we previously believed, and we may need to reassess the urgency of risk communication for swordfish eaters.

On page 147, in Appendix A, FDA discusses the first study by Jedrychowski et al. (2006), which they mistakenly cite as having been published in 2005. It is discussed in the context of comparing various outcome measures used to assess verbal development in recent epidemiological studies. Why this discussion did not appear earlier in the report, where the Oken et al. studies were discussed, is unclear. Much like its discussion of the Oken et al. study in the earlier section, the discussion of the Polish study is characterized here by misrepresentation of the study and scientifically invalid interpretations of its data.

FDA describes the Krakow study as "small." Size is relative. The Krakow study had three times as many subjects as the Iraq study that FDA used to derive its dose-response curve for mercury's effects. FDA states that the range of mercury exposures in this study was "lower than either the Seychelles or the Faeroe Islands." [sic] It certainly was that, but a much more relevant comparison would have noted that the Polish women's exposure was

far lower than that of American women; in fact, the geometric mean blood mercury level in the Krakow women was 0.55 μg/l, compared to 0.91 μg/l in the NHANES survey.

FDA does not say here what the results of the Polish study showed—large developmental deficits associated with methylmercury exposure (see our Table 4.) They do state that they obtained the data on individual subjects from the authors of the Polish study and did their own analysis of mercury's effects on the BSID-II scores. Their comments suggest that the effect was minor. To present their own analysis without mentioning the original author's findings at all is deceptive, to say the least. Although FDA had these data, and they measure an outcome on a widely used standardized developmental test that includes verbal development components, FDA clearly elected not to try to incorporate these data into their model's dose-response function.

Yet again, FDA's description of an important epidemiological study reveals either a deep lack of understanding of what such evidence means, a desire not to confront implications of recent research that they may find troubling, or perhaps both.

Pages 154-162 describe the Daniels et al. 2004 study and how FDA used its data in more detail than prior sections of the report had done. However, in this iteration, as in all the previous ones, FDA takes an uncritical approach to the study and its data, passing up yet another opportunity to recognize or express concern about methodological issues we have raised several times in this Appendix, problems that in our judgment call into question at least the quantitative reliability of the reported beneficial effects.

This extended discussion of the only study that FDA relied on for half of its "net effects" model on cognitive effects never compares the results of study with the results of other studies, and raises no concerns whatsoever about the reliability of these epidemiological data. On one hand, this is a very technical, scientific-sounding description of a complex data transformation; on the other hand, it is a revealing description of FDA's thoroughly uncritical attitude about the study.

The same phenomenon, on the same study, repeats itself again in Appendix D. FDA's only focus appears to have been how they could use the data in their model; whether the data were any good to begin with was apparently not something that concerned them.

In Appendix D, FDA describes an analysis they did with the original data from the Daniels et al. study, in which they transformed the study authors' data on mercury in umbilical cord tissue samples into maternal hair mercury estimates. This analysis is subject to the same flaws discussed earlier for FDA's algorithms for converting dietary mercury intake to hair mercury: Average point values are used to represent data that actually are distributed over a fairly wide range, which biases the analysis by forcing it to see only on average individuals, omitting information about individuals with higher than average (or much higher than average) values on each parameter.

In this case, however, there are four parameters involved, and thus three arbitrary average ratios in the formula, instead of two. The ratios describe relationships between mercury in

cord tissue and cord blood; cord blood and maternal blood; maternal blood and maternal hair. FDA chooses its point value average for each ratio based on a single study. For the cord blood/maternal blood ratio, for example, they choose a value of 1.7. While most experts would accept that as a reasonable average value for the dozen or so studies on the subject, individual studies have reported values ranging from close to 1 to greater than 2, and of course the data in each study also are distributed around the means. Choosing one average value from within that collective range is indeed arbitrary.

These choices had no effect on the model; the purpose of FDA's number-crunching in this Appendix was to estimate the mercury exposure of the UK mothers and children, for comparison with the US NHANES data. (Exposure may have been slightly lower in the UK, if one can get past the FDA's analytical choices.)

While it had no impact on the overall analysis, Appendix D offers another window into the mind-set of the FDA modelers, their overweening interest in how data can be used in the model, and the scant attention paid to the consequences of arbitrary assumptions and data conversions in terms of the accuracy and meaningfulness of their results.

We elected not to comment on Appendices B and C, or on the FDA's literature review on beneficial effects of fish consumption, because of limited time and expertise, and a need to set priorities. We also have not yet read the comments of the peer reviewers, or FDA's response to them; we wished to form our impressions of this report, without absorbing the judgments of others. Once we have submitted these Comments, we will review the Peer Review section with interest, to see whether other reviewers noted the problems we found, and if so, what FDA's response was.

This concludes our comments.