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**REPORT OF QUANTITATIVE RISK AND BENEFIT  
ASSESSMENT OF CONSUMPTION OF  
COMMERCIAL FISH, FOCUSING ON FETAL  
NEURODEVELOPMENTAL EFFECTS  
(MEASURED BY VERBAL DEVELOPMENT IN  
CHILDREN) AND ON CORONARY HEART  
DISEASE AND STROKE**

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## **EXECUTIVE SUMMARY**

Fish provides protein, is low in saturated fat, and is rich in many micronutrients; it also can be a source of certain omega-3 fatty acids. As the Institute of Medicine of the National Academies of Science (IOM) noted in a recent report, “[i]n the past several years, research has implicated seafood, particularly its contribution of EPA and DHA [two omega-3 fatty acids], in various health benefits identified for the developing fetus and infants, and also for adults, including those at risk for cardiovascular disease” (IOM 2006 at 1). However, as a result of natural processes and human activity, aquatic food sources, including fish, can contain methylmercury, which has been linked to adverse health consequences. Because of the presence of methylmercury in fish, FDA and the United States Environmental Protection Agency (EPA) issued an advisory to consumers, “What You Need to Know About Mercury in Fish and Shellfish” (<http://www.cfsan.fda.gov/~dms/admehg3.html>). The advisory, which was most recently revised in 2004, recommends that women who may become pregnant, pregnant women, nursing mothers, and young children avoid some types of fish and eat fish and shellfish that are lower in methylmercury, as specified in more detail in the advisory.

Researchers in the United States and elsewhere have attempted in recent years to develop approaches to better evaluate the net health impacts of fish consumption; in other words, to understand the relationship between the risk of not eating fish and the risk of eating fish that contains methylmercury at the levels currently found in the commercial fish available to consumers. As the IOM noted in its 2006 report, “A better way is needed to characterize the risks combined with the benefits analysis.” (IOM 2006 at 6). The draft summary of published research and benefit and risk assessment report were developed by FDA to provide further scientific information to help address this question for consumers of commercial seafood in the United States (i.e., fish shipped or sold interstate, as opposed to fish caught recreationally or for subsistence).

The risk and benefit assessment described in the risk benefit assessment report reflects an effort by FDA to quantify the impact of eating commercial fish on three human health endpoints: (1) neurodevelopment, as measured by verbal development, to assess effect from prenatal exposure to methylmercury as passed from the mother to the developing fetus; (2) risk of fatal coronary heart disease; and (3) risk of fatal stroke. Each of these health endpoints has been associated in the scientific literature both with adverse effects of methylmercury exposure (including through fish consumption) and beneficial effects of regular fish consumption. The risk and benefit assessment provides further scientific information about the likelihood and magnitude of both a beneficial net effect and an adverse net effect at current levels of commercial fish consumption and exposure to methylmercury through fish consumption in the United States. The risk and benefit assessment should not be construed as altering the existing fish advisory. Moreover, because this assessment does not distinguish among types of fish in terms of their

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beneficial constituents, it is not possible to translate the results of this analysis into fish-specific advice to consumers about maximizing benefits.

The methodology used for this quantitative assessment is novel for FDA in that, rather than attempting to quantify the risk resulting from the presence of a particular hazard in a food, it seeks to balance that risk and the benefit from consumption of the food in the same quantitative analysis. For fetal neurodevelopment, the assessment estimates this net effect by separately estimating: (1) the likelihood and size of an adverse contribution from methylmercury to the net effect; (2) the likelihood and size of a beneficial contribution to the net effect from fish; and (3) the likelihood, size, and direction of the net effect. For the methylmercury contribution, the assessment uses data on the association between methylmercury and early age verbal skills (as an indicator of neurodevelopment) and then compares the results against results developed elsewhere on methylmercury's effect on other aspects of neurodevelopment, including IQ. For the fish contribution, the assessment uses data on the association between fish consumption during pregnancy and early age verbal skills. For the net effect, the assessment combines the results from the methylmercury and fish contributions. This assessment builds on published work performed previously by FDA scientists on the estimation of a methylmercury effect as well as on recent articles by other investigators that quantitatively assessed this effect.

For fatal coronary heart disease and stroke, the assessment estimates the net effect on risk from fish consumption without separately modeling a methylmercury contribution and a fish contribution. Most data on this subject come from studies that measured an association between fish consumption and these health endpoints without measuring a methylmercury contribution. The modeling builds in part on dose-response functions for these endpoints that have been published in the scientific literature.

The risk and benefit assessment identifies and discusses assumptions made for the scientific models and analyses and sources of uncertainty with respect to each endpoint analyzed. Subject to the limitations and assumptions set forth in the analysis, the assessment estimated the net impact of consumption of different amounts of fish. The results indicate that consumption of fish species that are low in methylmercury has a significantly greater probability of resulting in a net benefit, as measured by verbal development. The highest net benefit modeled in our risk and benefit analysis was modest. When we modeled actual baseline consumption for the range of methylmercury concentrations (low to high) the assessment indicated a significant probability of a net adverse effect for one-tenth of one percent of children for the central estimate. The highest estimated net adverse effect was also modest.

For fatal coronary heart disease and stroke, commercial fish baseline consumption is averting a central estimate of over 30,000 deaths per year from coronary heart disease and over 20,000 deaths per year from stroke.

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The results of our quantitative risk and benefit assessment are generally consistent with research reported in recent years in the scientific literature.

A second document that is being made available along with this report is entitled “Summary of Published Research on the Beneficial Effects of Fish Consumption and Omega-3 Fatty Acids for Certain Neurodevelopmental and Cardiovascular Endpoints.” This summary of published research primarily identifies secondary analyses of the large body of scientific research on the impact of fish and omega-3 fatty acids on cardiovascular and neurologic endpoints, including research on both prenatal and post-natal exposures. In addition to the IOM report, these secondary analyses include reports by the American Heart Association, the European Food Safety Authority, the International Society for the Study of Fatty Acids and Lipids, the World Health Organization and a previous investigation by the FDA. This compendium of research was developed by FDA for use in developing its quantitative risk benefit assessment.

The summary of published research provides background for the risk benefit assessment report. It identifies and delineates the lines of scientific evidence that indicate the association of fish and omega-3 fatty acid consumption with cardiovascular and neurodevelopmental health outcomes. When available, the compendium of research also identifies reports of quantitative dose-response relationships which may be relevant for risk and benefit assessment modeling. The summary of research describes the context of the overall body of scientific evidence currently available for potential application to the risk and benefit assessment modeling and the risk benefit assessment report.

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## **SECTION I: THE PURPOSE OF RISK AND BENEFIT ASSESSMENT FOR METHYLMERCURY**

### **(a) Purpose of this Project**

The benefits and risks of fish that are commercially distributed for human consumption have both been the subject of much scientific research. On the one hand, fish provide a source of easily digestible protein of high biological value, micronutrients including vitamins A and D, minerals such as iodine and selenium, and high levels of the amino acids taurine, arginine and glutamine (EFSA 2005; He and Daviglus 2005). Additionally, many fish provide a uniquely rich food source of long chain omega-3 fatty acids (also called n-3) long-chain polyunsaturated fatty acids (n-3 LC PUFA), most notably docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). There is a large and growing body of research on the extent to which fish, and nutritional components of fish such as omega-3 fatty acids, convey health benefits, especially protection against heart disease and promotion of nervous system development. Specifically, a number of research studies have reported associations between consumption of fish, fish oil, or n-3 LC PUFA and reduced risk of cardiovascular events such as heart attack and stroke (Kris-Etherton et al., 2002). Moreover, the n-3 LC PUFA, docosahexaenoic acid, has been shown to be essential for development of the central nervous system (EFSA 2005) (page 30). Consequently, there is considerable interest in whether there is an association between fetal, infant or child neurodevelopment and maternal intake of fish or n-3 LC PUFA during pregnancy and lactation (SACN, 2004).

On the other hand there are safety concerns associated with the consumption of fish. The safety issue most frequently raised is that of methylmercury, a neurotoxin, since it is generally present in all fish, at least in trace amounts.

The National Academy of Science's Institute of Medicine (IOM) recently reviewed the science on human risks and benefits associated with of consuming commercially available fish. In October 2006, the IOM published its findings in a report titled, "Seafood Choices: Balancing Benefits and Risks" (IOM 2006). The report states that:

- "New tools apart from traditional safety assessments should be developed, such as consumer-based benefit-risk analyses. A better way is needed to characterize the risks combined with the benefits analysis."
- "Consolidated advice is needed that brings together different benefit and risk considerations, and is tailored to individual circumstances, to better inform

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consumer choices. Effort should be made to improve coordination of federal guidance with that provided through partnerships at the state and local level.”

This report reflects an effort by the U.S. Food and Drug Administration (FDA) to improve its understanding of the consequences of eating commercial fish for some health endpoints for which methylmercury is a potential risk factor. The current analysis takes the IOM recommendations into account by attempting to quantify the risk-benefit relationship for selected health endpoints. This type of analysis could lead to the development of better tools to inform decision-making about commercial fish consumption, e.g., to allow for the maximization of benefits consistent with the minimization of risk. A risk/benefit approach can provide a holistic view of the overall consequences of any risk management strategy.

The need to take health benefits from fish into account along with the risks that methylmercury and other hazards may pose has been recognized by other health organizations. For example, the Codex Alimentarius Commission (Codex 2006) has asked the Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization to convene an Expert Consultation to:

- “Develop a methodology and identify the data necessary for carrying out quantitative risk assessments of risks and benefits related to fish and other seafood consumption;” and
- ”Compare nutritional benefits against the possibility of adverse effects, including the uncertainties, taking into consideration all groups in the population, and, if possible, allowing quantitative comparisons of human health risks and benefits of fish and other seafood consumption.”

This FDA report presents a quantitative risk and benefit assessment of the effect of eating commercial fish on verbal development in young children as an indicator of fetal neurodevelopment, and on coronary heart disease and stroke in the general population. We refer to it as a risk and benefit assessment because it attempts to estimate the net effect of eating commercial fish on these selected health endpoints. A net effect can include an adverse contribution from the methylmercury in the fish and a beneficial contribution from the nutrients in the fish. The net effect could be adverse, or it could be neutral or even beneficial, depending on the circumstances. It is quantitative because it attempts to estimate the size and nature of the net effect through the range of exposures to methylmercury that U.S. consumers are experiencing through the consumption of commercial fish.

Verbal development is one of many aspects of neurodevelopment. We used verbal development in young children as an indicator of neurodevelopment because we had data on it sufficient to develop dose-response functions for both an adverse contribution of methylmercury to the net effect and a beneficial contribution of fish to the net effect. It is not necessarily the aspect of neurodevelopment that is most sensitive to methylmercury,

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however. In order to determine whether it is sufficiently representative in terms of its sensitivity to methylmercury, we performed a comparative analysis by matching the results against dose-response functions developed for the effect of methylmercury on IQ (Axelrad et al., 2007) and on a wide range of neurodevelopmental tests (Cohen et al., 2006b).

This assessment has several limitations. Because this assessment does not distinguish among types or species of fish in terms of their beneficial constituents, it is not possible to directly translate the results of this analysis into fish-specific advice to consumers about what types or species of fish to eat to maximize net health benefits. In addition, this assessment does not take a comprehensive look at all neurodevelopmental or cardiovascular endpoints. Furthermore, judgments about the clinical significance of the estimates themselves are beyond the scope of this report. Risk management decisions are not addressed in this report. Finally, the assessment is not intended to make a case one way or another for the adequacy of any proposed or existing “health claim” on labeling for any product. “Health claims” are evaluated under standards of evidence that have been developed specifically for that purpose.<sup>1</sup>

This assessment is intended to be nationally representative of the U.S. population. It does not address risk to segments of the population whose exposure to methylmercury or patterns of fish consumption may be substantially different from the population as a whole as a result, for example, of their own subsistence or sport fishing in localized bodies of water that might be subject to unusual conditions. Separate assessments would be needed to predict effects in such sub-populations. Because these kinds of situations would tend to not generally involve interstate commerce, they would not normally fall within FDA’s regulatory purview under the Federal Food, Drug, and Cosmetic Act..

There is a companion document to this report that inventories the research on the benefits of fish consumption relating to neurodevelopment and coronary heart disease and stroke. Much of the research has been on omega-3 fatty acids. The main purpose of the companion document is to explore potential biological explanations for the beneficial effects from fish that are being reported in the research studies. The companion document is entitled “Summary of Published Research on the Beneficial Effects of Fish Consumption and Omega-3 Fatty Acids for Certain Neurodevelopmental and Cardiovascular Endpoints.”

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<sup>1</sup> See section 403(r)(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 343(r)(3), 21 CFR 101.14(c), and FDA’s draft guidance entitled “Evidence-Based Review System for the Scientific Evaluation of Health Claims (FDA 2007).

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## **SECTION II: EXPOSURE TO METHYLMERCURY IN THE UNITED STATES**

This section discusses methylmercury and reviews sources of data on exposure within the U.S. population, primarily as a result of eating commercial fish, and compares U.S. exposures against exposures elsewhere.

### **(a) What Are Mercury and Methylmercury?**

Mercury occurs in three basic forms: metallic, or elemental mercury, inorganic mercury, and organic mercury. Each form can be toxic to humans when exposure is high enough, although they behave differently in terms of absorption into the body and the degree to which they migrate to body organs. Although it has been postulated that these different forms may interact at a cellular level, there is no scientific evidence to support this hypothesis and the available evidence (e.g., toxicokinetic differences and dissimilar clinical presentation) argues against such an interaction taking place at the relevant target organs (e.g., central nervous system) and levels of exposure. Because our focus is on estimating the impact to certain health endpoints of the consumption of commercial fish, the risk and benefit analysis focuses only on methylmercury.

Elemental mercury occurs naturally, mostly in the form of ores. It enters the environment as a result of volcanic activity and erosion from wind and water. Mercury is also emitted into the environment through human activity, mostly from the burning of fossil fuels, mining, smelting, and solid waste incineration.

Metallic, or elemental mercury, is also the form that is found in mercury thermometers and formerly in dental amalgams. Inorganic mercury compounds are used in small amounts in some antibacterial products.

Methylmercury is the most common organic form of mercury. It is converted in the environment from inorganic mercury through natural, biological processes, e.g., the activity of bacteria, phytoplankton and fungi. Methylmercury can enter the food chain by accumulating in fish and marine mammals.<sup>2</sup> Longer-lived predator fish tend to have

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<sup>2</sup> Traditional methods for measuring methylmercury concentrations in fish involve measuring the concentrations of total mercury and inorganic mercury. The difference between the two represents the concentration of methylmercury. Recent studies by FDA determined that methylmercury constitutes between 93-98 percent of total mercury in finfish and 38-48 percent in molluscan shellfish (Hight and Cheng, 2006). Molluscan shellfish, e.g., clams and oysters, have such small amounts of total mercury in

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more mercury in them than other fish because they spend their lives eating fish that also contain methylmercury and it is stored in tissue.

Methylmercury is easily absorbed from the gastrointestinal tract and readily enters the brain, including the brain of the developing fetus. It is excreted from the human body. The average half life has been measured at about 50 days with a range of 42-70 days (Sherlock et al., 1984).

## **(b) Exposure to Methylmercury**

The connection between fish consumption and exposure to methylmercury in the United States is well established<sup>3</sup> (CDC 2004; Hightower, et al., 2003). Levels in the body can be inferred from how much fish people eat and how much methylmercury is typically in these fish, but they also can be measured more directly from the amount of mercury in hair or blood.

The data on exposure presented in this section derive from a national survey of hair and blood levels in the U.S. conducted by the Centers for Disease Control and Prevention (CDC) and from FDA's surveillance database on concentrations of mercury in commercial fish in the United States. We also conducted exposure modeling for purposes of risk and benefit assessment, as described in Section IV and in Appendix A. Among other things, exposure modeling enables us to estimate what exposures would be in various hypothetical scenarios. It enables us to predict, for example, how exposures to methylmercury could change as a result of changes in fish consumption.

## **(c) Methylmercury Exposure as Revealed by the National Health and Nutrition Examination Survey of Blood and Hair Levels**

In 1999 CDC expanded its National Health and Nutrition Examination Survey (NHANES) to measure exposure to methylmercury in U.S. women of childbearing age and children aged one through five. NHANES is a continuous survey of the health and nutritional status of the U.S. population that collects data from individual participants through interviews and physical examinations and publishes collective results every two years.

Studies that have looked for an association between prenatal exposure to methylmercury and the results of neurodevelopmental tests in children have used mercury levels in

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them per FDA's monitoring program that the split between total mercury and methylmercury in those species has no public health significance.

<sup>3</sup> It is possible, however, that people can take in small but measurable amounts of methylmercury from other sources. For example, a study in Sweden among people who reported no fish consumption showed small concentrations of methylmercury in their blood that the authors attributed to eating chickens and pigs etc. that had been fed fish meal (Lindberg et al., 2004). The levels from sources other than fish in Sweden were too low to provide a meaningful contribution to overall exposure.

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pregnant women (e.g., concentrations of mercury in hair and blood) as a surrogate for fetal exposure. Consequently, data on mercury levels in women of childbearing age are relevant to an understanding of risk to the fetus. To date, CDC has released six years worth of data, from 1999 through 2004<sup>4</sup> (CDC 2003; CDC 2004; CDC 2005). Women of childbearing age and children through five years of age are included in all six years. The 2003-2004 data also include males ages 16 and above, and older women (CDC 2005).

NHANES takes advantage of the fact that it is possible to calculate the concentration of methylmercury in a person's body from the concentration of total mercury in blood and/or scalp hair so long as the individual has not been significantly exposed to forms of mercury other than methylmercury, i.e., inorganic and elemental. Variations in concentration along a hair strand can reveal differences in the person's exposure over weeks and possibly months, depending on the length of the hair. Hair cannot provide information, however, about exposure at the moment the sample was taken because of the time it takes for methylmercury to concentrate in hair. Conversely, concentrations in blood cannot reveal variations over time, but can provide information about recent exposure (McDowell, et al., 2004). Both blood and hair levels were measured during the first two years of mercury testing under NHANES; only blood levels have been measured thereafter.<sup>5</sup>

NHANES blood levels for all population groups surveyed are provided in Table II-1.

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<sup>4</sup> For purposes of statistical reliability, CDC has not published data, e.g., mean hair or blood concentrations, for those in the survey who exceed the 95<sup>th</sup> percentile of exposure because the number of such individuals is relatively small (Schober, et al., 2003, see p. 1670). However, the data on these individuals are available on the website for CDC's National Center for Health Statistics and we use them in this report.

<sup>5</sup> On the NCTR website, NHANES exposure data are available as both hair levels for 1999-2000 and blood levels for 1999-2004. The blood levels are divided into total mercury, which includes organic mercury (i.e., methylmercury) and inorganic mercury. Methylmercury levels can be calculated by subtracting the inorganic mercury from the total mercury. The remaining organic mercury is overwhelmingly methylmercury. (Another form for organic mercury to which adults can be exposed, ethylmercury from thimerosal preservative in some influenza vaccines, ophthalmic and otic drug products involves exposures that are extremely small, occur once-per-year at most, and are relatively short in duration since ethylmercury leaves the body more quickly than methylmercury.) Consequently, we regard the levels of organic mercury in blood to be the relevant data from NHANES for purposes of this report. We note that CDC's discussion of NHANES data in its Morbidity and Mortality Weekly Report (CDC 2004a) describes the total mercury results but not the organic mercury results.

For the 1999-2000 data, it is also possible to compare the NHANES hair data to the methylmercury blood data since NHANES obtained both types of data from each participant in the survey during those years. In the overwhelming majority of cases, blood levels exceed hair levels by an average of around five to one. At the high end of exposures, however, we see some hair levels that substantially exceed blood levels. The most striking case involves a woman with a mercury hair level of 849 ppm. Such a level would be high relative to the extreme poisoning events that occurred in Japan and Iraq in the last century. By contrast, her methylmercury blood level was relatively normal, although higher than average for the United States. A possible explanation for a hair level this high would be environmental contamination with inorganic mercury.

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**Table II-1: Population percentiles from NHANES 1999-2004**

<b>Percentile</b>	<b>Children 2-5</b>	<b>Men 16-45</b>	<b>Men 46+</b>	<b>Women 16-45</b>	<b>Women 46+</b>
<b>Mean</b>	1.10	1.01	1.14	1.32	1.32
<b>1<sup>st</sup></b>	0.1	0.14	0.14	0.2	0.14
<b>25<sup>th</sup></b>	0.3	0.3	0.3	0.4	0.3
<b>50<sup>th</sup></b>	0.6	0.6	0.6	0.8	0.7
<b>75<sup>th</sup></b>	1.2	1.2	1.3	1.6	1.5
<b>90<sup>th</sup></b>	2.4	2.2	2.8	3.4	2.9
<b>95<sup>th</sup></b>	4.1	3.4	4.2	5.5	4.5
<b>99<sup>th</sup></b>	8.8	7.2	7.8	12.0	9.5
<b>99.5<sup>th</sup></b>	12.8	8.5	10.3	14.0	12.6
<b>99.9<sup>th</sup></b>	15.1	13.7	11.1	22.7	24.6

**All values are in blood (ppb or µg/L). The values have been corrected for inorganic mercury content, meaning that inorganic mercury has been subtracted from total blood mercury in order to show the level of organic mercury in the blood.**

Presumably, exposure data from NHANES mostly reflects long term, or “steady state” exposure from fish consumption over time. NHANES is not designed to obtain information on relatively short term peaks in blood levels although it could sometimes include the results from such exposures. .

Because NHANES is designed to provide a nationally representative picture of exposure in the United States (CDC 2004a), it does not lend itself to regional analysis, i.e., it does not reveal whether there are regional exposures to methylmercury that are notably different from the national picture (McDowell, et al., 2004, see p. 1170; Schober, 2006). As a consequence, NHANES is likely to miss subgroups of high fish consumers such as sport and subsistence fishers (IOM 2006, page 124).

NHANES’ national focus would appear to reduce its utility in any assessment of risk for localized situations, or for exposures that largely involve recreational or subsistence consumption. However, the limitations do not significantly affect the utility of NHANES in a nationally representative assessment of risk relating primarily to commercial species. Modeling that FDA has performed to estimate methylmercury levels in U.S. consumers (Carrington and Bolger, 2002) closely track body levels as reported by NHANES. The exposure assessment described in this report builds on these models.

The NHANES data show that U.S. exposures to methylmercury tend to be low when compared against populations that eat a lot of fish. For example:

- On average, U.S. women of childbearing age are exposed to methylmercury at levels about 1/15<sup>th</sup> those of the women in the Seychelles Islands study and about 1/10<sup>th</sup> those of the women in the Faroe Islands study.

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- U.S. women of childbearing age are also exposed to methylmercury at levels that are: (a) about 1/8th of those in Japanese women on average, based on a survey of five districts in Japan (Yasutake et al., 2003); (b) at least 1/3<sup>rd</sup> of those in a study population of slightly more than 1,000 women of childbearing age in Hong Kong (Fok et al., 2006); and (c) about 1/9<sup>th</sup> those in 65 pregnant women in Taiwan who were participating in a study of the relationship between fish consumption and mercury levels (Hsu et al., 2007).
- U.S. children ages 1-5 are exposed to methylmercury at levels that are about 1/25<sup>th</sup> of those experienced by the children in the Faroe Islands study population (McDowell et al., 2004, page 1,169).

#### **(d) Methylmercury Concentrations in Fish Sold Commercially**

FDA and others have been analyzing commercial fish species in the United States for years for concentrations of methylmercury (measured as total mercury) in their tissues. The results can be found on the FDA web site at <http://www.cfsan.fda.gov/~frf/sea-mehg.html>. The findings are generally consistent with databases maintained in other countries for the same species (CCFAC 2006; Health Canada 2007; Montwill 2007).

For each listed species and product type (e.g., canned light tuna), the database includes the average mercury concentration in that species or product type, the median concentration, the minimum and maximum concentrations that have been found in individual samples, and the number of samples upon which the above values are based. The primary utility of the database is that it can be used to estimate how much fish of various species a person would have to eat on a regular basis in order to reach a certain concentration of methylmercury in his or her body. In the risk and benefit assessment described in this report we used the concentrations in the database to estimate how exposures to methylmercury would change if people ate more or less fish or if they changed the types of fish they ate. Previously, data on the concentrations of methylmercury in commercial species were used to estimate what methylmercury exposures would be if the FDA/EPA consumption advisory for methylmercury were followed by consumers.

##### Highlights from the Database:

- The range: The methylmercury concentrations in the FDA database include some fish for which the value has been nondetectable based on current methods of analysis. For the fish for which methylmercury has been detectable (most of them), the lowest average methylmercury concentrations are between 0.01 and 0.02 ppm. Those with the highest average concentrations have averages that are just under 1.0 ppm, although the highest average concentration is 1.4 ppm for tilefish from the Gulf of Mexico.

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- The average concentration for all commercial fish: An “average” commercial fish in the U.S. marketplace, weighted for consumption, contains 0.086 ppm methylmercury. “Weighted for consumption” means that the more popular a species is, the more “weight” it is given when calculating the average methylmercury concentration for all commercial fish. Most commercial fish are at the low end of the range, as described above.
- Methylmercury in the “top 10” fish: On a per-species basis, the average amount of methylmercury in the top 10 most consumed commercial species in the United States ranges from nondetectable to 0.2 ppm, with the exception of albacore canned tuna, which averages 0.35 ppm. The top 10 species comprise approximately 73 percent of commercial fish consumed in the United States (Montwill 2008).
- Canned tuna: One of the most highly consumed commercial fish products, canned tuna in the aggregate contains on average 0.17 ppm. As stated above, the average for canned albacore “white” or “solid” tuna is 0.35 ppm. Albacore accounts for about one-third of canned tuna (Montwill 2008).
  - NOTE: fresh or frozen tuna fillets/steaks average about 0.35 ppm, but are below the top 20 commercial species in terms of consumption. The top 20 represent about 90 percent of all commercial fish consumed in the United States (Montwill 2008; see also Table AA-3 in Appendix A).
- Mid-range species: There are not many species that can be considered “mid-range,” i.e., with averages above 0.2 ppm. With the exception of albacore canned tuna, all of them are outside the top 10 consumed commercial species. In addition to fresh or frozen tuna steaks/fillets (average of 0.35 ppm) and albacore as a subset of canned tuna, those commercial species occupying the mid-range between the lowest and highest average between 0.4 – 0.6 ppm (i.e., grouper, red snapper, moonfish, orange roughy, saltwater bass, freshwater trout) and each of them ranks below the top 20 in terms of U.S. consumption.
- High-end species: Long-lived predatory fish tend to accumulate the most methylmercury. Shark and swordfish, which average around 1.0 ppm, are outside the top 20 in terms of U.S. consumption. King mackerel (average of 0.73 ppm) and tilefish from the Gulf of Mexico (average of 1.45 ppm),<sup>6</sup> are also outside of the top 20 in terms of consumption. Collectively, these four species account for six-tenths of one percent of U.S. consumption (Montwill 2008).
- Variability of concentrations within species and product types: As a result of normal variation there is considerable overlap in mercury concentrations among species and

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<sup>6</sup> By contrast, the tilefish samples from the Atlantic in our database average 0.14 ppm.

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product types. For example, canned light tuna has an average concentration that is one-third the average concentration for canned albacore tuna, but the low-to-high range in our database for canned light tuna is nearly identical to that for canned albacore tuna (nondetectable to 0.852 ppm for light; nondetectable to 0.853 ppm for albacore). Consequently, some cans of albacore contain less mercury than some cans of light and some cans of light contain more mercury than some cans of albacore.

### **(e) Are Concentrations of Methylmercury Increasing in Commercial Fish?**

Most commercial fish species sold in the United States are harvested from the open ocean or from aquaculture sites. Aquacultured fish tend to be raised and harvested quickly without much opportunity to accumulate methylmercury. Moreover, aquacultured fish are not usually the large predatory types of fish that accumulate methylmercury over time by eating other fish containing methylmercury.

It has been estimated that human activity contributes over half of the total amount of mercury that is entering the atmosphere annually (EPA 1997). Increases in concentrations of methylmercury are more likely to occur in the vicinity of population sources, e.g., in bodies of water such as rivers downstream from certain types of mining operations, and in relatively small, enclosed bodies of water such as lakes (EPA 1997). Limited data suggest that methylmercury concentrations in commercial fish have not increased or decreased over time.

Studies of fish, including tuna and swordfish that were up to 90 years old (Miller et al., 1972; Barber et al., 1972) report levels consistent with today's levels. In both studies the researchers discounted the possibility that these findings could have been affected by the preservatives used to store the fish as well as other conditions of storage, although the researchers in one of the studies admitted that the possibility could not be "rigorously excluded" (Miller et al., 1972). In another study that focused on conditions of preservation, however, the researchers concluded that, depending on circumstances, preservation techniques could substantially alter heavy metal concentrations in museum specimens of fish (Gibbs et al., 1974). For this reason, comparisons of contemporary fish to museum specimens should not be regarded as definitive.

In a more recent timeframe, mercury concentrations in Yellowfin tuna caught off Hawaii in 1998 were found to be essentially identical to those caught in the same area in 1971 – a span of 27 years (Kraepiel et al., 2003). The researchers engaged in "mercury biogeochemistry" modeling for the equatorial and subtropical Pacific in an effort to explain why these fish showed no increase in methylmercury in spite of increases in global mercury emissions over the past century. The most likely explanation, they concluded, is that mercury is converted into methylmercury (the form of mercury in fish) in the deep ocean, with transfer to the upper layer of ocean taking a minimum of 400

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years. They noted that Yellowfin tuna and their prey swim in the upper layer. The researchers assumed that the total mercury concentration in the upper ocean layer had doubled between 1860 (the onset of the industrial revolution) and 1990. Nonetheless, that mercury would not convert to methylmercury or be absorbed by fish in the upper layer unless it first sank into the deep ocean and then circulated back over a long period of time.

Mercury concentrations in freshwater commercial species are low. In our database the average mercury concentration for commercial freshwater species is 0.08 ppm on a per species basis, and the highest average for any species is 0.14 ppm (FDA 2006). (Recall that the average for all commercial species, weighted for consumption, is 0.086 ppm.)

FDA's methylmercury database was reviewed for evidence of increases in concentrations over time. The database spans 30 years, starting around 1974. As described previously, for each species it includes the range of concentrations in the samples from highest to lowest and the mean concentration. For some species the database only includes recent sampling because interest in that species has been recent; for others the data span 20-25 years of sampling and for others the data span about 30 years. Overall, the database does not reveal a trend one way or the other, although the size of the database and the timeframes of collection are limited.

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## **SECTION III: SCIENTIFIC BASIS FOR RISK AND BENEFIT ASSESSMENT**

This section reviews results from research studies in humans<sup>7</sup> that are germane to evaluating the risks associated with methylmercury jointly with the benefits of commercial fish consumption<sup>8</sup>. The research studies reviewed here focus on health endpoints for which there are reports in the scientific literature of statistical associations *both* between methylmercury and adverse effects *and* between fish consumption and beneficial effects. These are:

- Neurodevelopmental effects in the fetus from the mother's consumption of food resulting in prenatal exposure to methylmercury and to nutrients in fish.
- Neurodevelopmental effects in children from their own consumption of food resulting in postnatal exposure to methylmercury and to nutrients in fish. The central nervous system continues to develop after birth so an important question is whether children are more sensitive than adults to a neurotoxin such as methylmercury.
- Fatal coronary heart disease and stroke in the general population as a result of eating fish. Methylmercury has been implicated as a potential risk factor for coronary heart disease and stroke in some studies in limited populations outside of the United States. Fish and some nutrients in fish have been widely studied for their potentially beneficial effect on these same endpoints.

This report does not review research regarding neurological effects in the general population from postnatal exposure to methylmercury or consumption of fish. For neurological effects the scope of this report is limited to potential consequences to the developing nervous system.

FDA does not conduct primary research in humans on either the toxicity of methylmercury or the benefits for health of eating fish. The Agency relies on studies that are published in the peer reviewed literature. With respect to toxicity, The National

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<sup>7</sup> For a review of the animal data on methylmercury we refer the reader to the Toxicological Profile on Mercury performed by the Agency for Toxic Substances and Disease Registry (ATSDR). This document contains the conclusion that "animal studies...provide irrefutable evidence that the central and peripheral nervous systems are target organs for organic mercury-induced toxicity" (ATSDR 1999, page 137). Animal data in support of an effect of methylmercury on cardiovascular effects is sparse (ATSDR 1999, see page 107).

<sup>8</sup> Section IV of this report identifies the studies that were used as the basis of the dose-response functions used in the risk/benefit analysis. These dose-response functions estimate the likelihood and magnitude of an effect at various "doses," or exposures to methylmercury, fish, or the combination of the two, i.e., the "net effect."

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Academies of Science’s “Toxicological Effects of Methylmercury,” published in 2000, offers a comprehensive evaluation of the scientific literature through that date (NRC 2000). Since then additional analyses of some of the same cohorts highlighted in the NAS review have been published, as have analyses of other cohorts. The goal of this Section is to provide the scientific basis for the risk and benefit assessment described later in this report as well as provide a context for interpreting the results of those analyses. Our review is not intended to serve as a substitute for reading the reports of the studies that have been published by the researchers or analyses of studies that have been published by others

Note that most of the studies discussed here have reported their findings in terms of total “mercury” (i.e., including molecular forms of that element that do not appear in fish in significant amounts, i.e., inorganic forms). Laboratory analyses for total mercury in hair and blood are easier and less costly to perform than analyses for methylmercury, the form of mercury that is primarily found in fish. For most studies it can be assumed that most of the total mercury found in hair has been methylmercury and that almost all the methylmercury has been from fish.

With respect to potential health benefits, there are a number of original (or primary) scientific studies on the health effects associated with consumption of fish or n-3 LC PUFA. The primary studies most relevant to the evaluation of the risks and benefits of fish consumption have been summarized and evaluated previously in a number of recent scientific reports and review articles (or secondary sources). Thus, the primary approach used to develop the benefits summary document accompanying this report (“Summary of Published Research on the Beneficial Effects of Fish Consumption and Omega-3 Fatty Acids for Certain Neurodevelopmental and Cardiovascular Endpoints”) was to inventory these secondary sources and to highlight any findings related to the health effects of fish consumption and of the n-3 LC PUFA found in fish on cardiovascular disease and neurodevelopment. Research has addressed the possible association of fish or of n-3 LC PUFA consumption with numerous other health outcomes, including neuropsychiatric disorders (including depression and psychotic disorders), cognitive decline and Alzheimer’s disease, neurodegenerative disorders, cancer risk reduction, and reduced risk of chronic degenerative diseases related to immune and auto-immune or musculo-skeletal function, acute macular degeneration and other visual impairments, although consideration of these outcomes is beyond the scope of this document. When available, the benefits summary document also identifies reports of quantitative dose-response relationships.

## **Section III-A: Studies on Neurological Endpoints**

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## **(a) Association between Fish Consumption and/or Omega-3 Fatty Acids and Neurodevelopmental Outcomes**

A detailed discussion of the association of maternal fish consumption with infants' and children's visual and cognitive indicators of neurodevelopment can be found in the accompanying document, entitled "Summary of Published Research on the Beneficial Effects of Fish Consumption and Omega-3 Fatty Acids for Certain Neurodevelopmental and Cardiovascular Endpoints." Below, we provide a brief summary.

**Observational studies:** In three cohort studies, children's visual function (Williams et al., 2001) and neurodevelopment (Daniels et al., 2004; Oken et al., 2005) were positively associated with mother's fish intake during pregnancy, with adjustment for covariates. The association with visual function is consistent with certain analyses of supplemented infant formula (Birch et al., 2005; Lauritzen et al., 2001; Morale et al., 2005; Uauy et al., 2003). Recent results estimated a positive, quantitative association between maternal fish consumption and children's developmental scores in Project Viva in the United States at three years of age (Oken et al., 2008a) and in the Avon Longitudinal Study of Parents and Children (ASPAC) cohort in the United Kingdom at eight years of age (Hibbeln et al., 2007a; Hibbeln et al., 2007b). The magnitude of the quantitative estimates from observational studies is considerably larger than estimates based on infant supplementation studies and a series of assumptions (Cohen et al., 2005a; Cohen et al., 2005c). The results of these studies within the context of the negative association with methylmercury is discussed in the next section.

A more detailed discussion of the studies that attempt to look at both fish consumption and methylmercury exposure is provided in the next section.

**Randomized trials of maternal supplementation in pregnancy and lactation:** Among the few available studies of maternal supplementation, women in the Helland et al. (2003) study were supplemented with fish or fish oil providing 1.2 grams of DHA per day during pregnancy and lactation and increased infant DHA blood levels were demonstrated biochemically (Eilander et al., 2007). Limitations included uncertain effect of the corn oil control supplement, the small subset of the population that received follow up IQ testing at age four years, and uncertain differences in background n-3 LC PUFA intake between Norwegian and U.S. women. However, the 4.1 point higher average K-ABC Mental Processing IQ scores of the children of fish oil supplemented mothers supports the plausibility of measurable neurodevelopmental benefits of maternal seafood consumption and gives one example of magnitude of dose-response. Additional maternal supplementation trials would be helpful to replicate this result, and to add features such as detailed background n-3 LC PUFA status, supplementation in pregnancy alone or including lactation, various levels of fish oil supplement dose, and several years of complete, planned follow up testing.

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**Randomized trials of infant formula supplementation:** The complexity and inconsistency of the literature on supplementation of infant formula with DHA is a barrier to demonstrating the plausibility of measurable neurodevelopmental benefits for infants and children. The potential for estimating a quantitative dose-response from these data is limited. Among the factors that differed across the randomized trials were: infant population (preterm or term birth), timing of supplementation (beginning at birth or after period of breastfeeding; duration of a few months to one year), test formula composition (presence of arachidonic acid (AA); levels of DHA, AA and alpha-Linolenic acid (ALA)), additional breastfed comparison group, neurodevelopment outcome (vision, cognitive, general development, other), visual acuity testing (behavioral or electrophysiologic), neurodevelopment testing (global or targeted assessment), age at testing (early infancy to three years or older). Systematic reviews and meta-analyses evaluated the randomized trials in subgroups according to various study conditions, and generally found the evidence for neurodevelopmental benefit of DHA supplemented formula to be inconsistent and inconclusive (Lewin et al., 2005; Simmer 2001; Simmer and Patole 2004; Simmer et al., 2008a; Simmer et al., 2008b; Smithers et al., 2008). Studies were grouped differently in different systematic reviews, and newer studies were available for more recent reviews, making comparisons difficult across reviews.

The analysis of Lauritzen et al. (Lauritzen et al., 2001) concentrated on a single age at testing (four months) and identified formula composition and visual acuity method as likely sources of heterogeneity among trials. These authors recommended that future trials use conditions from previous positive trials, including DHA as 0.36 percent of lipids in test formula and electrophysiologic method for visual acuity testing. The meta-regression of Uauy et al (Uauy et al., 2003) quantified the dose-response for DHA equivalents in 12 comparisons from seven controlled trials of term infant visual acuity at four months of age (Table 3). Morale et al., (2005) analyzed visual acuity at age 12 months in studies from a single laboratory and found a linear dose-response for duration of supply of LC PUFA from formula supplemented with DHA as 0.36 percent of lipids, breastfeeding, or both (Table 12). Birch et al. (2005) designed a trial to carry out the Lauritzen et al. recommendations regarding DHA level in test formula and electrophysiological visual acuity as well as adequate sample size (greater than 20 per group). Supplemented infants had significantly better visual acuity at six, 17, 39 and 52 weeks of age and better stereoacuity at 17 weeks.

Most studies showed little evidence of a positive effect of supplemented formula on infant neurodevelopment using global tests, such as the Bayley scales. A few studies reported positive effects using more specific, focused developmental assessments, but these assessment methods were not adopted by other research groups (Willatts et al., 1998). The study of Birch et al. (1998) did find a positive effect of supplemented formula for four months using Bayley's MDI at 18 months of age. In a follow up at four years of age, infants supplemented with DHA plus AA had mean Wechsler Performance, Verbal and Full Scale IQ scores that were 4.4, 5.7 and 6.5 points higher, respectively,

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than scores of control infants (Birch et al., 2007). However, the statistical significance of this comparison was not tested directly but in a research design including a breastfed group and a DHA (with no AA) supplemented group. A secondary analysis of the IQ comparison for DHA plus AA supplemented and control infants from Birch et al. (2007) would show whether the result is statistically significant and if not significant, what sample size would be needed to replicate the results with adequate power.

Cohen et al. (2005a; 2005c) pooled the results of nine unique trials of supplemented formula and neurodevelopmental outcomes. Based on the average DHA level in supplemented formulas, the authors estimated an effect size of 4.6 IQ points for each one percent DHA (as percent of lipids) in infant formula (Table 9). In the supplemented formula of Birch et al. (2007), the DHA level was 0.36 percent, giving a Full Scale IQ effect size of 18 points ( $6.5/0.36$ ) per one percent DHA in formula, considerably larger than the 4.6 point effect size of Cohen et al. (2005a; 2005c) Cohen and coauthors reported only a point estimate and did not state whether their result was significantly different from no effect.

## **(b) Association between Methylmercury Exposure and Neurodevelopmental Effects in the Fetus from Prenatal Exposure**

Table IIIA-1 lists the major peer reviewed studies that explored the effect of prenatal exposure to methylmercury on neurodevelopment. The table is subdivided by the level of exposure. The first set of studies in this table is based on contamination incidents in Japan and Iraq. These incidents demonstrate that methylmercury can cause overt neurological abnormalities and even death when levels in the body approach and exceed 100 times more than average body levels in the United States (Harada et al., 1995; Marsh et al., 1987; McDowell et al., 2004). In the Minamata, Japan poisoning incident, methylmercury concentrations in fish ranged from 40 times to over 300 times higher than the average concentration in commercial fish in the U.S. marketplace today (Harada et al., 1995). The events provided evidence that an expectant mother's exposure to high amounts of methylmercury could result in neurological injury to her offspring even when the mother was not significantly affected (Harada et al., 1995; Marsh et al., 1987).

A number of research projects have investigated whether neurodevelopment in the fetus is being affected at much lower levels of exposure (than that seen in the Minamata population and in Iraq) as a result of day-to-day maternal consumption of fish. These investigations have been conducted in populations where fish is a mainstay of the diet and thus consumed much more frequently than it is on average in the United States (and as a result, exposure to methylmercury is also relatively higher). Daily fish consumption (and consumption of pilot whale in the Faroe Islands) results in concentrations of methylmercury in the bodies of these peoples that are well above those found in the vast majority of fish consumers in the United States and other countries with consumption patterns similar to those in the United States. The researchers anticipated that effects would reveal themselves as subtle differences in scores on neurodevelopmental tests

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between children who had been prenatally exposed to less methylmercury and those who had been prenatally exposed to more methylmercury within a study population (Marsh et al., 1995a; Myers et al., 2007).

Two large studies in the Seychelles and Faroe Islands produced apparently contradictory results. The Seychelles study found no consistent significant association between prenatal exposure to methylmercury and results on a wide battery of neurodevelopmental tests administered at several ages while the Faroe Islands study found adverse associations on a number of neurodevelopmental tests administered there (Grandjean et al., 1995 & 1998; Debes et al., 2006; Myers et al., 1995, 1997 & 2003; Davidson et al., 1995a & 1998). They found that in order to achieve body levels that are about 10-fold higher than average U.S. levels, the women in the Seychelles Islands study routinely ate about 12 fish meals per week (Shamlaaye et al., 1995). The researchers in the Faroe Islands concluded that the strongest associations they saw between methylmercury and neurodevelopmental test scores were the result of “stable,” rather than “variable” exposures (Grandjean et al., 2003).

A considerable amount of attention was paid to possible explanations for the seemingly different outcomes in these studies (NRC 2000). A study in New Zealand had produced results similar to those in the Faroe Islands (Kjellström et al., 1986 & 1988). Since 2004, however, a significant number of studies have been published, many of which have involved populations in the United States and in countries where exposures to methylmercury are similar to those in the United States. These studies are described below.

### **(c) Observational Studies of both Fish Consumption and Methylmercury Exposure**

One of the first such studies to look at both the beneficial effects of fish consumption while examining methylmercury exposure was from a cohort in the United Kingdom (Daniels et al., 2004). They found a beneficial association between maternal consumption of fish during pregnancy and neurodevelopmental test scores in their children but no adverse association between prenatal exposure to methylmercury in the fish and the same test scores. The authors stated that methylmercury exposures in their cohort were “low” (Daniels et al., 2004, page 398), with the comparison apparently being to much higher exposures in the Faroe Islands, where adverse effects had been reported (Daniels et al., 2004, page 400).

A number of studies since then have found a beneficial association between maternal fish consumption and test scores and, in addition, an adverse association between the methylmercury in the fish and the test scores (Oken et al., 2005; Oken et al., 2008; Hibbeln et al., 2007a). In these studies, the methylmercury levels in the fish typically reduced some of the beneficial outcome associated with fish consumption but did not often eliminate the beneficial outcome entirely. In one study (Oken et al., 2005), the

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authors provided information by which the size of the beneficial fish contribution could be compared to the size of the adverse methylmercury contribution. Using such a calculation, each additional weekly fish serving was associated with an average increase of four points on a test of “visual recognition memory” (VRM) while the methylmercury in each additional serving was associated with an average decrease of 1.28 points on this test.<sup>9</sup>

Four analyses suggested that eating more than 12 ounces of fish per week may convey more benefits than eating less than 12 ounces (Oken et al., 2005; Oken et al., 2008; Hibbeln et al., 2007a; Oken et al., 2008a) even though this finding could include some reduction from methylmercury as described above. In Oken et al. (2005), those who ate more than two servings of fish per week had infants with VRM scores that were 12 points higher than infants whose mothers consumed two or fewer weekly servings; however, those who ate the highest amounts of fish and had lower hair mercury levels had infants with higher VRM scores than infants whose mothers ate similar amounts of fish but had higher hair mercury levels. Similar findings were reported in Oken et al. (2008). Collectively, the results suggest that the higher the methylmercury in the fish, the greater the reduction in benefits, to the point where the net effect could even be adverse.

The results from the earlier New Zealand and Faroe Islands studies could be interpreted to be consistent with those results. In the New Zealand study, adverse effects were seen in a population that apparently ate a lot of fish high in methylmercury (shark) (Kjellström et al., 1986). Although the overall net effect from eating fish was not measured (the reported association was between the methylmercury in the fish and neurodevelopmental test scores), the results from this study suggest that the net effect can become adverse when the diet includes enough high methylmercury fish.

A similar conclusion can be drawn from the Faroe Islands study. There, more methylmercury came from eating pilot whale than from eating fish (Grandjean et al., 1999). The fish primarily consumed in the Faroe Islands (cod) were low in mercury, with a reported average concentration of 0.07 ppm (Weihe et al., (1996, page 142). With the methylmercury from the pilot whale added to the diet, however, it would have been equivalent to eating fish with much higher concentrations of methylmercury. Structural equation modeling of neurodevelopmental test data at seven and 14 years of age from the Faroe Islands showed that, after mutual adjustment for both variables, there was an

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<sup>9</sup> The authors reported that an increase of 1.0 ppm in maternal hair mercury was associated with a decrement in VRM score of 7.5 points. In order to compare size of gains from fish (4 points per each additional weekly fish serving) against size of losses from methylmercury, it is necessary to calculate the average loss per fish serving. This can be done by calculating how many weekly fish servings had to be consumed in order to achieve an increase of 1.0 ppm in maternal hair mercury in this cohort. According to the authors, each weekly fish serving resulted in an increase of 0.17 ppm in maternal hair mercury. Dividing 0.17 ppm into 1.0 ppm reveals that 5.88 weekly fish meals are needed to achieve an increase of 1.0 ppm. Dividing 5.88 weekly fish meals into 7.5 VRM points lost (per each 1.0 ppm) results in 1.28 VRM points lost per weekly fish meal due to methylmercury.

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independent, positive association with maternal fish intake as well as a negative association with maternal mercury exposure (Budtz-Jørgensen et al., 2007). Preliminary results from the Seychelles nutrition cohort suggested that children’s developmental tests were positively associated with maternal n-3 LC PUFA blood levels and negatively associated with maternal hair mercury (Myers et al., 2007). These associations were stronger when mutually adjusted for the other variable.

**Table IIIA-1: Studies involving prenatal exposure in which the effect of methylmercury on neurodevelopment was the focus of the study.<sup>10</sup>**

<b>Where Exposures to Methylmercury Approached and Exceeded 100x Average U.S. Exposures from Commercial Fish</b>		
<i>Location</i>	<i>Outcome Measures</i>	<i>Findings</i>
<b>Japan</b> (Harada et al., 1995)	All neurological effects reported from the poisoning event	Adverse neurological effects ranging from mild to severe and including fatal.  Fetus often more severely affected than the mother.
<b>Iraq</b> (Marsh et al., 1987) Study pop.: 81	--Neurodevelopmental milestones: ages of first walking and talking --Neurological examination	Significant adverse association found between prenatal exposure and milestones and examination results.  Fetus often more severely affected than the mother.
<b>Where Exposures to Methylmercury Were Roughly 10x Average U.S. Exposures (and Higher than Most U.S. Exposures) from Commercial Fish</b>		
<i>Location</i>	<i>Outcome Measures</i>	<i>Findings</i>
<b>New Zealand</b> (Kjellström et al., 1986 & 1988) Study pop.: --38 at age 4 --61 at age 6 ("high exposure" part of the study)	Neurodevelopmental tests at ages 4 & 6, including IQ at age 6	Significant adverse associations found between prenatal exposure and some results, including IQ.
<b>Faroe Islands</b> (Grandjean et al., 1995 & 1998; Debes et al., 2006) Study pop. : 900+	--Neurodevelopmental milestones: ages of first sitting, creeping, standing --Battery of neurodevelopmental tests at ages 7 & 14 years of age	Significant adverse associations found between prenatal exposure and some results.
<b>Faroe Islands</b> (Budtz-Jørgensen et al., 2007) Study pop.: 900+	Reanalysis of results from battery of neurodevelopmental tests at ages 7 & 14 years of age.	<ul style="list-style-type: none"> <li>Beneficial associations found between maternal fish consumption and some test results. The beneficial association reflected the fish contribution to net effect independent of methylmercury. The net effect was not calculated.</li> <li>The adverse associations between methylmercury and test results were</li> </ul>

<sup>10</sup> (NOTE: the studies actually measured total mercury but we assume that the results apply to methylmercury, the organic form found in fish.)

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		found to be stronger when the fish benefits were removed from the calculation.
<b>Seychelles Islands</b> (Myers et al., 1995, 1997 & 2003; Davidson et al., 1995a & 1998) Study pop.: 700+	--Neurodevelopmental milestones: ages of first walking and talking --Battery of neurodevelopmental tests at ages 6.5 mo., 19 mo., 29 mo., 66 mo., & 9 years (including IQ)	No consistent significant adverse associations found between prenatal exposure and test results.
<b>Where Exposures to Methylmercury Occurred in the U.S. or in Locations with Exposures Largely Within the Range of U.S. Exposures from Commercial Fish</b>		
<i>Location</i>	<i>Outcome Measures</i>	<i>Findings</i>
U.K. (Daniels et al., 2004) Study pop.: 7,421	Neurodevelopmental tests at ages 15 & 18 months	No significant adverse association found between prenatal exposure and test results
U.S. (Oken et al., 2005) Study pop.: 135	Test of visual recognition memory at ages 5.5 – 8.4 months	<ul style="list-style-type: none"> <li>• Maternal fish consumption was associated with improvements on the test while the methylmercury in the fish was associated with reductions in those improvements.</li> <li>• Each additional weekly fish serving was associated with a 4 point improvement on the test while each 1.0 ppm of mercury was associated with a decrement of 7.5 points on the test. [Note, when we converted these to common metric of “additional weekly fish serving,” the result was a gain per serving of 4 points and a decrement per serving of 1.28 points.] See discussion of this study in the text, above.]</li> <li>• Eating over 2 servings per week was associated with higher scores than eating below 2 servings per week.</li> </ul>
U.S. (Oken et al., 2008) Study pop.: 341	Neurodevelopmental tests at 3 years of age.	<ul style="list-style-type: none"> <li>• Maternal fish consumption was associated with improvements on the tests while the methylmercury in the fish was associated with reductions in those improvements.</li> <li>• The greatest average benefits were associated fish consumption during pregnancy of over 2 servings per week when that consumption resulted in lower exposures to methylmercury.</li> <li>• Average benefits were lower when over 2 servings per week during pregnancy resulted in higher exposures to methylmercury.</li> <li>• Average benefits were lower still when mothers ate no fish during pregnancy.</li> </ul>

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		<ul style="list-style-type: none"> <li>Average benefits were lowest when mothers ate less than 2 servings per week when that consumption resulted in high exposures to methylmercury (presumably because the fish contained more methylmercury).</li> </ul>
<b>Poland</b> (Jedrychowski et al., 2006) Study pop.: 233	Neurodevelopmental tests at 1 year of age.	Significant adverse association found between prenatal exposure and test results.
<b>Poland</b> (Jedrychowski et al., 2007) Study pop.: 374	Neurodevelopmental tests at 2 & 3 years of age.	No significant adverse association found between prenatal exposure and test results. The significant adverse association seen at age 1 (above) could no longer be found.

**Table IIIA-2: Studies involving prenatal exposure in which the effect of fish consumption on neurodevelopment was studied but the exposure to methylmercury from that fish consumption was not measured.**

<i>Location</i>	<i>Outcome Measures</i>	<i>Findings</i>
<b>U.K.</b> (Williams et al., 2001) Study pop.: 435	Stereoscopic vision at age 3.5 years	Significant beneficial association found between maternal consumption of oily fish and stereoscopic vision.
<b>U.K.</b> (Hibbeln et al., 2007a) Study pop. : 9,000	Neurodevelopmental tests ages 6 months through 8 years, including IQ	Greater fish consumption, including above 2 servings per /week, associated with higher scores including IQ.  NOTE; Methylmercury exposure was subsequently estimated by the authors. They concluded that methylmercury reduced the size of the benefit from fish somewhat but that the net effect remained beneficial.
<b>United States</b> (Lederman et al., 2008) Study pop.: 329	Bayley Scales of Infant Development II at 12, 24, and 36 months of age; Wechsler Preschool and Primary Scale of Intelligence at 48 months of age.	This study was initially designed to study outcomes from contamination from the World Trade Center collapse in N.Y. The study reported that mercury was associated with lower scores but that fish consumption during pregnancy was associated with higher scores.
<b>Denmark</b> (Oken et al., 2008a) Study pop.: 25,446	Various developmental milestones at 6 & 18 months of age	Significant beneficial associations found between higher maternal fish consumption and attainment of developmental milestones.

#### **(d) Neurodevelopmental Effects in Children from Postnatal Exposure**

Children may be especially sensitive to the effects of neurotoxins because their nervous systems are still developing.

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Whether children are experiencing adverse effects as a consequence of exposure to methylmercury after birth has been studied in the Faroe and Seychelles Islands. The studies in both locations have reported no adverse effects in children who had levels of exposure that are substantially higher than average U.S. exposures. The two studies reported improvements on neurological tests scores as the children's exposure to methylmercury (as measured by blood and hair samples from the children) increased. Presumably these results were not due to methylmercury but to increases in postnatal fish consumption.

In an early phase of their study, the Faroe Islands researchers looked for an association between postnatal mercury exposure and delays in the developmental milestones of first sitting, creeping and standing (Grandjean et al., 1995). They found that infants who achieved these milestones the earliest had the highest hair mercury levels at 12 months of all those in the study population. The researchers noted that these children had also experienced the longest breastfeeding and they hypothesized that the contents of mother's milk, including n-3 long-chain fatty acids, might have been responsible for their early development.

The Faroe Islands researchers also addressed postnatal exposure at a later age. In their discussion of neurological test results when the children were 14 years old, they state that "Postnatal methylmercury exposure had no discernible effect" and that this outcome, among others, was similar to those obtained when the children were seven years old. They also indicate that they saw improvements, i.e., "many coefficients suggesting effects in the direction opposite to expectation," although they do not appear to have been statistically significant (Debes et al., 2006).

The Seychelles research team reported a similar outcome. In its paper on outcomes at 66 months of age, the team describes dividing the study population into five groups based on the children's mercury hair levels. The group with the highest mean mercury hair level, 14.9 ppm, scored slightly better on four of six neurological development scores than the group with the lowest mean of 2.2 ppm (Davidson et al., 1998). The NHANES survey has shown a mean of 0.22 ppm for U.S. children one to five years of age. This average is nearly 1/70<sup>th</sup> the highest mean level in the Seychelles with slightly improved scores (McDowell et al., 2004, p. 1,167).

The Daniels et al. (2004) study of ALSPAC data from the United Kingdom reported an association between increases in children's fish consumption and small but statistically significant improvements in scores on neurodevelopmental tests within a study population of slightly over 7,400. Methylmercury levels in the children were not measured as they were in the Seychelles and Faroe Islands, so it is necessary to assume that increases in postnatal fish consumption in this study population were accompanied by increases in methylmercury exposure.

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The U.K. children were younger (15 and 18 months) than the children in the Seychelles (66 months) and Faroe Islands (14 years) when they were tested for behavioral performance. The beneficial association between children's fish consumption and test scores reported by Daniels et al. (2004) is consistent with the results in the Seychelles and Faroe Islands at the later ages, although exposure to methylmercury in the Daniels et al. cohort was lower.

A related question about children is whether infants can be adversely affected by methylmercury in mother's milk. One way of considering this question is to examine whether an infant's postnatal exposure through lactation will be the same as its prenatal exposure. The transport of methylmercury from maternal blood into human milk is less efficient than the transport across the blood-brain and blood-placenta barriers. The ratio between methylmercury in maternal blood serum and methylmercury in maternal milk is small and results in very low concentrations in maternal milk. Consequently, if a mother continues to eat the same types and amounts of fish during lactation as she did while pregnant, the infant's exposure to methylmercury can be expected to drop as compared to what occurs *in utero* (Björnberg et al., 2005; Dorea 2004; FAO/WHO JECFA, 2007). The limited transfer of methylmercury into maternal milk is consistent with the fact that adverse associations between methylmercury and neurodevelopment have been reported only for prenatal methylmercury exposure but not for postnatal exposure.

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## **Section III-B: Studies on Coronary Heart Disease and Stroke**

### **(a) Association between Fish Consumption or Omega-3-Fatty Acids and Cardiovascular Disease**

Several lines of evidence, taken together, suggest the association of fish or n-3 LC PUFA consumption and decreased Coronary Heart Disease (CHD) risk:

- Primary and secondary prevention, randomized clinical trial of fish oil consumption. The recently published large-scale clinical trial called the Japan EPA Lipid Intervention Study (JELIS) from Japan included over 18,000 men and women (Yokoyama et al., 2007). Almost 15,000 participants had no record of coronary artery disease (primary prevention). Results showed a 19 percent decrease in major coronary events (fatal plus nonfatal) for all subjects, a 19 percent decrease for secondary prevention subjects and an 18 percent decrease for primary prevention subjects. The decrease in risk was similar in magnitude for primary and secondary prevention, but was not statistically significant for primary prevention alone ( $p = 0.13$ ). For the full study and for both subgroups, there was no significant decrease in sudden cardiac death or coronary death alone, probably reflecting that the high baseline fish intake in Japan is above a possible threshold for effect on risk of sudden death or CHD death.
- Secondary prevention, randomized clinical trials of fish or fish oil consumption. The large, well-conducted secondary prevention trial, GISSI, included over 10,000 men and found a 15 percent decrease in all deaths plus nonfatal heart attacks and strokes, a 26 percent decrease in cardiovascular deaths plus nonfatal heart attacks and strokes and a 45 percent decrease in sudden death, all significant (GISSI 1999; Marchioli et al., 2002) Results of the DART1 study were consistent with GISSI, but results differed for the poor quality DART2 study (Burr et al., 2003; Burr et al., 1989).
- Meta-analyses of randomized controlled trials of fish or fish oil consumption. Mozaffarian and Rimm (Mozaffarian and Rimm 2006) conducted a meta-analysis including five randomized controlled trials and 15 prospective cohort studies of fish or fish oil intake and CHD death among >300,000 subjects. There was a significant, 17 percent decrease in total CHD mortality. A total 36 percent reduction in risk was estimated for intakes of 250 mg/day EPA/DHA.
- Observational studies of blood levels of n-3 LC PUFA and CHD risk. As summarized by (SACN 2004) and others, additional evidence for the cardiovascular benefits of fish and fish oil consumption is provided by several cohort or case control studies that found decreased CHD risk associated with higher blood levels of DHA and EPA. SACN stated that, “Taken together, these data support the hypothesis that

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n-3 LC PUFA are responsible for the observed inverse association between fish consumption and sudden cardiac death.”

- Meta-analyses of observational studies of fish consumption and risk of cardiovascular disease. There are several meta-analyses of observational studies of fish consumption and risk of CHD or stroke with fairly consistent results among the meta-analyses. The prospective studies of CHD death included more than 200,000 men and women and the prospective studies of stroke also included more than 200,000 men and women. For example, the meta-analyses of He et al (He et al 2004a; He et al 2004b) found a 15 percent decreased risk of CHD death and a 13 percent decreased risk of stroke associated with fish intake once per week compared with less than once per month.
- A meta-analysis (Studer et al 2005) of 97 studies, with 137,140 individuals in intervention and 138,976 individuals indicated that the benefits of n-3 LC PUFAS were comparable to (or greater) than the benefits of statins for overall mortality.

A detailed discussion of these studies is available in the accompanying document entitled ”Summary of Published Research on the Beneficial Effects of Fish Consumption and Omega-3 Fatty Acids for Certain Neurodevelopmental and Cardiovascular Endpoints,” which is available at <http://vm.cfsan.fda.gov/~tdms/mehg109.html>.

## **(b) Association between Methylmercury Exposure from Fish Consumption and Cardiovascular Disease Toxic Effects**

The extreme exposures to methylmercury that occurred in the poisoning events in Japan and Iraq do not appear to have resulted in CHD. In the Japan poisoning events, nine percent of deaths among chronic patients who died from 1975 to 1982 were from cardiac failure as compared to the Japanese national average of 21.3 percent for the same time period (Harada 1995, page 18; Chan and Egeland 2004, page 69). In the Iraq poisoning event, involvement of the cardiovascular system was reported to be rare (Bakir et al., 1973), however there has been no long-term follow-up of this endpoint from that event.

A relationship between methylmercury and CHD and stroke was initially studied in Finland beginning in 1984 as part of a search for an explanation for why men in eastern Finland were experiencing one of the highest mortality rates in the world from cardiovascular disease even though they tended to eat a lot of fish (mainly lean lake fish that were low in omega-3 fatty acids and selenium). Studies conducted around the world have pointed to an association between fish consumption, or the consumption of omega-3 fatty acids that are a natural component of fatty fish, and a reduced incidence of CHD. Why did eastern Finland appear to be so different in that respect and did the difference involve methylmercury?

The researchers found an association between methylmercury from nonfatty freshwater fish and the incidence of CHD and stroke in eastern Finland (Salonen et al., 1995).

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Results were first published in 1995, with follow-up results published in subsequent years.

We are aware of subsequent studies that looked for an association between methylmercury and cardiovascular endpoints in four additional populations: (1) Swedish women in a city in southwestern Sweden (Ahlqwist et al., 1999); (2) Swedish women and men in northern Sweden (Hallgren et al., 2001); (3) individuals from eight European countries and Israel (Guallar et al., 2002); (4) U.S. men (Yoshizawa et al., 2002). The findings are mixed and there are questions about how to interpret the results from each study. The study of the eight European subpopulations plus Israel reported an association between methylmercury and increased CHD risk but the remaining three studies did not, although the U.S. study reported a non-statistically significant association in one aspect of the study. One of the Swedish studies looked for an association between methylmercury and stroke but found none.

In contrast to the relatively limited data from these five populations on possible associations between methylmercury and CHD and stroke, there exist a substantial quantity of data, collectively involving hundreds of thousands of individuals, from many studies that have looked for an association between eating fish (although not typically differentiated by species), or from ingesting omega-3 fatty acids, and risk of CHD or stroke morbidity and mortality. Although these studies did not measure methylmercury levels in the individuals who participated in them, it is reasonable to assume that the fish contained methylmercury. Our risk and benefit assessment utilizes data from these studies, as explained in Section IV of this report and Appendix A.

Below are tables that summarize: (a) the studies involving methylmercury; and (b) the studies involving “fish.” Because the fish studies have been the subject of meta-analyses that consolidated the results from each study, the “fish” table focuses on the meta-analyses and thus also presents the results in a consolidated format.

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**Table IIIB-1: Human studies of the association between methylmercury (MeHg) exposure and clinical CHD outcomes. Adopted from Konig et al. (2005). CHD, coronary heart disease; CVD, cardiovascular disease; Hg, mercury; MeHg, methylmercury; MI, myocardial infarction; RR, relative risk**

Study	Population and follow-up	Exposure measure(s)	Control for n-3 exposure	CHD outcome	Findings for MI and CHD death
Salonen (1995) Rissanen (2000) Virtanen (2005)	1833 (Salonen) or 1871 (Rissanen and Virtanen) men in eastern Finland 42–60 yrs with no CHD, CVD stroke history, claudication, or cancer at baseline. Follow-up: 7 yrs (Salonen), 10 yrs (Rissanen), 14 yrs (Virtanen)	Hair Hg ( $\mu\text{g/g}$ ), fish intake (g/day)	No (Salonen) Yes (Rissanen, Virtanen)	Salonen: Acute MI, CHD death, CVD death, and all-cause death Rissanen: Acute MI, acute chest pain Virtanen: Acute coronary event, CHD death, CVD death, and all-cause death	Salonen: CHD mortality: RR=1.21 (1.04–1.40) per $\mu\text{g/g}$ Hg in hair Total MI: RR=1.07 (0.97–1.18) per $\mu\text{g/g}$ Hg in hair. Virtanen: CHD mortality: Highest hair Hg tertile RR=1.21 (0.71–2.06) vs lowest tertile, p for trend 0.4.
Ahlqwist (1999)	1462 Swedish women aged 38–60 at baseline. Follow-up: 24 years	Serum Hg	No	MI	When controlled for age and education, $p > 0.2$ for MI, $p=0.144$ for fatal MI. Correlation $<0$ , suggesting higher Hg exposure reduces risk
Hallgren (2001)	78 first-ever MI cases from Northern Sweden matched to 156 controls on gender, age, date of health survey, region	Blood Hg	Yes	First MI	No consistent association with Hg exposure
Guallar (2002)	684 first-ever MI cases matched with 724 controls. Population included men $\leq 70$ yrs from any of 8 European countries or Israel	Toenail Hg	Yes	First MI	Highest Hg exposure quintile RR=2.16 (1.09–4.29) vs lowest Hg exposure quintile
Yoshizawa (2002)	470 cases and 464 controls drawn from 33,737 male health professionals with no cancer, MI, angioplasty at baseline. Follow-up: 5 yrs	Toenail Hg	Yes	CHD (fatal CHD, nonfatal MI, coronary-artery bypass surgery, angioplasty)	No consistent association with Hg exposure. Highest Hg exposure quintile RR=1.03 (0.65–1.65) vs lowest Hg exposure quintile

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**Table IIIB-2: Meta-analyses of observational studies of fish consumption and coronary heart disease or stroke**

Study	Health Outcome	Number of study populations	Number of subjects	Follow-up time	Results
	<b>Coronary Heart Disease</b>				
He et al., 2004a	Coronary heart disease death	13*	222,364	11.8 years	<ul style="list-style-type: none"> <li>• 15% decrease in risk of CHD mortality associated with fish intake once per week, 23% decrease in risk with fish intake 2 to 4 times per week, 38 % decrease in risk with fish intake 5 or more times per week, all statistically significant.</li> <li>• Each 20-g/d increase in fish intake related to statistically significant 7% lower risk of CHD mortality.</li> </ul>
Whelton et al., 2004	Coronary heart disease death	13	215,705	5 to 30 years	<ul style="list-style-type: none"> <li>• Fish consumption versus little to no fish consumption associated with statistically significant 17% decrease in risk of fatal CHD.</li> </ul>
	Total coronary heart disease				<ul style="list-style-type: none"> <li>• Fish consumption versus little to no fish consumption associated with statistically significant 14% decrease in risk of total CHD</li> </ul>
	Cohorts	7	190,262	5 to 19 years	
	Case control	5	4,964	-----	
König et al., 2005	Coronary heart disease death	7	157,835	6 to 30 years	<ul style="list-style-type: none"> <li>• Consuming small quantities of fish associated with 17% reduction in CHD mortality risk, with each additional serving per week associated with further reduction in this risk of 3.9%, both statistically significant.</li> </ul>
	Nonfatal coronary heart disease	3	133,493	6 to 16 years	<ul style="list-style-type: none"> <li>• Small quantities of fish consumption compared with no consumption associated with 27% reduced risk of nonfatal heart attack, but additional fish consumption conferred no incremental benefits.</li> </ul>

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	<b>Stroke</b>				
He et al., 2004b	Stroke	9	200,575	12.8 years	<ul style="list-style-type: none"> <li>• 13% decreased risk of stroke associated with fish intake once per week, 18% decreased risk with fish intake 2 to 4 times per week, 31% decreased risk with fish 5 or more times per week, all statistically significant.</li> </ul>
Bouzan et al., 2005	Stroke				<ul style="list-style-type: none"> <li>• Any fish consumption associated with statistically significant 12% decreased risk of stroke and each additional one serving per week may be associated with an additional 2.0% decreased risk.</li> </ul>
	Cohorts	4	129,767	12 to 30 years	
	Case control	1	823	-----	

**Included studies are cohort studies unless otherwise noted.**

**\*11 independent studies**

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### **(c) Blood Pressure in Children Through Age 15 (Seychelles and Faroe Islands)**

The researchers in the Faroe Islands reported that at seven years of age, the boys in the study group showed an association between prenatal exposure to methylmercury and increased blood pressure, although the blood pressure was not elevated beyond normal ranges (Grandjean et al., 2004). When checked again when the children were 14 years of age, the association was no longer observed.

In the Seychelles Islands, Thurston et al. (2007) measured blood pressure at ages 12 and 15 years. They found no association between prenatal exposure to methylmercury and increased blood pressure at age 12, but at 15 years they found an association between prenatal exposures and increased diastolic blood pressure in boys. Thurston et al. (2007) was unable to identify a biological reason for an association that only involves diastolic blood pressure in boys at 15 years. They advocated further study, but concluded that their finding “does not suggest a consistent association between methylmercury and blood pressure” (Thurston et al., 2007, page 928). They noted that elevated blood pressure was not a major symptom in the extreme poisoning events in Japan and Iraq.

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## **SECTION IV: QUANTITATIVE RISK AND BENEFIT ASSESSMENT MODELING FOR SELECTED INDICATORS OF FETAL NEURODEVELOPMENT, CORONARY HEART DISEASE, AND STROKE**

### **(a) Conceptual Framework**

This section provides an overview of the logic and design of the quantitative risk and benefit assessment. The assessment uses simulation modeling for uncertainty and variability to estimate:

- (a) The net effect of eating commercial fish in the United States on early age verbal development in children as an indicator of neurodevelopment in the fetus. For purposes of this assessment, the net effect includes an adverse contribution from methylmercury and a beneficial contribution from fish, both of which are estimated in the assessment.
- (b) The net effect of eating commercial fish on fatal coronary heart disease and stroke in the general population.

For neurodevelopment, our modeling is based on data on early age verbal comprehension from children who were prenatally exposed to methylmercury, or to nutrients from fish, or to both, as a result of their mothers' exposures while pregnant. Fetal exposure is not directly measured. The mother's exposure during pregnancy serves as a surrogate for fetal exposure without any adjustment.

For coronary heart disease (CHD) and stroke we model only fatal events. For this component of the analysis we divide the general population into four subpopulations and model them separately since the baseline risks and consumption patterns for each subpopulation are different. These are: (a) women of childbearing age (16-45); (b) women age 46 and older; (c) men age 16-45; and (d) men age 46 and older. Even for CHD and stroke, women were subdivided based on most likely childbearing years because the current fish advisory (thus consumption behavior) is driven by concern regarding neurodevelopmental effects on the fetus. Men are divided into the same age groups as women partly for ease of comparison as well as to capture differences in baseline risk by age.

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The assessment is designed to estimate the consequences of current fish consumption and exposure to methylmercury (the “baseline”) as well as the consequences of changes in fish consumption and exposures to methylmercury by U.S. consumers. Box IV-1 lists the questions about “baseline,” that this assessment was designed to address. Results for these analyses are presented in Section V.

We modeled net effect three different ways:

1. We estimate the likelihood and magnitude of effects at “baseline.” We define “baseline” as being essentially commercial fish consumption and resulting exposure to methylmercury for women of childbearing age in accordance with the results of our exposure modeling of U.S. consumption and exposure. This modeling gives us a picture of consumption and exposure as of about the year 2005, since the data available for exposure modeling will always be subject to some time lag. Consumption at the “baseline” involves eating mostly fish that are at the lower end of the spectrum for methylmercury (since most commercial fish tend to be low in methylmercury, including most of the most popular commercial fish) but it also includes consumption of fish that are higher in methylmercury.
2. In a separate analysis for fetal neurodevelopment effects, we estimate the likelihood and magnitude of effects at “baseline” U.S. levels of exposure to methylmercury but we assume that women of childbearing age eat only commercial fish that are at the low end of the spectrum for methylmercury. This modeling allows us to estimate whether maintaining current levels of exposure to methylmercury but only obtaining it through the consumption of lower methylmercury fish produces the same or different results as compared to the “baseline” results.
3. We modeled various “what if” scenarios in which we estimate what would happen if women of childbearing age ate more or less fish or if the amount of methylmercury in the fish they ate were reduced (similar to the modeling in number two, above). The scenarios are listed in Box IV-2, below, and then discussed in detail later in this section.

We present the results in terms of the magnitude of the change on population-level effects. The simulations are based on two-dimensional population models that describe frequency of outcome in the population and the uncertainty associated with the estimates. The results are presented as population shifts above or below the “baseline.” We described the “baseline” previously as recent levels of fish consumption and the resulting exposures to methylmercury experienced by women of childbearing age in the United States.

A potential limitation on the results from this “what if” modeling, however, is that for those scenarios involving increases or decreases in fish consumption, we were

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not able to take into account health consequences from corresponding increases or decreases in consumption of foods other than fish. Such modeling was beyond the scope and resources of this risk and benefit assessment. Analyses by the 2005 Dietary Guidelines Committee (2004) and by Mozaffarian and Rimm (2006) suggest, however, that the effects of food substitution might not have a significant impact on the outcomes (see the discussion on substitution under “2005 Dietary Guidelines Committee” in Section A of the companion document entitled “Summary of Published Research on the Beneficial Effects of Fish Consumption and Omega-3 Fatty Acids for Certain Neurodevelopmental and Cardiovascular Endpoints”).

Hypothetical scenarios involving changes in the baseline are posed in terms of “what if” questions shown in Box IV-2. As noted, the “what if” modeling does not take into account health effects from eating more or less of other foods as a consequence of eating more or less fish. Such modeling was beyond the limited purposes and resources of this project. The public health consequences of eating more or less of other foods can be relevant to the overall consequences of any risk management strategy that FDA might employ or contemplate, and may be worth considering for future analysis.

**Box IV-1:**

**Risk and Benefit Assessment Question Relating to Baseline (Current) Risk**

For the health endpoints that we model (selected indicators of fetal neurodevelopment, fatal coronary heart disease and fatal stroke), what is the range of effects, from adverse to beneficial, that could be occurring in the U.S. population as a consequence of eating commercial fish? What are the uncertainties associated with these estimates, i.e., what is the range of possible effects in addition to the most likely effect estimated by the risk and benefit assessment (what are the confidence intervals surrounding the central estimates)?

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**Box IV-2:**

**The Risk Assessment Questions We Posed that Involved “What if” Scenarios.**

What would be the effect on health endpoints if:

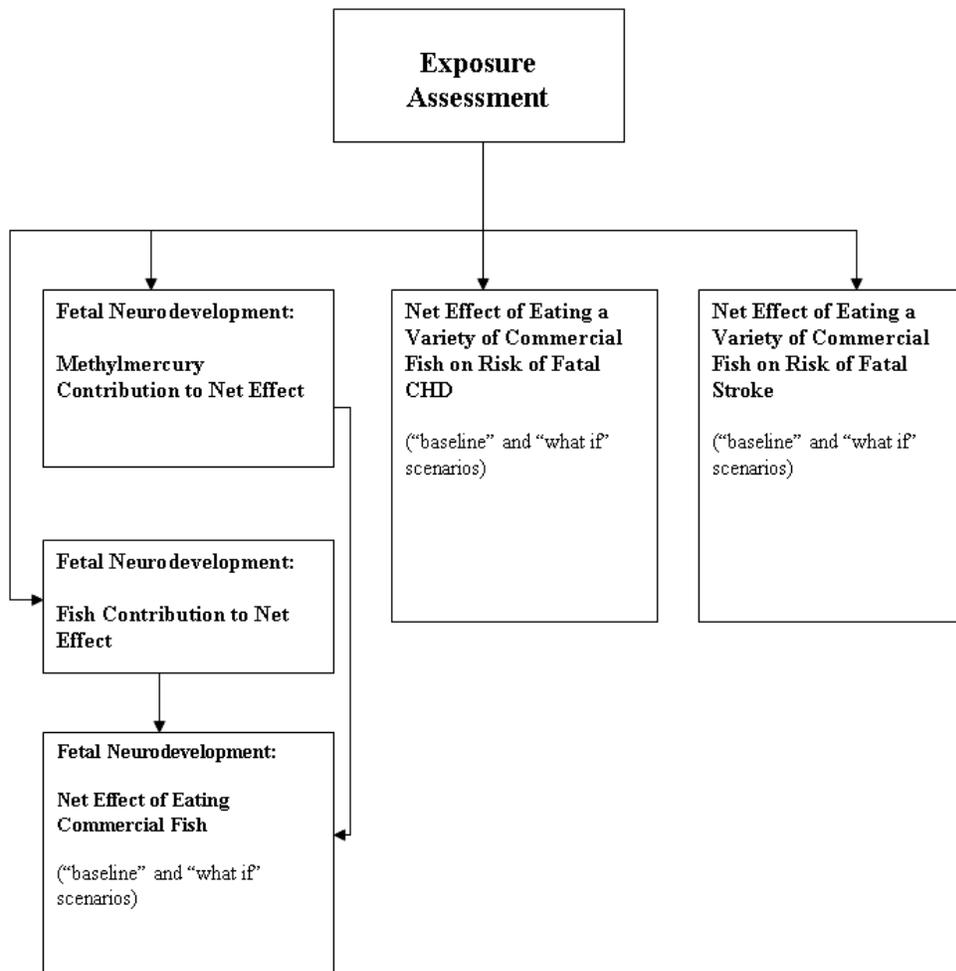
- Women of Child-bearing age (age 15-45):
  - Consume a maximum of 12 ounces per week? In other words, those who are consuming more than 12 ounces reduce their consumption to 12 ounces.
  - Consume a maximum of 12 ounces per week of fish with relatively low concentrations of methylmercury? In other words, those who are consuming more than 12 ounces reduce their consumption to 12 ounces and those who are eating fish that average above “low” (as we define it in the scenarios) switch to only “low” fish.
  - Consume any amount of fish with only relatively low concentrations of methylmercury?
  - Consume exactly 12 ounces per week? In other words, those who are consuming less increase their consumption to 12 and those who are consuming more decrease their consumption to 12.
- Other subpopulations (women 46+ and all adult men):
  - Decrease fish consumption across the board by 10 percent?
  - One percent of fish eaters stop eating fish?
- All populations modeled:
  - Increase fish consumption by 50 percent?

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### (b) Conceptual Model

For all endpoints we modeled the net effect from eating commercial fish. To assess the net effect of eating commercial fish on early age verbal development as an indicator of neurodevelopment, it was necessary to individually model components of net effect and then bring them together as a final step. We did so by combining the adverse methylmercury contribution and the beneficial fish contribution into a single dose-response function for net effect. For fatal coronary heart disease and fatal stroke we simply calculated a dose-response function from eating fish, thus these models involved fewer components. Figure IV-1 provides a visual description of the overall conceptual model. This section provides an overview of the modeling approach, with more detail provided in later sections.

**FIGURE IV-1 Basic Modeling Structure**



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## Exposure

The assessment was designed to estimate net effect of a range of U.S. exposures to a combination of: (1) methylmercury; and (2) nutrients in fish that could beneficially affect the endpoints we considered. In order to model these exposures we had to determine how much methylmercury is in each commercial species and how much of each species people appear to be eating. The major components of this modeling were:

- Estimating the amounts of fish that people eat. Amounts of fish eaten over time depend on the frequencies with which people eat fish and the serving sizes, i.e., the amount that people eat per meal.
- Estimating the species of fish that people eat. Different species of fish contain different average concentrations of methylmercury.
- Estimating how much methylmercury would likely be in each of these fish. In addition to variation among species, fish of the same species vary from one another in their methylmercury concentrations.
- Estimating dietary intake of methylmercury. This calculation is based on the previous three estimates.
- Estimating body levels of methylmercury. Over time, body levels are largely a result of dietary intake minus excretion. The average half life in the human body has been measured at about 50 days with a range of 42-70 days (Sherlock et al., 1984). We estimate body levels in terms of parts per million in hair. Many studies that have looked for associations between body levels of methylmercury and adverse effects have measured hair levels as the biomarker for body levels, although blood levels and other biomarkers have also been used. Hair is regarded as being a more reliable indicator of long term exposure than is blood. Blood is regarded as a good measure of current short-term exposure.

## Adverse Effects from Methylmercury on Fetal Neurodevelopment

For fetal neurodevelopment we selected early age verbal development as an indicator of neurodevelopment and then developed dose-response functions for the adverse contribution that methylmercury could make to the net effect. This was the first dose-response function we modeled. In the United States, the fetal effect derives almost entirely from the methylmercury in the fish eaten by the mother and passed to the fetus. Available dose-response functions were then combined with information from the exposure assessment described above in order to estimate the size and likelihood of an adverse contribution through the range of U.S. exposures to methylmercury. In this report we present estimates for this contribution from the 10<sup>th</sup> percentile of exposure through the 99.9<sup>th</sup> percentile of exposure.

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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 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.

### Beneficial Effects from Commercial Fish on Fetal Neurodevelopment

For the chosen indicators of fetal neurodevelopment it was necessary to estimate a dose-response function for the beneficial contribution from the nutrients that can affect fetal neurodevelopment and that are passed to the fetus due to the mother's consumption of fish. Because estimating the contribution from individual nutrients is beyond the scope of this assessment, we modeled fish as a "package" of nutrients and assumed that all commercial fish are alike in terms of beneficial contribution.

Once a dose-response function was calculated, it was then combined with information from the exposure assessment to estimate the size and likelihood of a fish contribution independent of methylmercury attributable to a range of commercial fish consumptions in the United States. In this report we present estimates for this contribution from the 10<sup>th</sup> percentile of fish consumption through the 99.9<sup>th</sup> percentile of consumption.

### **(c) Criteria for Selecting Studies for Input into the Dose-Response Functions**

The key challenge for modeling is identifying studies that can be used to inform the calculation of the dose-response functions.

#### Selected Indicators of Fetal Neurodevelopment: Methylmercury Adverse Contribution

- Methylmercury Effect Not Confounded: To estimate the effect from methylmercury alone, it was necessary to find data that measured an association between prenatal exposure to methylmercury and neurodevelopment where we could have reasonable confidence that the methylmercury effect was essentially not confounded (not offset or mitigated by) a beneficial effect from fish.
- Indicative of the Effect Magnitude: We could not model all aspects of neurodevelopment in a single assessment, i.e., all possible milestones and results from the myriad tests that exist for measuring all aspects of neurodevelopment, motor skills and verbal skills. Consequently, we had to model some aspects of neurodevelopment that we could assume to be reasonable indicators of at least part of the methylmercury's adverse effect on neurodevelopment as a whole.
- Individual Subject Data: We looked for studies from which individual subject data were available so that we could model individual variability into the

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assessment. Fetal neurodevelopmental endpoints are “continuous” in that the outcome in an individual is a matter of degree, e.g., the results on a test of neurodevelopment, or when an infant first talks (as opposed to whether an infant ever talks). Individual variability cannot be modeled from summaries of data because summaries presume a distribution (usually normal) that precludes the possibility of modeling individual variability as part of the dose-response function.

Another concern we had about using statistical summaries of data for a “continuous” endpoint is that the assessment would have to rely on how the investigators used and treated the data and the statistical techniques they used to evaluate them. We were especially reluctant to use statistical summaries that had been subject to a log(dose) transformation because the impact of the transformation on the secondary modeling results is difficult to determine.

#### Selected Indicators of Fetal Neurodevelopment: Fish Beneficial Contribution

- Fish Effect Not Confounded: To estimate the effect from fish independent of methylmercury, it was necessary to find data that measured an association between maternal fish consumption during pregnancy and neurodevelopment in their children where the beneficial fish effect was not significantly confounded by the methylmercury in the fish. (“Confounding” is an epidemiologic term that describes a variable that is associated with the health outcome of interest and is also associated with the exposure of interest). Since virtually all fish contain methylmercury if only in trace amounts, some confounding is probably inevitable but it can be minimized and taken into account in the modeling.
- Fish Effect Rather than Effects from Individual Nutrients: As mentioned previously, fish presents a “package” that includes lean protein, omega-3 fatty acids, selenium, and other mineral and nutrients. We did not use data from studies that only measured the contribution from individual nutrients
- Comparability: We wanted fish contribution data that measured essentially the same underlying aspect of neurodevelopment as the methylmercury contribution data so that the dose-response functions from each of them could be combined into a single dose-response function for net effect.
- Individual Subject Data: We looked for studies from which individual subject data were available for the reasons described above for the methylmercury contribution.

#### Fatal Coronary Heart Disease and Fatal Stroke

- Association Between Fish and Risk: We looked for studies that measured associations between fish consumption and risk of fatal coronary heart disease and fatal stroke. We concluded the literature supporting a direct link between

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methylmercury and these endpoints was not strong enough to support independently modeling that effect.

In four of the five studies that looked at methylmercury and CHD, data on exposure to methylmercury were obtained through methodologies that make comparison of exposures from one population to another, or to U.S. exposures, difficult. These methodologies involved measuring methylmercury levels in toenail clippings and blood serum (as opposed to whole blood). Without the ability to make such comparisons, it is not possible to know the methylmercury levels in the study participants as revealed by the established biomarkers, e.g., whole blood and hair. That knowledge would be essential for a quantitative assessment keyed to levels of exposure to methylmercury.

Data Have Already been Subject to Meta-Analysis: In this context, a meta-analysis looks for an association between fish consumption and risk of coronary heart disease and stroke by combining the results of several studies that address the same question. Meta-analyses utilize their own criteria to determine whether individual studies are credible for inclusion in the analysis. We looked for meta-analyses with inclusion criteria that would be acceptable to us applying the criteria described below. We also looked for meta-analyses that calculated dose-response functions from the combined studies that they reviewed.

- Inclusion Criteria for Individual Studies: Our inclusion criteria, i.e., the characteristics that each study must possess, for the individual fish studies (also the inclusion criteria employed by the meta-analysis we selected for coronary heart disease (He et al., 2004a)) were:
  - The study must have been a human study of clinical cardiovascular events. Therefore, studies that were *in vitro* or in animals do not meet this criterion. Similarly, studies that measured effects only in terms of biomarkers, rather than coronary events, do not meet this criterion.
  - The study must have been conducted in adults with no history of heart disease (primary prevention). Studies in adults with existing heart disease (secondary prevention/intervention) will provide qualitative scientific support, but cannot be used quantitatively in the analysis.
  - The study must have been an observational epidemiology study in populations. (There are no randomized clinical trials for primary prevention.) Randomized clinical trials for secondary prevention will provide qualitative scientific support.
  - The study must have measures of exposure that are in terms of fish consumption and amount of fish eaten per unit of time (e.g., days, weeks). Studies based only on exposure to omega-3 fatty acids do not meet this criterion.
  - The study must have included at least three levels of fish consumption (that is, the study cannot just have compared no fish to some fish but must

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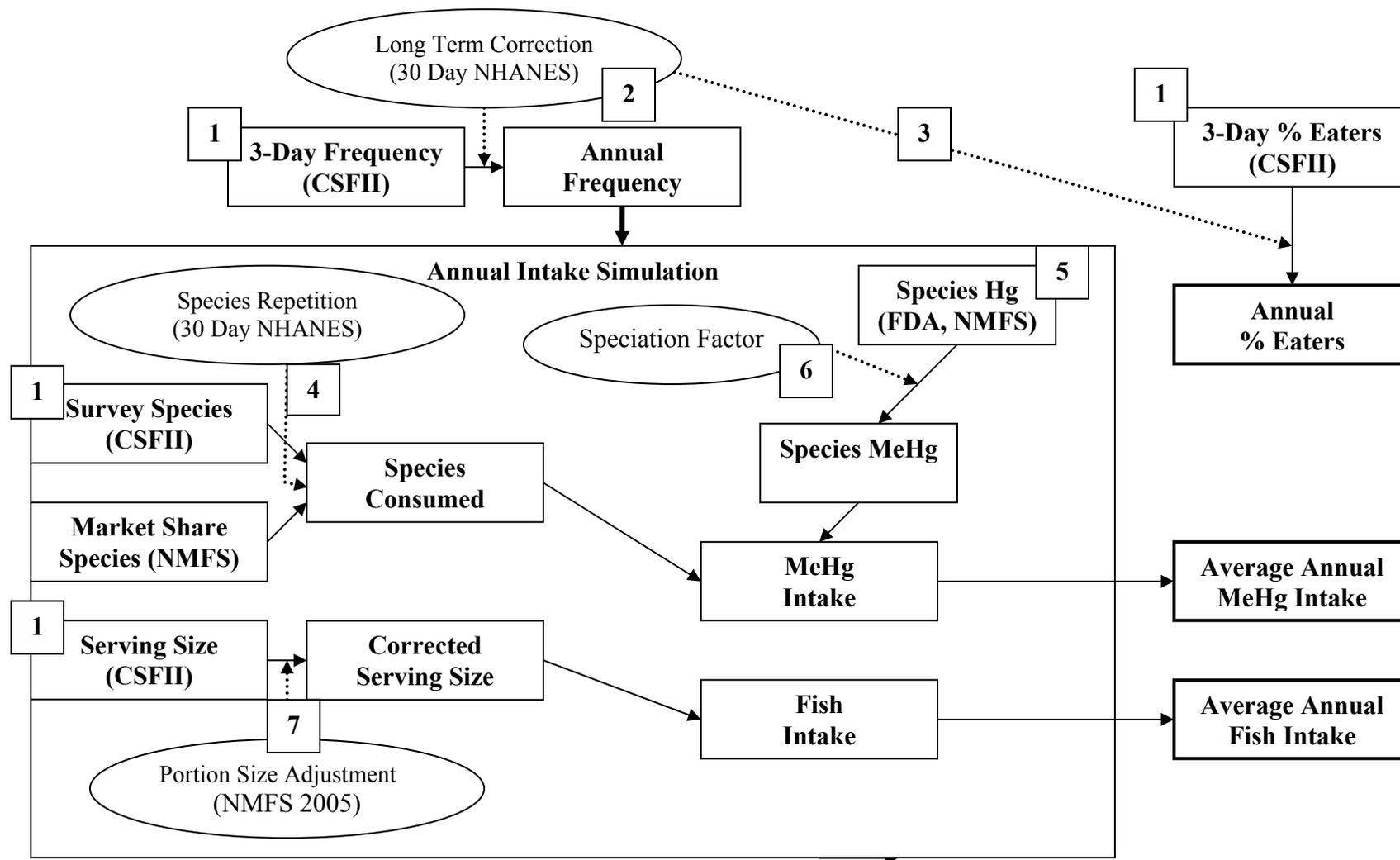
- have included at least three levels of fish consumption), in order to be able to develop a quantitative dose-response function.
- The study must have reported relative risk and corresponding 95 percent confidence intervals of CHD mortality relating to each exposure level (that is, amount of fish consumed).
- The study must have been a prospective cohort study design that was published in an English language journal.
- Summary Data Were Acceptable: The availability of individual subject data for fatal coronary heart disease and stroke was not a criterion. Unlike fetal neurodevelopment, where effects can involve subtle variations in test scores, fatal coronary heart disease and stroke have clearer criteria for diagnosis. We determined that summary data would be adequate for modeling under such circumstances.

#### **(d) Exposure Modeling Overview**

The following flow diagram and table provide an overview of the exposure modeling and the key input parameters. Each of the model components and the associated input data are described in detail below. Table IV-1 presents a summary the knowledge gaps, assumptions used to fill those gaps, and the implications of those assumptions. The assumptions primarily address how the available data are used and adjusted to provide a national picture of exposure for both commercial fish consumption and methylmercury. This study is based on previously published work by Carrington and Bolger. A discussion about the modeling is provided after the flow diagram and table.

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Figure IV-2: Flow diagram of the exposure modeling. The numbers at various steps in flow correspond to numbers in Table IV-1, located immediately behind this flow diagram.



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**Table IV-1: Exposure Modeling: Knowledge Gaps, Assumptions That Address Those Limitations, and Implications for the Results. This table should be read in conjunction with Figure IV-2. The numbers corresponding to exposure modeling steps numbered in that figure.**

#	Knowledge Gap	Assumptions	Implications
1	<p><i>Consumption:</i> How much and what types of commercial fish do people eat over a one year period? There is no consumer survey that covers an entire year.</p>	<p>To the data from the CSFII 3-day survey is presumed to be nationally representative for:</p> <ul style="list-style-type: none"> <li>• 3 day frequency of intake;</li> <li>• % of U.S. consumers eating seafood over a 3 day period;</li> <li>• Characterization (in part) of the variety of fish people eat;</li> <li>• Serving size</li> </ul>	<p>Although newer NHANES have similar average fish consumption for most adults, there is some indication that fish consumption in women of childbearing age may have decreased since the CSFII survey was conducted. If this is so, then the implication for the risk &amp; benefit assessment results would be a slight overestimation of fish consumption and thus a slight overestimation of net effect.</p>
2	<p><i>Short-to-Long Term Frequency Extrapolation:</i> How much and what types of commercial fish do people eat over a one year period? There is no consumer survey that covers an entire year.</p>	<p>For those individuals consuming fish, the 30 day survey is presumed to also represent annual (365-day) frequency</p> <p>An exponential function is used to map short term frequency of consumption (CSFII) to the 30 day frequency (NHANES). While the model itself is well grounded empirically, there is an uncertainty in the extent to which the relative position of individuals in the short term survey corresponds to the long-term survey (i.e. a 90<sup>th</sup> percentile short-term consumer may be higher or lower than 90<sup>th</sup> percentile long-term consumer).</p>	<p>The extent to which relative position varies is treated as a source of uncertainty in the model. Persons who consume seafood very rarely (less than once per month) are not well characterized. The implication for the risk &amp; benefit assessment is that it may mischaracterize small effects in those consumers who eat fish less than once per month.</p>
3	<p><i>% of Consumers Eating Fish Over an Entire Year:</i> How much and what types of commercial fish do people eat over a one year</p>	<p>As part of the long-term correction, an adjustment is made to account for the fact the number of fish consumers increased as the length of the survey period increases. A range of 85-95% consumers who eat fish was presumed for annual intake, with the lower bound being the percentage that ate fish in the 30-day survey.</p>	<p>The percentage of consumers eating fish over a year is a very minor source of uncertainty in the modeling.</p>

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	period? There is no consumer survey that covers an entire year.		
4	<i>Long-term Species Consumption Patterns:</i> How much and what types of commercial fish do people eat over a one year period? There is no consumer survey that covers an entire year.	Data from the 30 Day Survey can be used to reasonably determine the extent to which each individual in the CSFII varies their pattern of fish consumption. The CSFII data associated with the individual can be used to reasonably determine repeated consumption, whereas market share data can be used to reasonably determine varied consumption.	There are fairly substantial changes in the composition of the seafood market since the CSFII survey was conducted. Although newer data are employed for the majority of the meals consumed, the estimates for individuals who consistently eat the same species are dominated by older data. Therefore species with greatly increased market share (e.g. shrimp and tilapia) are underrepresented while tuna is overrepresented. The implication is that the methylmercury adverse contribution to net effect may be slightly overstated for some repeat eaters.
5	Mercury concentration distributions in commercial species are known from years of sampling, but not known with 100% accuracy.	Three different approaches were taken to generating estimates for the range of mercury concentrations in each species. 1) Empirical distributions of FDA survey data with no uncertainty, 2) modeled FDA survey data with model uncertainty, 3) surrogate distributions based on older NMFS data with model uncertainty. Which is assumed to still be representative	The greatest source of uncertainty involves mercury concentrations of a small (<10%) portion of the market, which might not be current. The uncertainty is minimized by the fact that no clear trend toward increased methylmercury concentrations in commercial species can be seen in the data (see Section III of this report). The implication for the risk and benefit assessment results appears to be negligible.
6	<i>Mercury Speciation Factor:</i> Most of the mercury in fish is methylmercury, but for ease of lab analysis the amount of total mercury in fish is typically measured, rather than the methylmercury. How much of the	Fixed conversion factors were used to adjust for mercury content. While most of the total mercury is methylmercury in most seafood species, there is good evidence that shellfish is much less. The conversion factors are based on a study published by Height and Cheng (2006) in which they estimated how much mercury was methylmercury in finfish and shellfish. The assumption is that these conversion factors enable us to correctly estimate the amount of methylmercury in fish based on the previously measured amount of total mercury.	Although there are minor variations among and between species in the inorganic contributions to the total content, these variations are considered negligible.

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	total mercury is methylmercury?		
7	<i>Serving Size Adjustment:</i> Are serving sizes the same as they were when measured in the CSFII survey?	Because current per capita consumption is more accurately measured by market share disappearance, we applied a correction factor of 11% to make the CSFII-derived serving estimates consistent with market data.	Using CSFII serving sizes without a correction factor would generate slightly lower estimates of exposure to both fish and mercury.

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### Estimating Species and Amounts of Fish that People Eat

The objective for the stage of the exposure assessment was to estimate commercial fish consumption, i.e., the amounts and species that people consume, for the U.S. population over a period of time long enough to capture infrequent fish consumption and to characterize chronic (i.e., steady state) exposure. We chose a one year time period for this purpose.

In order to estimate amounts and species consumed over a period of one year, we extrapolated average daily fish consumption over a one year period from the results of short term food consumption surveys in which people were asked to recall what they ate on three days. We assume that this extrapolation yields a distribution that is reasonably representative of amounts and species of commercial fish consumed in the United States over a one year period.

We estimated U.S. fish consumption, i.e., amounts and species, using three sources of data:

- 1) The U.S. Department of Agriculture's Continuing Survey of Food Intake by Individuals (CSFII) survey conducted between 1989 and 1991 (three day survey)
- 2) The NHANES survey data from 1999-2002 (30 day survey)
- 3) National Marine Fisheries Service market share data on consumable commercial fish (2005).

The three-day survey was the U. S. Department of Agriculture Continuing Survey of Food Intake by Individuals (CSFII) (USDA 1993). It surveyed both men and women and obtained information about portion sizes that they ate. These data were statistically representative of the U.S. population.

The 30-day survey was a fish and shellfish consumption frequency questionnaire that had been administered as part of the NHANES survey during 1999-2000. It captured information about frequency and various categories of fish type, e.g., clams, tuna, swordfish, and salmon. However, this survey only involved women of childbearing age and children up to 11 years of age and did not obtain information about serving size. These omissions made it impossible for us to rely solely on the 30-day survey for our exposure assessment. Since the three-day survey provided information lacking in the 30-day survey, and vice versa, we used the two surveys together.

We used data from the National Marine Fisheries Service of the U.S. Department of Commerce (NMFS 2007) on "edible (for human use) meat weight" for individual commercial fish species that are imported into, or landed in, the United States in order to develop a rank order of popularity for commercial fish. We used these data to help estimate the types of fish consumed over a year. These data were used to supplement the short term survey data for characterization of long-term variation in species consumed over an entire year. NMFS market share data were also used to adjust portion sizes to

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reflect current levels of consumption. Since the NMFS data are more recent, they more accurately reflect current national patterns of fish consumption.

### Variations in the Species that People Consume

In order to estimate the species of fish that people eat, we developed and implemented the following process:

Using the 30-day survey: For each individual in the survey who ate at least four fish meals during the survey period, we developed a “repetition ratio” to reflect the extent to which the individual ate the same fish or ate a variety of fish. The mathematics of the “repetition ratio” are provided in Appendix A. We assume that the distribution of “repetition ratios” from this survey is representative of the entire U.S. population, even though the survey only involved women of childbearing age. This distribution is described in detail in Appendix A. We then applied the “repetition ratios” to the results of the three-day survey since that survey was representative of the U.S. population rather than just women of childbearing age.

Using the three-day survey and the NMFS market share data: The individuals in the three-day survey reported eating fish from zero to four times during the survey period. For each of the 3,525 individuals in the survey who ate at least one fish meal during the period of the survey, we randomly selected one of the “repetition ratios” developed from the 30-day survey. On the basis of the “repetition ratio” that was selected for this individual, we would either assume that the types of fish reported for that person in the three-day survey were the only types of fish eaten by that person all year or that the individual ate other types of fish during the year in addition to the fish he or she reported eating during the three days, with the proportion of other fish determined by the repetition ratio. For example, if the “repetition ratio” were 0.5, we would assume that half of the person’s fish meals consisted of the fish he or she reported in the survey. We would fill in the other half with fish selected randomly from the NMFS market share data after “weighting” those fish based on popularity.

### Amounts of Fish that People Consume

Estimating amount of fish consumed in a year involved extrapolating the data on frequency and serving size from the three and 30 day surveys to (a) the entire U.S. population; and (b) a year’s worth of fish consumption. We developed formulas for this purpose as described in Appendix A.

### Estimating Levels of Methylmercury in Commercial Fish

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Data: Total mercury concentrations in most commercial fish species are available from FDA surveillance data (1990-2004) (FDA 2006). Data for a small number of minor species were obtained from reports from a National Marine Fisheries Survey (NMFS 1978) and the EPA (EPA 2000, page 59). These data are summarized in Table AA-2 in Appendix A.

Method: A realistic estimate of exposure to methylmercury requires consideration of the variations in concentrations of methylmercury that occur across and within commercial fish species. Variations in methylmercury concentrations from fish to fish are generally attributed to differences in size (Barber et al., 1972, page 638; Kraepiel et al., 2003, page 5,554) and age of the fish as well as differences in the concentrations of methylmercury in what the fish consumed.

The primary source of data for this part of the assessment was FDA's database of mercury concentrations in commercial species of fish. For many species in the database, FDA provides a mean, median, high-low range, and standard deviation based on all the samples in the database for the species in question. These values are for the total mercury in the fish, rather than for methylmercury, because the standard laboratory analysis is for total mercury. Recent analysis by FDA scientists has shown that for finfish, methylmercury constitutes about 95 percent of the total mercury in the fish, and about 45 percent of the total mercury in molluscan bivalve shellfish (e.g., clams, oysters, mussels) (Hight & Cheng 2006). Consequently, for purposes of this exposure assessment, we reduced the mercury values in the FDA database by five percent for finfish and 55 percent for bivalve molluscs. The methylmercury concentrations in bivalve molluscs tend to be low to the point of being essentially nondetectable, so the actual reductions for these species had a minimal impact even though the percentage was relatively high.

Rather than using only one number, like an average or another type of "best estimate," to represent this variation, we used a statistical simulation approach that allowed for the inclusion of a range of concentrations for individual fish in each species. Approaches for developing distributions of mercury in fish are described in "Mercury Concentrations in Individual Species" in Appendix A.

#### Estimating Methylmercury Intake from Consumption of Commercial Fish

The model for the fetal neurodevelopmental endpoint requires that we calculate the exposure to methylmercury for women of childbearing age. Such a calculation is not essential to the modeling for fatal coronary heart disease or stroke, however, since the data employed in those models come from studies of fish consumption in which the exposures to methylmercury were not measured.

The modeling involved extending our statistical simulation modeling for amounts and types of fish by selecting a value for the concentration of methylmercury in each type of

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fish from the distribution of methylmercury values for that fish. A new value was randomly selected for each iteration of the model.

### Converting Dietary Methylmercury Intake to Hair Levels of Methylmercury

The next step involved estimating the actual level of methylmercury in the body on the basis of dietary intake. As indicated previously, methylmercury is excreted with a half life of around 50 days; consequently, the level of methylmercury in a person's body would not be identical to their accumulated daily intake.

As also indicated previously, mercury concentration in scalp hair is the most commonly used biomarker of a person's body level of methylmercury. Much of the data from scientific studies that we use in the assessment of neurodevelopmental risk to the fetus measure the "dose" of methylmercury to the fetus in terms of the concentrations of methylmercury in the mother's hair. We retain this measure of dose in the fetal neurodevelopment assessment.

In order to do so, however, we first had to convert dietary intake to mercury blood levels and then convert from blood levels to hair levels. We converted to blood levels by using the results from a study (Sherlock et al., 1984) with controlled exposures to fish that related dietary mercury to blood levels. Estimations of hair levels from given methylmercury blood levels were calculated with a distribution developed from the 1999-2000 NHANES survey. The impact of body weight on blood mercury was calculated using a function of body weight to the power of 0.44. The data and methodology we used for converting dietary intake into blood levels and then into hair levels are described in Appendix A.

Also, for purposes of conveying information in Table V-7, we wanted to estimate what hair levels of methylmercury would be from eating certain amounts of commercial fish over time. The main purpose of the table is to show the size of a beneficial effect on fetal neurodevelopment from eating various amounts of commercial fish (10<sup>th</sup> percentile of consumption through the 99.9<sup>th</sup> percentile of consumption). For the sake of context, we wanted to show what the methylmercury hair levels were likely to be for most people at each level of consumption. In order to do that, we had to assume how much methylmercury there was likely to be in the fish. We chose the average concentration of methylmercury in commercial fish weighted for consumption, i.e., popularity, 0.086 ppm. We then estimated the exposure to methylmercury by using the following equations:

$$\text{Blood } (\mu\text{g} / \text{L}) = \frac{\text{Hair ppm}}{0.303} \text{ (Weighted average ratio from NHANES 1999-2000 data)}$$

$$\text{Diet } (\mu\text{g} / \text{day}) = \frac{\text{Blood } \mu\text{g} / \text{L}}{0.85} \text{ (from Sherlock et al., 1984)}$$

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$$Fish (g / day) = \frac{Diet (\mu g / day)}{0.086 ppm}$$
 (0.086 ppm is average methylmercury concentration in U.S. fish, weighted for consumption.)

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Differentiating Between “Mercury” and “Methylmercury”  
For Purposes of Exposure Assessment

Much of the data available to us on exposure to methylmercury is actually reported as exposure to total mercury that includes both inorganic and organic forms of mercury. Inorganic mercury in the body primarily comes from sources other than fish. An important issue for our quantitative risk and benefit assessment, therefore, is estimating how much mercury in a person’s hair or blood is likely to be methylmercury from eating fish. In summary:

- We know that most mercury in fish is methylmercury. As stated previously in this report, methylmercury constitutes between 93-98 percent of total mercury in finfish and 38-48 percent in molluscan shellfish (Hight and Cheng, 2006). (Molluscan shellfish, e.g., clams and oysters, have such small amounts of total mercury in them per FDA’s monitoring program that the quantity of mercury that is not methylmercury in those species is tiny.) We took these percentages into account when calculating methylmercury exposure from fish.
- Most methylmercury in the U.S. diet comes from fish. Small exposures are possible, however, from eating other animals that were fed fish meal (Lindberg et al., 2004). As described in Appendix A, we calculate that about 0.1 ppb of methylmercury in the diet is from sources other than fish. We took this amount into account in our exposure assessment.
- People have mercury in their bodies in addition to methylmercury. We excluded mercury other than methylmercury. To do this, we used data from NHANES, described in Section II, that show both the total mercury and the inorganic mercury in each person surveyed. We can calculate the amount of methylmercury (i.e., organic mercury) in an individual by subtracting the inorganic mercury from the total mercury. This calculation also tells us what the ratio is between total mercury and methylmercury.
- People have mercury in their bodies even though they eat no fish. In NHANES there are respondents who reported eating no fish but whose hair or blood showed the presence of mercury. These people can be found through the 15<sup>th</sup> percentile of mercury exposure per NHANES.

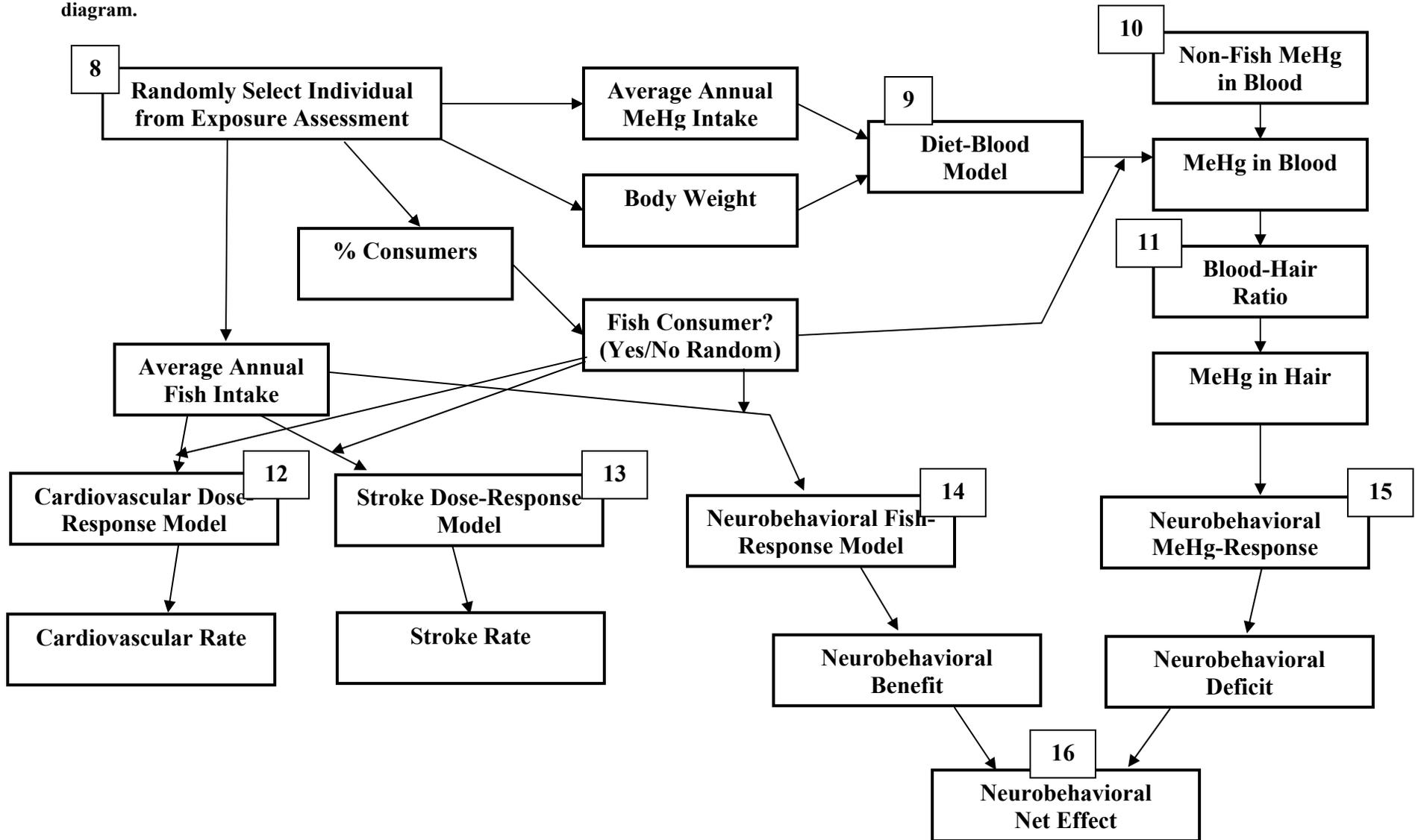
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## **(e) Data Selections and Dose-Response Models**

### Dose-Response Modeling Flow Diagram and Table

The following flow diagram and table provide an overview of the dose-response modeling and the key knowledge gaps, assumptions, and implications at each step. The assumptions primarily address how the available data are used and adjusted to provide a national picture of health effects associated with both commercial fish consumption and methylmercury. A discussion about the modeling is provided after the flow diagram and table.

Figure IV-3: Flow Diagram for the Dose-Response Modeling. The numbers correspond to numbers in Table IV-6 that describe knowledge gaps, assumptions and implications. The numbers start with “8”, Figure IV-2. Box “8” here carries the results of the exposure modeling over to this flow diagram.



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**Table IV-2: Dose-Response: Limitations in knowledge, Assumptions that Address those Limitations, and Implications for the Results. This table should be read in conjunction with Figure IV-3. The numbers corresponding to exposure modeling steps numbered in that figure.**

#	Knowledge Gap	Assumptions	Implications
8	Exposure Assessment Integration	Individual estimates of average daily intake of methylmercury and fish are carried over into the dose-response assessment, along with the body weight of the individual and the number of assumed eaters for each uncertainty estimate. As is widely assumed in the scientific literature, long-term average exposure from fish consumption is considered to be the best dose metric; other options are not considered. All dose-response data available to us for modeling have measured long-term exposure.	Implications for health of, higher exposures for shorter periods of time are not addressed in this modeling exercise.
9	Blood methylmercury concentrations were estimated based on dietary exposure.	The distribution of blood levels developed for this estimation is based on a 90-day human study with controlled exposures to methylmercury. We assume that this estimation provides reasonably accurate blood methylmercury concentrations.	Model uncertainty and sampling error are represented in the model. Again average, or steady-state, chronic exposure is presumed to be the best measure of dose. Since the confidence intervals are relatively narrow, this is likely to be a minor source of uncertainty.
10	Non fish exposures to methylmercury. What percentage is coming from other sources?	We assume a very small contribution from other sources, based on studies that have shown that animals such as chickens that have been fed fish meal will contain very small amounts of methylmercury.	This part of the model has no impact on assessing the health impact of consuming fish – it is included in order to make the model consistent with the NHANES survey values at the low end of the population distribution.

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11	Blood-Hair Relationship	<p>This relationship is characterized with an empirical distribution constructed from U.S. survey values (NHANES). As a result of potential environmental contamination at high concentrations and measurement error at low concentrations, However, for several reasons, some of the observed variability in hair/blood ratios may not be attributable to actual pharmacokinetic variation. Therefore, we assume:</p> <ul style="list-style-type: none"> <li>(1) That the actual distribution is narrower than the empirical distribution by some amount, i.e., that some of the observed variability is irrelevant. Therefore, we truncated the empirical distribution at both ends, with an uncertainty range of up to zero (i.e., no truncation) to 20% of each tail, which effectively attributes some of the variation to uncertainty.</li> <li>(2) That the relationship between blood and hair mercury is presumed to have the same proportion at all doses (i.e. linear).</li> </ul>	<p>This is significant source of uncertainty at the tails of the population distribution for the methylmercury-neurobehavioral effect, which uses hair-mercury as a measure of exposure. The implication is that the model has wider confidence intervals for the methylmercury effect than would otherwise have been the case.</p> <p>Regarding assumption (2): Sherlock et al. (1984) employed multiple dose levels of methylmercury in fish and demonstrated that the relationship is approximately linear. Consequently, this assumption is not a source of significant uncertainty.</p>
12	Shape of relationship between the fish consumption and CHD mortality	<p>Two different dose-response functions were used (the “meta-analysis” model, herein referred to as “CM,” and the “pooled analysis” model, herein referred to as “CP.” They were based on different assumptions in three key areas:</p> <p>1:  “CM”: Assumes a linear dose-response function.  “CP”: Assumes the possibility that it is not linear.</p>	<p>1: The “CM” function does not predict a ceiling on benefits (more fish always = greater benefits) but the “CP” function contains a ceiling at 20 grams per day of fish. Implication: the baseline central estimates are similar but beyond 20 grams per day the predictions would diverge. The “CM” function probably overestimates benefits at high levels of consumption and under represents the uncertainty associated with lower levels of exposure.</p>

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		<p>2:  “CM”: Assumes that the underlying mean value estimated from the different studies that were incorporated into the dose-response function represents the true value.  “CP”: Assumes that each study that was incorporated into the dose-response function represents a plausible true value.</p> <p>3:  “CM”: When dose = zero, there is no uncertainty about the rate of disease.  “CP”: When dose = zero, there is uncertainty about the rate of disease.</p>	<p>2: While the central estimates are similar for both functions, the confidence intervals for “CP” are notably wider, to the point where they include a small possibility of deaths caused by fish consumption.</p> <p>3: The “CM” function expresses less uncertainty at lower levels of exposure while the “CP” function expresses greater uncertainty.</p>
12 & 13	The health benefits of individual nutrients in fish.	Assumed that all commercial fish are alike for purposes of benefits. (The dosimetry for both dose-response functions treats all forms of fish equally).	The modeling exercise is not able to provide advice on the mix of fish types needed to maximize the benefits from fish consumption. However, the modeling for fetal neurodevelopment indicates that avoidance of higher methylmercury fish can reduce the attenuation of these benefits and minimize the likelihood of an adverse effect.
13	Shape of relationship between the fish consumption and stroke mortality.	Two different dose-response functions were used (the “meta-analysis” model, herein referred to as “SM,” and the “pooled analysis” model, herein referred to as “SP.” They were based on different assumptions in three key areas:  1:	<p>A significant source of uncertainty in the simulation model. While the central estimates are similar for both functions, the low-dose confidence intervals are notably wider in the “SP” analysis.</p> <p>1: The “SP” confidence intervals being wider to account for more uncertainty at low doses.</p>

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		<p>“SM”: Assumes a low dose slope that is different from a high dose slope, with most of the effect (and less of the uncertainty) being at low doses and less effect (but more uncertainty) at the high doses.  “SP”: Assumes less certainty at the low doses but is similar to SM at the high doses.</p> <p>2:  “M”: Assumes that the underlying mean value estimated from the different studies that were incorporated into the dose-response function represents the true value.  “P”: Assumes that each study that was incorporated into the dose-response function represents a plausible true value.</p> <p>3:  “SM”: When dose = zero, there is no uncertainty about the rate of disease.  “SP”: When dose = zero, there is uncertainty about the rate of disease.</p>	<p>2: The confidence intervals for “SP” are notably wider, to the point where they include a small possibility of deaths caused by fish consumption.</p> <p>3: The “SM” function expresses less uncertainty at lower levels of exposure while the “SP” function expresses greater uncertainty.</p> <p>The implications for all of the above are that while central estimates are similar, the size of the confidence intervals are dependent on some of the modeling assumptions made.</p>
14	Choice of indicator for neurobehavioral benefits	<p>Assume that early age verbal comprehension is a useful indicator of neurobehavioral development. The specific tests were MacArthur Communicative Development Inventory at 15 months of age and the language component of the Denver Developmental Screening Test at 18 months of age. Verbal comprehension, as measured by these tests, was selected because it matched criteria we developed</p>	<p>This is a significant source of uncertainty in the model because we used data from one large study only, and could not develop dose-response functions for other beneficial fish effects for purposes of comparison. However, the results from the modeling are generally consistent with results from studies that have been published in the scientific literature involving other aspects of neurodevelopment</p>

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		<p>for the inclusion of data for the fish beneficial contribution to net effect: (1) availability of individual subject data; (2) the “dose” was maternal fish consumption; (3) minimal confounding by methylmercury; (4) comparability, i.e., same general aspect of neurodevelopment, with age of talking endpoint. We lacked data on any other beneficial aspect of neurodevelopment that met these criteria. ....Endpoint choice; reason</p>	<p>measured at later ages in life.</p>
14	<p>Shape of the relationship between fish consumption and neurobehavioral benefits</p>	<p>One function with a linear slope derived from two measures of verbal comprehension performance in a single cohort. A linear function does not include a “plateau” above which greater fish consumption does not lead to greater benefits. Uncertainty bounds were placed on the linear slope to reflect that inclusion of other studies or endpoints would provide a wider range of plausible interpretation. Linear only – no model uncertainty, The central estimate is based on verbal measures in one cohort. No maximum effect parameter in the model.</p> <p>Major Assumptions:          (1) the use of a linear dose-response function with no ceiling on fish benefits          (2) Use of verbal comprehension for this set of health endpoints is indicative of the magnitude of the beneficial effect of fish on neurodevelopment.          (3) That the results have not been substantially confounded by methylmercury.          (4) That all commercial fish are alike in terms of</p>	<p>The uncertainty represented in the model is the primary source of uncertainty in the simulation model estimates.</p> <p>(1): Although the omission of a maximum effect is not likely to have an impact on the scenarios presented here, it could result in overestimation of benefits were seafood consumption greatly increased.          (2): See previous entry, above.          (3)2: Significant confounding could result in an underestimation the beneficial effect. This uncertainty is taken into account in the confidence intervals.</p> <p>(4)3: The fact that the dosimetry treats all forms of fish equally means that the model does not differentiate between species with respect to neurobehavioral benefits. The implication is that net effects could vary from diet to diet, within the range of the confidence intervals.          (5): Daniels et al. (2004) divided its cohort into four</p>

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		<p>benefits conferred.</p> <p>(5) The use of food consumption recall questionnaires to measure exposure to fish did not cause the beneficial fish effect to be under or overestimated to any significant extent.</p>	<p>fish consumption categories, from never eating fish through 4+ meals per week. Our regression analysis was conducted across all four categories so the consequences of misclassification would be small. An error in recall might mean that a person was placed in an incorrect consumption category, but the most likely consequence would be that the error would only span one of the four categories rather than span multiple categories. For that reason, we believe that errors in recall would not significantly affect the regression analysis.</p>
15	Choice of indicator for neurobehavioral deficits from methylmercury exposure	<p>Assume: a) age of talking is an useful indicator of neurodevelopment;</p> <p>b) the magnitude and size of the methylmercury effect on age of talking is similar to the methylmercury effect on a wide range of other neurodevelopmental endpoints measured when children were older.</p> <p>c) age of talking and early age verbal comprehension are similar enough to allow combining in a net benefits model</p>	<p>Regarding assumption a): From the scientific literature: age of talking requires the effective integration of a large number of complex sensory neural mechanisms (Marsh et al., 1995b).</p> <p>Regarding assumption b): Comparative analysis with other endpoints: the effect of methylmercury on age of talking per the modeling results are similar to the methylmercury effect on age of walking, IQ (Axelrad et al., 2007), and a wide battery of neurodevelopmental tests (Cohen et al. 2005b). The consistency occurs despite differences in study populations, age of children, outcome measures, and differences in analytical approaches.</p> <p>Regarding assumption c): from response to comment (per yesterday's discussion, needs rewrite)They both are in the same domain (verbal) of neurodevelopment. Moreover, as incorporated into the modeling, they were measured at essentially the same ages. The tests administered in the U.K. were</p>

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			at ages 15 & 18 months. The age of talking data from Iraq involved children who talked both sooner and later than these ages.
15	Shape of the relationship between methylmercury exposure and neurobehavioral deficits	<p>Three different functions. One extrapolates high dose (Iraq) effects developmental milestones using a combination of linear and nonlinear dose-response relationships. . A second produces a linear slope for IQ with the SEM serving as the uncertainty characterization, based on data from Faroes, Seychelles, and NZ. The third analyses, based on the same three studies, generated a distribution of Z-score slopes that reflect a wide range of different neurobehavioral performance measures. When converted to Z-scores, all three functions yield very similar central estimates. Consequently, there was no need to rely on any one function.</p> <p>Key assumptions:</p> <p>a)The methylmercury estimate was not significantly affected by a beneficial effect from fish.</p> <p>b)the Iraq data can be used to estimate age of first talking &amp; walking even though the exact ages of the children were unknown.</p> <p>c)The measures used adequately characterize the methylmercury effect on fetal neurodevelopment.</p>	<p>The uncertainty represented in the model is the primary source of uncertainty in the simulation model estimates. The three analyses taken together pretty much cover the landscape of possible sources of uncertainty. However, since each analysis taken on its own has some additional uncertainty, there may be some additional uncertainties associated with each function. The models may not be ideal for characterizing some specific neurobehavioral effects (e.g. effects motor or cognitive development).</p> <p>Regarding assumption a): We modeled Iraq alone and compared it to the combination of Iraq and Seychelles. There was only a small difference, mainly because the Iraqi data dominate the dose-response function.</p> <p>Regarding assumption b): The Iraqi mothers were able to place the ages of their children within 6 month blocks of their actual birth dates. Since the mothers knew the times of year (e.g., season) that their children were born, errors were likely to be no more than 3 months on either side of the actual birth date. The size of such errors would be small relative to the size of the effects seen in Iraq, where delays of over a year, including delays of several years, were</p>

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			<p>reported.          Regarding assumption c): the measures used were age of first talking (which was later combined with data on beneficial fish effects in order to measure overall net effect), age of first talking; IQ from Seychelles, Faroe Islands, and New Zealand; and a wide battery of test scores from Seychelles, Faroe Islands, and New Zealand. Since only age of talking was later incorporated into the net effect modeling, the other results (age of walking, IQ, and wide battery of test scores) were used for purposes of comparison and support. The results from the age of talking model are similar to the results from these other models. Collectively they reflect a wide range of neurodevelopmental performance.</p>
16	Metric for combining beneficial and adverse effects	Net effects are estimated through the use of Z-scores that convert the original measures to relative measures that scale each effect by the amount of variation that occurs in a normal population. This conversion is somewhat dependent on what population is taken to represent a normal population.	The standard deviations used to calculate Z-scores for the analysis of the pooled Iraq and Seychelles data are taken from the Seychelles (SD= 2.57 months for talking and 1.97 for walking). Iraq data were not used because there are very few data at low levels of exposure that can be used to characterize normal variation in the milestones. We believe that these that values are close to those for the U.S. and elsewhere. For age of walking, this assumption is supported by a study of children in six different countries, including the U.S., which yielded a standard deviation of 1.8 (WHO, 2006). We are unable to find reports of statistical descriptions or raw data in the U.S. or elsewhere on the verbal milestone (three words) used in Iraq and Seychelles.

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### Fetal Neurodevelopment: Adverse Methylmercury Contribution to Net Effect – Age of First Talking and Walking

The study of the poisoning event in Iraq, where methylmercury was ingested in bread, provides data on an association between prenatal exposure to methylmercury independent of fish and neurodevelopment. Unlike most studies of the effects of methylmercury, the Iraq data do not involve fish consumption. These data are probably the least ambiguous data on methylmercury toxicity in humans currently available, with effects unlikely to reflect methylmercury from fish consumption. If we were to use data from other studies, it would be necessary to statistically separate two closely correlated variables – methylmercury and fish – in order to estimate the methylmercury contribution. It is highly uncertain whether separation of such highly correlated variables can be done. .

The researchers in Iraq collected data on ages of first walking and talking that showed dose-response relationships between delays and prenatal exposures to methylmercury (Marsh et al., 1987). Moreover, they published individual results from each of the study participants. For these reasons, we used data on the attainment of early age milestones from Iraq to measure the methylmercury effect independent of fish.

We modeled dose-response functions for both age of first talking and age of first walking. However, as explained later in this section, we only used the function for age of first talking to represent the methylmercury contribution to the net effect. The results for age of walking were included for purposes of comparison along with IQ results and results from a range of neurodevelopmental tests.

One source of uncertainty from the data on age of first talking and walking from Iraq is the exact age of the children when they first walked and talked, since birthdays were not recorded in Iraq. The mothers provided the ages of their children within six month time frames. We believe these estimates are sufficiently accurate. Likely errors were no larger than a few months either way, which would be within a range of normal variation for these milestones. Moreover, we would not expect errors in recollection to be biased in favor of the children being either older or younger than estimated. Finally, at high doses, the adverse effects were larger than the six month time frames and could span years.

We were concerned, however, that a model that only used the data from Iraq would produce results of limited utility due to the small size of the study population (81 mother-infant pairs) and the fact that few subjects within this population experienced relatively low levels of exposure (Marsh et al., 1987). Because the Iraq data come from one of the most extreme exposures ever to occur with methylmercury, they might be viewed as anchoring the model at the upper end of observed effect but are much less robust at the low end. For these reasons we looked for additional sources of data where the endpoints measured were ages of first talking and walking.

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Another potential source of data for the consumption of methylmercury other than from fish was the study conducted in the Faroe Islands. The primary source of methylmercury in that study population was from pilot whale, although fish was also a source of methylmercury. The Faroe Islands study obtained early age developmental milestone data on age of first creeping, sitting, and standing (Grandjean et al., 1995), rather than walking and talking as were measured in Iraq. Because the milestones measured in Iraq and the Faroe Islands were not identical, we concluded that we could not combine them into the single dose-response function model that underlies this assessment. If we had used the milestone data from the Faroe Islands, we would have had to do so in lieu of the Iraq data. An additional impediment was that individual scores on developmental milestones (or on neurodevelopmental tests that were administered when the children were older) have not been made available from the Faroe Islands study. We would have had to use summary data that had undergone log(dose) transformation. For these reasons we did not incorporate data from the Faroe Islands for this aspect of the modeling (although data from the Faroe Islands were employed in IQ and other modeling described below).

The only other studies that measured age of first talking and walking were the studies in Peru (Marsh et al., 1995b) and in the Seychelles Islands (Myers et al., 1997). The individual subject data from Peru were never published and are not available primarily due to the age of the study (conducted between 1981 and 1984).

On the other hand, we have obtained the individual subject data on age of talking and walking from the Seychelles Islands. A potential problem with these data is that they derive from exposure to methylmercury solely from maternal consumption of fish ((Shamlaye et al., 1995, page 601). Nonetheless, we combined these data with data from Iraq in order to model a methylmercury effect independent of fish for the following reasons:

- Adding data from the Seychelles helps characterize the variation in the response at low doses where the contribution of methylmercury to the overall variation is relatively small. Also, adding data from 680 mother-infant pairs from the Seychelles produces a more robust assessment.
- Offsetting effects from fish were minimized. The model's characterization of the dose-response relationship (adverse) was still driven primarily by the Iraq data because the effects attributable to methylmercury were much larger in Iraq. As a consequence, the dose-response function from the Iraq-Seychelles was not substantially different from a dose-response function we calculated solely from the Iraq data. If we were to model solely from the Iraq data, the median estimate would be a delay of 0.048 months for each additional part per million of mercury in maternal hair. The Iraq and Seychelles combined median is a delay of 0.045 months for each additional part per million of mercury in maternal hair. (A general description of an “Iraq only” analysis can be found in Carrington et al., 1997.)

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The results from this modeling reflect several major assumptions. The first is that the predicted methylmercury effects have not been offset to any substantial degree by benefits obtained elsewhere in the diet. For example, we assume that the predicted effect has not been reduced by selenium obtained from vegetables or another source. The second assumption is that methylmercury might have a threshold of effect, i.e., that methylmercury might not produce an adverse effect below a certain level of exposure. Because we do not know what a threshold level might be for methylmercury, the probabilistic modeling that we employed included simulations of various possible thresholds, including no threshold. Third, we assume that the standard deviations we used to calculate Z-scores are close to those for the United States and elsewhere. We used a standard deviation from the Seychelles of 2.57 months for talking and 1.97 for walking. For age of walking, this assumption is supported by a study of children in six countries, including the United States, which yielded a standard deviation of 1.8 (WHO, 2006). Any difference between the standard deviation we use from the Seychelles and the standard deviation for the United States would not affect the original estimates for the adverse methylmercury contribution but it could slightly affect the estimates for net effect in the United States. The results from the adverse methylmercury contribution were converted to Z-Scores so that they could be incorporated in the net effect modeling. In any case, since milestone standard deviations do not vary greatly among populations, the choice of reference population represents a minor source of uncertainty for the Z-Score estimates.

A fourth assumption is that ages of first talking and walking are useful measures for neurological health. As stated by Marsh et al. (1995b):

“Age at which an infant talks, stands alone and walks without assistance may appear to be crude indices of development. However, they all require the effective integration of a large number of complex motor and sensory neural mechanisms, and when supported by neurological observations of behavior, vocalization, understanding, motor and sensory functions, they provide very good standards for comparisons on an individual infant or group basis.”

Both early speech and motor development have been associated with greater IQ at eight years of age; early speech development has been associated with reading comprehension at 26 years of age (Murray et al., 2007).

There is another perspective on these endpoints, however, as expressed by Crump et al. (1998): “The measures of effect in the Iraqi study (late walking, late talking, and neurological score) are relatively crude measures of neurological deficit and may not be as sensitive to methylmercury as more subtle but equally important effects that could be occurring, such as effects upon IQ.”

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To address this concern, we included in this risk and benefit assessment two analyses that were developed outside of FDA, one of which was on the effect of prenatal exposure to methylmercury on IQ (Axelrad et al., 2007) in the Seychelles, Faroe Islands and New Zealand; while the other was on the effect of prenatal exposure to methylmercury on a battery of tests administered in these three locations (Cohen et al., 2005b). We used these results in a comparative analysis against the results from age of talking. This comparative analysis reveals a consistency of outcome in certain respects.

#### Fetal Neurodevelopment: Comparative Analysis on the Adverse Methylmercury Contribution to Net Effect – IQ and Battery of Tests

One of these dose-response models used the single metric of IQ (Axelrad et al., 2007). Although there are some uncertainties associated with this metric, one advantage is that it incorporates a range of sub-tests in several “domains” of neurodevelopment, each of which increases the likelihood that it includes tests that could be sensitive to effects of methylmercury at low doses. Moreover, IQ’s predictive value for achievement throughout life has been studied extensively. There is a body of literature that can provide insight into the potential consequences for achievement later in life of very small changes in IQ that modeling might predict. Another advantage provided by the IQ model is that it addresses neurodevelopmental results that were measured from ages six through nine. If, as been hypothesized, effects from prenatal exposure to methylmercury are difficult to detect until a child becomes older, they could be more likely to appear at ages six through nine than at ages of first talking and walking.

As stated above, this model calculated changes in IQ as the response to methylmercury exposure using test results from the Seychelles Islands, Faroe Islands, and New Zealand studies. In the Seychelles and New Zealand studies, the researchers looked for an association between IQ score and prenatal exposure to methylmercury. The Faroe Islands study did not test for IQ per se, but Axelrad et al. incorporated results from some tests administered at age seven because these were regarded as being significant components of IQ. The three slopes were weighted and averaged into one linear IQ slope for methylmercury exposure. The model predicts a loss of 0.18 of an IQ point for each part per million of methylmercury in maternal hair.

Another dose-response model, published by Cohen et al. (2005b), calculated dose-response slopes from a wide battery of neurodevelopmental tests from Seychelles, New Zealand, and the Faroe Islands. These three slopes were combined into one linear slope, using weighted averages.

Cohen et al. (2005b) conducted two analyses with data from the Faroe Islands. The first analysis linearized the published log linear function in the range of U.S. exposures while the second analysis linearized in the range of exposures in the original study. Because the first analysis was based on a model in which effects become larger as doses become smaller (log(dose) transformation), we regard the second analysis as being the more

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plausible of the two. The authors calculated their dose-response function as if the effect involved IQ points. The second, more plausible analysis, predicts a loss equivalent to 0.2 of an IQ point for each part per million of methylmercury in maternal hair (Cohen et al., 2005b, page 362).

An uncertainty associated with these dose-response functions is the extent to which they reflect methylmercury's contribution to the net effect without being significantly confounded by fish. As explained previously, we interpret both our age-of-first talking and age-of-first walking models as roughly indicative of a methylmercury effect independent of any offsetting benefits from fish consumption. We interpret these results similarly.

The majority of methylmercury in the Faroe Islands was from the consumption of pilot whale rather than fish (Grandjean et al., 1999). The nutritional profiles of pilot whales and fish are not the same (Julshamn et al., 1987) so there was less opportunity for confounding by nutrients in fish than there would have been if the source of the methylmercury had only been fish. The IQ results from New Zealand also appear to reflect high exposures to methylmercury relative to the amounts of fish consumed, i.e., exposures that derive from consumption of shark. The Seychelles results involved lower methylmercury fish than were consumed in New Zealand but the IQ slope calculated from these data by Axelrad et al. (2007) was adverse, suggesting that fish confounding was not substantial. In total, we assume that confounding by fish did not significantly alter these results, although it probably did occur to some degree.

#### Fetal Neurodevelopment: Beneficial Fish Contribution to Net Effect – Early Age Verbal Comprehension

In order to develop a dose-response function for the beneficial fish effect we looked for data that showed an association between maternal consumption of fish and beneficial neurodevelopmental outcomes. Because we wanted to calculate a dose-response function that we could then combine with the adverse dose-response function for methylmercury, we looked for endpoints that were either identical or reasonably comparable to early age milestone data on first talking (early age verbal) and/or first walking (early age motor). We also looked for individual subject data rather than data summaries. We wanted to use an association from fish rather than from nutritional supplements, but with only minimal confounding from methylmercury.

The study that met these criteria was that of 7,421 mother-infant pairs in the ALSPAC study in the United Kingdom (Daniels et al., 2004). The study measured associations between maternal fish consumption and subsequent test scores. For a subset of its cohort it also measured associations with prenatal methylmercury exposure and test scores but

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found none.<sup>11</sup> For that reason we concluded that the fish consumption results were not confounded by methylmercury to any significant degree. Although the neurodevelopmental outcomes measured in the children did not include age of talking, the tests did include verbal comprehension at young ages, i.e., vocabulary comprehension on the MacArthur Communicative Development Inventory (MCDI) at 15 months of age and the language component of the Denver Developmental Screening Test (DDST) at 18 months of age. Furthermore the children were of the same age as children who first talk. In light of the similarity in age to age of first talking, we assume that these results were comparable -- even though not identical -- to the milestone results on age of first talking from Iraq and the Seychelles Islands. Moreover, individual subject results from these tests were available to us.

By contrast, the data available to us from that study did not include individual subject data on early age motor skills that would be comparable to age of first walking from Iraq and Seychelles. The DDST total scores included a motor component, but it could not be separated from total score. Consequently, for the fish contribution to the net effect, we developed a dose-response function based on early age verbal comprehension results from the United Kingdom. As an aside, because we now had data on early age verbal development for both the methylmercury contribution to the net effect and the fish contribution to the net effect, we elected to use the dose-response function for age of walking as part of the comparative analysis

We chose a linear dose-response function for this effect. A linear function does not include a “plateau” above which greater fish consumption does not lead to greater benefits. We did not use a model with a maximum effect parameter or other non-linear models because we have not yet discerned a shape to the dose-response function (the “fish” effect is small relative to the other sources of variance to allow model discrimination). We assume that such a plateau must exist but the results of several studies suggest that it must exist somewhere above the 95<sup>th</sup> percentile of consumption (12 ounces per week). Future modeling efforts may be in a better position to model a plateau, assuming it is not so high as to be irrelevant to U.S. consumption patterns. Daniels et al. (2004), which modeled dose response using quartiles for fish consumption, suggests a plateau but no other studies have investigated the existence of such as plateau.

The following table provides a study-by-study review from the standpoint of whether a study was included into, or excluded from, the modeling for fetal neurodevelopment. The table shows which studies were used and how they were used. For the studies that were not used, the table briefly explains why. Decisions about inclusion/exclusion essentially followed the criteria for selecting studies as provided in section (c), previously.

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<sup>11</sup> Appendix D contains an estimation of the exposures to methylmercury that were experienced by this cohort and compares them to U.S. exposures.

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It is worth noting that these studies involve exposures to methylmercury that are longer than “episodic,” e.g., single meal or a few meals clustered together. Most involve long term exposure. Consequently, the data on associations between methylmercury and fetal neurodevelopment provide a basis for evaluating risk from long term consumption of fish over time, but not from isolated meals that might cause a shorter term elevation in methylmercury. Whether exposure from a single meal or a series of meals eaten over a short period of time has the same impact on risk as a sustained exposure over time at identical levels cannot be determined from these data. The risk to the fetus from shorter term exposure to methylmercury, e.g., from a single meal, remains an untested question.

**Table IV-3: Primary study-by-study basis for including/excluding data in the risk and benefit assessment for fetal neurodevelopment.**

Study (location, authors, year)	Size of Study Pop.	Source of MeHg	Outcome Measures	Availability of individual subject data	Application to the Risk and Benefit Assessment
<b>Iraq</b> (Marsh et al., 1987)	81	Mother’s consumption of bread	--Age of first talking --Age of first walking --Neuro examination	Yes	Age of talking & walking data used in modeling performed in FDA for MeHg effect independent of any countervailing effect from fish.
<b>Seychelles Islands</b> (Myers et al., 1995)	Approx. 700	Mother’s consumption of fish	--Age of first talking --Age of first walking	Yes	Age of talking & walking data were combined with similar data from Iraq in modeling a MeHg effect described above.
<b>Peru</b> (Marsh et al., 1995b)	131	Mother’s consumption of fish	--Age of first talking --Age of first walking --Neurological examination	No	Not used. Individual age of talking data not available.
<b>Faroe Islands</b> (Grandjean et al., 1995)	583	Mother’s consumption of fish and pilot whale	-- Age of first sitting -- Age of first creeping -- Age of first standing	No	Not used. Individual subject data not available. Also, the developmental milestones that were measured (sitting, creeping, standing) are different from ages of first

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					talking & walking.
<b>Quebec: Cree Native Americans</b> (McKeown-Essen et al., 1983)	234	Not reported	Ages 12-30 months: --Denver Developmental Scale --Neurological examination	No	Not used. Individual subject data not available. Also, whether exposure to MeHg was solely from fish or also from marine mammals was not published.
<b>New Zealand</b> (Kjellström et al., 1986 & 1988)	38 at age 4; 61 at age 6 (“high exposure” part of study pop.)	Mother’s consumption of fish	Age 4: --Denver Developmental Screening Test --Neurological Screening Tests Age 6: --battery of tests including IQ	No	--Not used in modeling performed in FDA. Individual subject data not available. Also, data not comparable to early age verbal. -- IQ data were used in IQ modeling performed outside FDA and these results are included in this assessment.
<b>Seychelles Islands</b> (Myers et al., 1997 & 2003; Davidson et al., 1995a & 1998)	Approx 700	Mother’s consumption of fish	Battery of neurodevelopmental tests at ages 6.5 mo., 19 mo., 29 mo., 66 mo., & 9 yrs. IQ at age 9 yrs.	No	--Not used in modeling performed in FDA. Individual subject data not available. -- IQ data and other test results were used in modeling performed outside FDA and these results are included in this assessment.
<b>Faroe Islands</b> (Grandjean et al., 1998; Debes et al., 2006)	900+	Mother’s consumption of fish and pilot whale	Battery of neurodevelopmental tests at ages 7 & 14.	No	--Not used in modeling performed in FDA. Individual subject data not available. Summary data would be subject to log(dose)

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					transform. Also, data not comparable to early age verbal. -- 9-yr data that constitute aspects of IQ were used in modeling performed outside FDA and these results are included in this assessment.
<b>U.K.</b> (Daniels et al., 2004)	7,421	Mother's consumption of fish	15 mo.: --MacArthur Communicative Development Inventory 18 months: --Denver Developmental Screening Test	Yes	Data on verbal skills at 15 & 18 months used in modeling performed in FDA of net effect from fish consumption.
<b>U.K.</b> (Hibbeln et al., 2007a)	Approx. 9,000	Mother's consumption of fish	Ages 6 mo. through 8 yrs: --various neurodevelopmental tests including IQ	No	To the extent that Hibbeln et al. used the same data from the U.K. as Daniels et al., above, the data were used through the use of the Daniels et al., data.
<b>U.S.</b> (Oken et al., 2005)	135	Mother's consumption of fish	Ages 5.5 – 8.4 mos: --visual recognition memory test	No	Not used. Individual subject data not available. Also, data not comparable to early age verbal.
<b>U.S.</b> (Oken et al., 2008)	341	Mother's consumption of fish	Age 3 yrs: --Wide Range Assessment of Visual Motor Abilities test --Peabody Picture Vocabulary Test	No	Not used. Individual subject data not available. Also, data not comparable to early age verbal.
<b>U.S.</b> (Lederman et al., 2008)	329	Mother's consumption of fish	Age 3 yrs: --Bayley Scales of Infant Development psychomotor score Age 4 yrs: -- IQ	No	Not used. Study was published after completion of our assessment. Also: (1) individual subject data not available;

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					(2) summary data would have been subject to log(dose) transform; and (3) the outcomes that were measured were not comparable with early age communication.
<b>Poland</b> (Jedrychowski et al., 2006)	233	Mother's consumption of fish	Age 1 yr: --Bayley Scales Mental and Motor	No (with qualifications)	We have the Bayley Scales Mental Scores but the verbal component is not distinguishable from the total. (We did model dose-response from the Bayley scores separately in order to determine the size of the dose-response function.)
<b>Poland</b> (Jedrychowski et al., 2007)	374	Mother's consumption of fish	Ages 2 & 3 yrs: --Bayley Scales Mental and Motor	No	Not used. Individual scores not available.
<b>Denmark</b> (Oken et al., 2008a)	25,446	Mother's consumption of fish	Ages 6 & 18 mos.: --range of neurodevelopmental milestones	No	Not used. Study was published after completion of our assessment. Also: (1) individual subject data not available; and (2) the developmental milestones that were measured were different from ages of first talking & walking.

Fetal Neurodevelopment: The Net Effect from Eating Commercial Fish

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In order to estimate the net effect on fetal neurodevelopment from maternal consumption of commercial fish, we developed this model by combining the results from age of talking in Iraq and the Seychelles (representing “methylmercury”) with early age verbal comprehension results from the United Kingdom (representing “fish”), using Z-Scores (as described in Section V). We assume that this combination includes a certain amount of double counting but not to the extent that it would skew the results significantly one way or the other. That is, presumably it double counts methylmercury slightly from both the Iraq-Seychelles data and U.K. data (the U.K. results showed no adverse effect from methylmercury but we know that there were methylmercury in the fish) but presumably it also double counts fish benefits slightly through the inclusion of Seychelles data in the methylmercury modeling. In any event, we doubt that the beneficial fish contribution is overstated in this model since the size of the beneficial association seen in the Daniels et al. (2004) study (the source of the fish contribution data for this modeling) is not as large as beneficial effects reported in other studies.

### Fatal Coronary Heart Disease

A meta-analysis by He et al. (2004a) that examined the association between fish consumption and fatal CHD also included quantitative dose-response modeling. Consequently, we performed risk and benefit assessment modeling using both the data from the studies that He analyzed and the published He et al. (2004a) dose-response function. We reviewed each study that passed the He et al. (2004a) inclusion criteria, which we adopted as our own for purposes of the risk and benefit assessment. Based on these criteria, we added some studies to our own modeling that were published after He et al. (2004a) published their meta-analysis.

Because CHD death is a binary endpoint there is less information lost by using the population level statistics than would be for a continuous variable. This type of endpoint prompted us to develop a population model for CHD death rather than an individual-severity model, i.e., a model based on degrees of severity, as we did for neurodevelopment.

The studies included in He et al. (2004a) meta-analysis are listed as studies 1-13 in Table AA-14 in Appendix A. We used results from these studies in our assessment. Additional studies (14-16 in Table AA-14) are those that we identified through a literature search as having met the inclusion criteria but that were published after the He et al. (2004a) cut-off date. We incorporated these studies into a second model (the “CHD pooled analysis model”) that we performed in addition to the “CHD meta-analysis model,” as described below.

Of the 13 studies that He et al. (2004a) analyzed and that we modeled, six involve U.S. study populations. A substantial U.S. contribution to the data can be important because risk factors for CHD, including the potential risk factor of methylmercury in fish, may be affected by population characteristics. Different populations appear to experience

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different overall risks based on such things as diet (including the types of fish they eat), lifestyle, and genetics.

One of the studies analyzed by He et al. (2004a) included participants from Finland, the location of studies that initially reported an association between relatively high levels of methylmercury in fish and increased risk of CHD<sup>12</sup> (Salonen et al., 1995). The Finland study that was incorporated in He et al. (2004a) is not from the identical population that was studied by Salonen et al. and others. However, data from the Salonen et al. (1995) study population were included in another meta-analysis along with data from various other countries, including the United States (Whelton et al., 2004), that produced results similar to those produced by He et al. (2004a). Whelton et al. (2004) found an association between fish consumption and an approximately 20 percent reduction in the risk of fatal CHD.<sup>13</sup>

As stated previously, we divided the population by age and gender into the following categories: females aged 16-45, males aged 16-45, females aged 46 and above, and males aged 46 and above. The primary question for our assessment was whether fish consumption reduces the risk of fatal coronary heart disease, has no effect, or increases the risk in these population categories. Death rates from coronary heart disease vary by age and gender. For purposes of this modeling, ages 16-45 represent childbearing age for females.

For use in conjunction with our modeling, we estimated baseline rates for fatal coronary heart disease in the United States for these subpopulations by dividing the number of deaths from CHD per year for each subpopulation (NCHS, 2006) by the number of people in each subpopulation per the U.S. Census Bureau. Because the data from NCHS and the Census Bureau are in five year increments, the closest increment to “women of childbearing age” as we are defining it (16-45 years of age) is 15-44 years of age. Consequently, we calculated death rates for the age range of 15-44 and we assume that it is essentially the same as the death rate for the 16-45 age group. We then adjusted these rates for sex differences using data from Ho et al. (2005). Because Ho et al. (2005) did not contain rate information for persons under the age of 45, we used the relative rates for men and women in the youngest age group covered by Ho et al. (2005) (45-50) to correct for sex differences in the 15-44 subpopulations of both sexes. The resulting baseline rate estimates are presented in Table IV-4.

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<sup>12</sup> Because methylmercury exposure has been hypothesized to be a risk factor, it is important for this analysis to include data that can help to investigate the question of effect of methylmercury on CHD.

<sup>13</sup> We did not use the Whelton et al. (2004) meta-analysis as the basis for our modeling because it did not include a dose-response function. He et al. (2004a) included such a function.

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**Table IV-4: 2003 CHD Death Rates for each U. S. Subpopulation**

Sex	Age 15-44	Age 45 and above
Female	0.14 per 10,000	38 per 10,000
Male	1.3 per 10,000	51 per 10,000

“CHD Meta-Analysis Model:” He et al. (2004a) used a pooled meta-regression of relative risk to combine the results from all 13 studies into one estimate of effect. Details on the methodology are available in He et al. (2004a). We characterize results as being from the “CHD meta-analysis model” in order to differentiate them from the results from our “CHD pooled analysis model,” as explained later. The “CHD pooled analysis model” used a different approach in developing its dose-response function in order to reflect various uncertainties in the data.

“CHD Pooled Analysis Model:” We also estimate the effect of fish consumption on CHD death with an alternative model (the “CHD pooled analysis model”). This model incorporated results from the same studies as were used in the “CHD meta-analysis model” (i.e., studies 1-13 in Table AA-14 in Appendix A), plus three additional studies (i.e., studies 14-16 in that table). However, its methodological approach produces results that can be more reflective of uncertainties in the estimates than those predicted by other models.

The description of the differences between the “CHD pooled analysis model” and the “CHD meta-analysis model” is explained in detail in Appendix A. A brief summary follows.

First, the “CHD pooled analysis model” used separate dose-response functions that were developed from the data in each of the individual studies. These dose-response functions were then integrated into a common dose-response function by weighting according to sample size. By contrast, the “CHD meta-analysis model” involved averaging across studies to yield a single dose-response function, essentially treating all the data as if they were drawn from the same underlying population. This treatment does not allow for the possibility that these populations have significant differences in terms of confounding risk factors for CHD.

Second, the confidence intervals for the “CHD pooled analysis model” were based on sampling error for each individual data point. This was done so that we did not have to assume a common variance across all studies and dose groups, as was done in the “CHD meta-analysis model.”

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Third, in addition to a linear model, alternative non-linear (“sigmoidal”) models were used to describe the data. The linear model included a maximum effective dose parameter, meaning that the benefits from fish consumption peak at some point. All these models permitted greater effects at particular dose ranges than did the simple linear model used by He et al. and incorporated into the “CHD meta-analysis model.” A probability tree was used to include model choice as a source of uncertainty.

Finally, rather than using relative risk, the “CHD pooled analysis model” used adjusted group events. This approach allows sampling error from the low dose group to be represented instead of being fixed to a relative risk of one. As a result, the model is not forced through the illness rate reported for the control group.

The practical consequence of this approach is that the “CHD pooled analysis model” has confidence intervals that are wider than those produced by the “CHD meta-analysis model.” These wider confidence intervals reflect the uncertainty that arises from using data from different study populations, each with its own risk factors for CHD, and applying those results to the entire U.S. population. The narrower confidence intervals in the “CHD meta-analysis model” derive from the assumption that the study populations are collectively analogous to each other. In addition, because the models employed a maximum effect parameter, the dose-response function was nonlinear, with most of the benefit being conferred at levels of consumption below 25 g. per day.

### Fatal Stroke

Stroke is the third leading cause of death in the United States and the leading cause of adult disability according to the National Stroke Association (NSA 2008). It involves interrupted blood flow to an area of the brain due to an obstruction of an artery (ischemic stroke) or a break in a blood vessel (hemorrhagic stroke). Our modeling involved both types of stroke.

A meta-analysis that estimated a quantitative dose-response relationship between fish consumption and stroke was Bouzan et al. (2005). We developed a risk and benefit assessment on the basis of the Bouzan et al. (2005) dose-response relationship and the data that Bouzan et al. (2005) had incorporated into their meta-analysis. We refer to this model as the “stroke meta-analysis model.” We also estimated the effect of fish consumption on stroke death with an alternative model, as described below (the “stroke pooled analysis model”).

Because CHD death is a binary endpoint there is less information lost by using the population level statistics than would be for a continuous variable. This type of endpoint (death) prompted us to develop a population model for stroke death rather than an individual-severity model, i.e., a model based on degrees of severity, as we did for neurodevelopment.

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Table IV-5 shows the studies that were used in the “stroke meta-analysis” and “stroke pooled analysis” models. The “stroke meta-analysis model” used the six studies that Bouzan et al. (2005) used in their meta-analysis.<sup>14</sup> One of these studies (Caicoya 2002) did not involve multiple exposure groups per the inclusion criteria but we regarded the use of the Bouzan et al. (2005) published dose-response function as sufficiently important to justify using all the data that Bouzan et al. (2005) used. It would not have been possible to extract one study from that dose-response function. We could fully apply the inclusion criteria to the data used for the “stroke pooled analysis model,” however, since it involved the development of our own dose-response function. The “stroke pooled analysis model” did not incorporate the results from the Caicoya (2002) study.

Another meta-analysis, by He et al. (2004b), also investigated the relationship between fish consumption and stroke, but did not estimate a dose-response relationship. The “stroke pooled analysis model” used all but one of the studies identified in the He et al. meta-analysis. Consequently, the “stroke pooled analysis model” utilizes a larger database than does the “stroke meta-analysis model.” As Table IV-5 shows, the “stroke pooled analysis model” used five of the six studies that were used in the “stroke meta-analysis model” (there was significant overlap in the studies used by Bouzan et al. and He et al.) in addition to three used solely by He et al. and two others that were published after the He meta-analyses but that met the inclusion criteria: Nakamura et al. (2005), and Mozaffarian et al. (2005). In addition to omitting the Caicoya (2002) study, the “stroke pooled analysis model” also omitted the study by Keli et al. (1994) used by He et al. (2004b) because it only contained two exposure groups.<sup>15</sup>

**Table IV-5: Stroke Studies**

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<sup>14</sup> The point of departure for Bouzan et al. was a literature search conducted of Medline by Wang et al. (2004). Wang et al. screened the studies they found based on matters such as size and age of the study group, duration of the study, whether the study reported exposure only in terms of biomarker levels, and similar matters. Bouzan et al. then imposed three more criteria to ensure that the studies were appropriate for the purpose of quantitative dose-response evaluation, as follows:

- 1) The studies had to quantify risk relative to a no-intake or very-low-intake reference group
- 2) Only studies with designs rated by Wang et al. as "A" (least bias, results are valid) or "B" (susceptible to some bias but not sufficient to invalidate the results) are included
- 3) Includes both fatal and non-fatal strokes.

The application of these criteria lead Bouzan et al. to the five studies they utilized in their meta-analysis as listed in Table IV-5.

<sup>15</sup> Unlike the He et al., (2004a) meta-analysis for CHD, the He et al. (2004b) meta-analysis for stroke did not require that studies include more than two exposure groups due to the relatively limited number of studies available on stroke. For that reason He et al. (2004b) does not include a dose-response estimate for stroke.

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Study	Population Size	# of Events	Average Age	Avg. Follow up (yrs)	% Male	Site	Bouzan 2005	He et al., 2004 b	“Stroke Pooled Analysis Model”
Orencia et al. (1996)	1,847	76	47.6	30	100	USA	X	X	X
Gillum (1996)	2,059	262	62	12	100	USA	X	X	X
Gillum (1996)	2,351	252	62	12	0	USA	X	X	X
Iso et al. (2001)	79,839	574	34	14	0	USA	X	X	X
He et al. (2002)	43,671	608	53.4	12	100	USA	X	X	X
Caicoya (2002)	440 cases/ 473 controls			n/a		Spain	X		
Morris et al. (1995)	21,185	281	52	4	100	USA		X	X
Yuan et al. (2001)	18,244	460	54	12	100	USA		X	X
Sauveget et al. (2003)	40,349	1,462	56	16	100	Japan		X	X
Keli et al. (1994)	552	42		15	100	Netherlands		X	
Nakamura et al. (2005)	8,879	288	58.3	12	44	Japan			X
Mozaffarian et al. (2005)	4,775	626	58.3	12	42	USA			X

To parallel the risk and benefit assessment for coronary heart disease, we divided the population by age and gender into the following categories: females aged 16-45, males aged 16-45, females aged 46 and above, and males aged 46 and above. The primary question for our assessment was whether fish consumption reduces the risk of stroke, has no effect on stroke, or increases the risk in these population categories. We present the results in terms of population-level effects. The results are reported in terms of median (50<sup>th</sup> percentile) and a range of lower and upper bounds (5<sup>th</sup> and 95<sup>th</sup> percentiles, respectively).

For use in conjunction with our modeling, we first estimated baseline rates for stroke death in the United States for females ages 15-45 and ages 46+ and for males ages 15-45 and ages 46+ by dividing the number of stroke deaths per year for each subpopulation (NCHS 2006) by the number of people in each subpopulation per the U.S. Census Bureau. NCHS and the Census Bureau provide data in five year increments. The closest such increment to “women of childbearing age” as we are defining it (16-45 years of age) is 15-44. Consequently, we calculate the death rates for the 15-44 age groups and assume that it is essentially the same as the death rate for the 16-45 age groups.

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The baseline rates of death from stroke are shown in Table IV-6.

**Table IV-6: 2003 Stroke Death Rates for each U. S. Subpopulation**

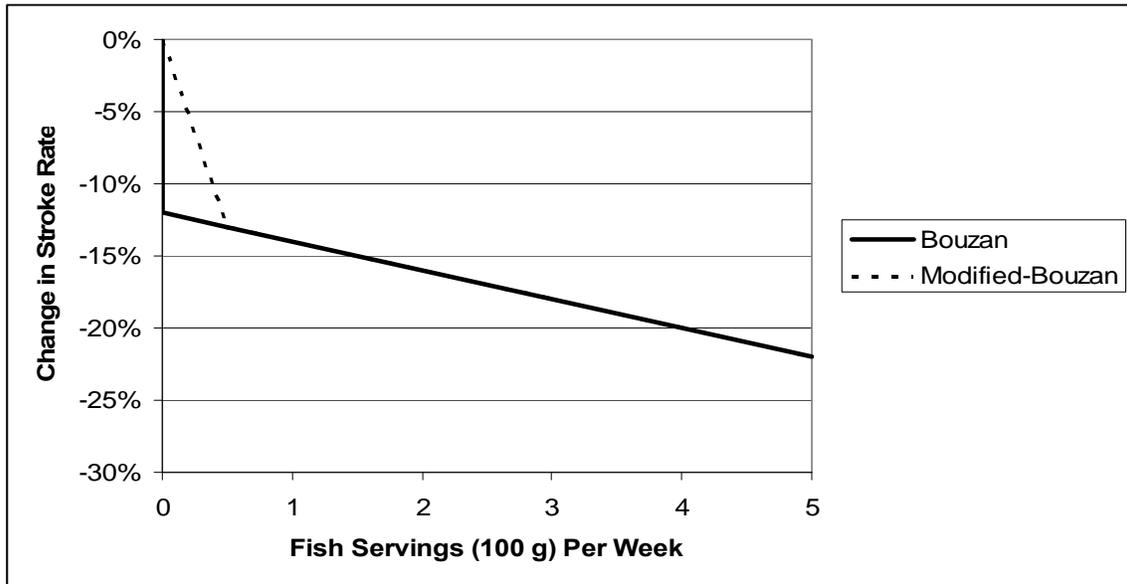
<b>Sex</b>	<b>15-44</b>	<b>45 and above</b>
Female	0.25 per 10,000	18 per 10,000
Male	0.24 per 10,000	13 per 10,000

“Stroke Meta-Analysis Model:” Bouzan et al. (2005) conducted a regression analysis with data from the five studies listed in Table IV-5 that investigated the relationship between the frequency of fish consumption and stroke. Their regression analysis generated a linear slope that did not go through zero, as shown in Figure IV-4. Bouzan et al. (2005) interpreted the intercept at the y-axis as an indicator of risk reduction associated with any quantity of fish consumption, even a small quantity.

We were not willing to adopt an assumption that a minute amount of fish consumption could have a substantial health impact. Consequently, we modified the Bouzan et al. (2005) dose-response function in order to reflect a more biologically plausible relationship between fish consumption and stroke. Specifically, we assumed that the effect at low doses occurs between zero and 50 grams of fish per week. This amount roughly corresponds to the low end of the range of the data used in the Bouzan et al. (2005) analysis. Thus, the Bouzan et al. (2005) model’s 12 percent reduction in risk that it had attributed to a fish consumption of zero was modeled, instead, as a gradual increase up to 50 grams of fish per week. The resulting dose-response function is shown in Figure IV-4.

**Figure IV-4. Dose-response function for Stroke. The intersection of the dotted line and the straight line represents the lowest dose that Bouzan et al. (2005) modeled.**

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“Stroke Pooled Analysis Model:” As explained previously, we developed a second model for the effect of fish consumption on risk of fatal strokes that used the data from four of the studies used in the “stroke meta-analysis model” as well as most of the data that had been evaluated in the meta-analysis conducted by He et al. (2004b). In addition to utilizing a larger database, the “stroke pooled analysis model” used a methodological approach in which the uncertainties produced larger confidence intervals than were produced by the “stroke meta-analysis model.”

The “stroke pooled analysis model” developed separate dose-response functions from the data in each of the individual studies. These dose-response functions were then integrated into a common dose-response function by weighting according to sample size. By contrast, the “stroke meta-analysis model” involved averaging across studies to yield a single dose-response function, essentially treating all the data as if they were drawn from the same underlying population. This treatment does not allow for the possibility that these populations have significant differences in terms of confounding risk factors for stroke.

The confidence intervals for the “stroke pooled analysis model” were based on sampling error for each individual data point. This was done so that we did not have to assume a common variance across all studies and dose groups, as was done in the “stroke meta-analysis model.”

Finally, rather than using relative risk, the “stroke pooled analysis model” used group disease rates. This approach allows sampling error from the low dose group to be represented instead of being fixed to a relative risk of one. As a result, the model is not forced through the illness rate reported for the control group.

As with the CHD analysis, the practical consequences of these methodological approaches are wider confidence intervals, particularly at low doses, and a non-linear dose-response relationship with most of the benefits occurring with fish intake levels of 25 g. per day or less.

#### CHD and Stroke: Non-Fatal Events

The risk and benefit assessment for coronary heart disease and stroke estimated the effect of commercial fish consumption on fatal events only and did not estimate the effect on non-fatal events. For modeling purposes there were more data available on fatal than non-fatal events so we chose to defer modeling non-fatal events at this time. This would be an important area for future research.

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**SECTION V:  
QUANTITATIVE RISK AND BENEFIT ASSESSMENT  
RESULTS FOR SELECTED INDICATORS OF FETAL  
NEURODEVELOPMENT,  
FATAL CORONARY HEART DISEASE,  
AND FATAL STROKE**

**(a) Exposure Assessment**

Amount of Fish Consumed

Table V-1 shows daily fish consumption, by population group. The consumption is provided in terms of grams per day. To place grams per day in context, we can convert it into servings per week. Serving sizes vary among individuals and there is no universal serving size. If we assume a serving size of 100 grams, it produces a range of 0.97 – 1.38 servings per week for the mean daily consumption represented along the top row of the table. If we assume a serving size of 175 grams, which is about the size of a serving in the joint FDA/EPA consumption advisory on methylmercury (2004), the range becomes 0.55 – 0.79 servings per week for the mean daily consumption. The table also indicates that 12 ounces of fish per week (i.e., about 50 grams per day) -- the consumption advisory's recommended maximum for women who are pregnant or considering getting pregnant -- represents consumption in the vicinity of the 95<sup>th</sup> percentile for women of childbearing age (i.e., approximately five percent of women consume this much fish or more).

In addition to the results from our exposure modeling, Table V-1 provides average daily consumption taken from the 2003-2004 NHANES survey for purposes of comparison. Because our model is based in part on data from 1989-1991, Table V-1 also contains the most recent NHANES results in order to verify that our results are consistent with current consumption patterns.

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**Table V-1: Daily Fish Consumption (g/day); Median (5<sup>th</sup> percentile, 95th percentile)**

	<b>Women 16-45</b>	<b>Women 46+</b>	<b>Men 16-45</b>	<b>Men 46+</b>
Average	13.4 (12.7, 13.9)	15.1 (14.3, 16.1)	18.3 (17.1, 19.2)	19.0 (18.0, 20.6)
10th %tile	0.1 (0.0, 0.9)	0.2 (0.0, 1.3)	0.2 (0.0, 1.2)	0.3 (0.0, 1.7)
25th %tile	2.8 (2.0, 3.6)	3.4 (2.7, 4.3)	3.7 (2.7, 4.6)	4.6 (3.5, 5.8)
50th %tile	7.2 (6.4, 7.9)	8.4 (7.4, 9.1)	9.6 (8.3, 10.6)	10.8 (9.5, 11.9)
75th %tile	16.3 (14.9, 17.7)	18.4 (16.9, 19.6)	21.9 (19.6, 23.1)	22.7 (21.0, 24.5)
90th %tile	32.3 (29.3, 34.4)	36.4 (33.7, 39.5)	43.7 (40.1, 47.6)	44.4 (40.5, 49.5)
95th %tile	46.4 (42.1, 50.7)	53.7 (47.4, 60.5)	65.5 (58.5, 74.7)	65.1 (58.2, 75.3)
99th %tile	88.3 (74.4, 114.3)	101.5 (85.0, 128.3)	136.0 (106.8, 179.3)	131.8 (108.3, 178.4)
NHANES average for comparison	10.3	14.2	16.8	20.8

### Dietary Intake of Methylmercury

Table V-2 shows the results for women of child-bearing age (16-45). Recall that the mother's hair-mercury level during pregnancy is serving as a surrogate, or biomarker, for fetal exposure.

**Table V-2: Dietary MeHg from Fish (µg per day)**

	<b>Women 16-45<sup>16</sup> Median (5<sup>th</sup>, 95<sup>th</sup>)</b>
Average	1.4 (1.3, 1.4)
10 <sup>th</sup> %tile	0.0 (0.0, 0.1)
25 <sup>th</sup> %tile	0.2 (0.1, 0.3)
50 <sup>th</sup> %tile	0.7 (0.6, 0.7)
75 <sup>th</sup> %tile	1.6 (1.5, 1.8)
90 <sup>th</sup> %tile	3.4 (3.1, 3.6)
95 <sup>th</sup> %tile	4.9 (4.5, 5.5)
99 <sup>th</sup> %tile	10.3 (8.1, 12.8)

<sup>16</sup> Note that these are mercury levels in the mothers, not in the children. The dose-response data that are available on effects on the fetus are in terms of mothers' levels of mercury, not infants' levels. Therefore the conversion from what's in the mother to what's in the infant is part of the dose-response function and does not have to be estimated.

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Table V-3 shows the results from Table V-2 along with our conversions from dietary methylmercury from fish to blood and hair concentrations. These results in terms of hair mercury can now be used as input for the dose-response modeling.

**Table V-3. Model Estimates of Blood and Hair Mercury levels in Women of Childbearing Age (16-45)**

<b>Blood Hg (<math>\mu\text{g/L}</math>)*:</b>	<b>Population Percentile</b>	<b>Hair Hg (ppm)</b>
1.2 (1.2, 1.3)	Average	0.3 (0.2, 0.3)
0.1 (0.1, 0.1)	10th Percentile	0.0 (0.0, 0.0)
0.3 (0.2, 0.3)	25th Percentile	0.0 (0.0, 0.1)
0.6 (0.5, 0.7)	50 <sup>th</sup> Percentile	0.1 (0.1, 0.1)
1.5 (1.3, 1.6)	75th Percentile	0.3 (0.2, 0.3)
2.9 (2.7, 3.2)	90th Percentile	0.6 (0.5, 0.7)
4.3 (3.8, 4.8)	95th Percentile	1.0 (0.8, 1.2)
8.8 (7.4, 10.7)	99th Percentile	2.2 (1.8, 2.7)

\*parts per billion

## **(b) Fetal Neurodevelopment**

### Adverse Methylmercury Contribution to the Net Effect

How the Modeling Results are Expressed: As stated previously, FDA used results from age of first talking to represent the methylmercury contribution to the net effect. Results from age of first talking, IQ, and a battery of tests as described below were used for purposes of comparative analysis.

The age of talking and walking models estimate methylmercury’s contribution to the net effect in terms of length of delays. The other two models express the methylmercury effect in terms of decrements in IQ scores. One of these (Axelrad et al., 2007) actually involved measurements of IQ from the Seychelles and New Zealand, The other (Cohen et al., 2005b), involved measurements from a battery of tests administered in the Seychelles, Faroe Islands and New Zealand, the results from which the authors presented as being IQ. Consequently, in order to compare the age of talking and walking results against the results from Axelrad et al. (2007) and Cohen et al. (2005b), we converted the delays in talking and walking into Z-Scores, which are statistical tools described below that essentially measure the size of an effect. Z-Scores facilitate the comparison of results from one model to another. They also facilitate combining results from different models into a single model. We then converted the Z-Scores into a unit of measurement that is equivalent to the size of an IQ point. We refer to this units of measurement as “IQ Size Equivalents (IQse),” since they are not really IQ points.

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A Brief Explanation of Z-Scores: A Z-Score describes where a particular measurement or result (e.g., a child's weight) stands relative to other measurements or results within a group (e.g., the weights of other children in the group). Assuming that the data follow a normal distribution, a Z-Score describes how far a particular result is (above or below) from the average of all the results in the group. When a Z-Score is positive, the result exceeds the average, e.g., a child is heavier than the average weight in the group. When a Z-Score is negative, the result is below the average, e.g., a child that is lighter than the average. A positive Z-Score of exactly 1.0 means that the result exceeds the average by one standard deviation. In a normal distribution, 68 percent of all the results within a group will fall within one standard deviation of the average. A Z-Score of 1.0 typically means that a particular result is about 34 percent above the average for the group. A fraction of a Z-Score means that the result is above or below the average by that fraction of a standard deviation.

Z-Scores are used to indicate the relative size of a change in a result in a population. For example, if, as result of maternal consumption of fish containing methylmercury, a child talks slightly later or slightly sooner than otherwise would have been the case, the size of the change can be expressed as the difference between what the Z-Score would have been without any exposure to methylmercury and what it is as a consequence of that exposure. In this respect we are providing "net Z-Scores," i.e. the difference between one Z-Score and another.

Another feature of Z-Scores is that they can be used to compare results from different groups. A simple example involves two identical exam scores (e.g., two scores of 75) obtained in two different college classes. Converting each exam score to a Z-Score (which compares that exam score to the other exam scores in the class) will reveal whether they are likely to produce the same or different grades (assuming that both are graded on a curve). If one exam score produces a positive Z-Score, it means that the exam result was above the average for that class. If the other exam score produces a negative Z-Score, it means that the exam score was below average. In such a situation, the Z-Scores reveal that the grades will be different even though the exam scores were identical. If the two exam scores each produce positive Z-Scores, but one is larger than the other, the one with the larger Z-Score may result a higher grade even though both are above average.

Because Z-Score and IQ scores are linked to standard deviation, a Z-Score can be converted to IQ (or at least to the size equivalent of IQ) and vice versa. The standard deviation for IQ scores in the population is 15 IQ points. Consequently, Z-Scores can be converted into IQ points by multiplying them by 15 (Cohen et al., 2005c).

Age of First Talking: The model estimates that without any contribution by methylmercury to the net effect, the age of first talking would range from 10.9 months

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through 18.8 months, with a central estimate of 15.1 months.<sup>17</sup> This timeframe provides a frame of reference for the size of the methylmercury contribution. The table provides a median estimate and 95 percent confidence interval for the size of the methylmercury contribution at various percentiles of U.S. exposure (the 10<sup>th</sup> percentile through the 99.9<sup>th</sup> percentile). In the simplest terms, the size of the methylmercury contribution probably falls within the range provided by the confidence intervals. The median estimate is at the midpoint of that range so that half the values in the range are above it and half are below. Since no other value in the range meets this criterion, we regard it as the “best” estimate.

Table V-4 shows that the most likely delays are less than a day through the 95<sup>th</sup> percentile of exposure. As reflected by the confidence intervals, there is a small possibility of no delay through the 50<sup>th</sup> percentile of exposure. This possibility suggests that methylmercury has a threshold of effect, i.e., that below some level of exposure methylmercury does not produce an adverse effect. At the 99<sup>th</sup> percentile of exposure the median estimate reaches a delay of slightly over two days and then jumps to slightly over four days at the 99<sup>th</sup> percentile. Exposure to methylmercury essentially doubles between the 99<sup>th</sup> and 99.9<sup>th</sup> percentiles.

We converted units of time into Z-Scores by dividing the age of talking in months by 2.76, which is the standard deviation of the age of talking data from the Seychelles. We then converted the net Z-Scores to IQ Size Equivalents in order to compare these results to the IQ modeling results from Axelrad et al. (2007) and the results from a battery of tests that Cohen et al. (2005b) calculated on an IQ scale.

When compared to the size of an IQ point in the far right column of Table V-4, the delays are all equivalent in size to a fraction of an IQ point (median estimates), although at the highest confidence limit at the 99.9<sup>th</sup> percentile of exposure, it slightly exceeds one IQ point in size.

**Table V-4: Methylmercury’s adverse contribution to the net effect on fetal neurodevelopment as measured by delay in age of first talking. The effects are provided as delays in both days and hours. These delays are also provided in terms of changes in both Z-Scores and “IQ size equivalents (IQse).”**

<b>Hg Dose (ppm in maternal hair)*</b>	<b>Percentile of U.S</b>	<b>Delay in talking (days)</b>	<b>Delay in talking (hours)</b>	<b>Change in Z-Score</b>	<b>Change in IQse</b>
0.02	10th	<b>-0.0158</b> (-0.0277, 0.0000)	<b>-0.3788</b> (-0.6647, 0.0000)	<b>-0.0002</b> (-0.0003, 0.0000)	<b>-0.0029</b> (-0.0050, 0.0000)

<sup>17</sup> This estimate was calculated from data from the Seychelles Islands. We would expect an estimate for the U.S. population to differ somewhat, but not substantially. We made the estimate to provide a sense for how the delays predicted by the model compare to the total length of time that it takes a child to first talk.

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0.04	25 <sup>th</sup>	<b>-0.0399</b> (-0.0701, 0.0000)	<b>-0.9583</b> (-1.6814, 0.0000)	<b>-0.0005</b> (-0.0008, 0.0000)	<b>-0.0072</b> (-0.0127, 0.0000)
0.12	50 <sup>th</sup>	<b>-0.1109</b> (-0.1946, 0.0000)	<b>-2.6616</b> (-4.6695, 0.0000)	<b>-0.0013</b> (-0.0023, 0.0000)	<b>-0.0201</b> (-0.0352, 0.0000)
0.30	75 <sup>th</sup>	<b>-0.2713</b> (-0.4759, -0.0520)	<b>-6.5106</b> (-11.4217, -1.2487)	<b>-0.0033</b> (-0.0057, -0.0006)	<b>-0.0491</b> (-0.0862, -0.0094)
0.63	90 <sup>th</sup>	<b>-0.5914</b> (-1.0224, -0.1818)	<b>-14.1938</b> (-24.5364, -4.3643)	<b>--0.0071</b> (-0.0123, -0.0022)	<b>-0.1071</b> (-0.1852, -0.0329)
0.98	95 <sup>th</sup>	<b>-0.9258</b> (-1.5794, -0.2816)	<b>-22.2188</b> (-37.9047, -6.7589)	<b>-0.0112</b> (-0.0191, -0.0034)	<b>-0.1677</b> (-0.2861, -0.0510)
2.16	99 <sup>th</sup>	<b>-2.0671</b> (-3.4954, -0.6835)	<b>-49.6107</b> (-83.8904, -16.4035)	<b>-0.0250</b> (-0.0422, -0.0083)	<b>-0.3745</b> (-0.6332, -0.1238)
2.83	99.5 <sup>th</sup>	<b>-2.7131</b> (-4.5905, -0.8962)	<b>-65.1140</b> (-110.1711, -21.5093)	<b>-0.0328</b> (0.0554, -0.0108)	<b>-0.4915</b> (-0.8316, -0.1624)
4.37	99.9 <sup>th</sup>	<b>-4.3902</b> (-7.4202, -1.4505)	<b>-105.3653</b> (-178.0840, -34.8128)	<b>-0.0530</b> (-0.0896, -0.0175)	<b>-0.7953</b> (-1.3442, -0.2628)

\* These hair levels have been calculated from our exposure assessment. They differ slightly, but not significantly, from the average hair levels in the NHANES sampling. The results of our modeling and the NHANES averages are both estimates. The NHANES results are estimates because they involve extrapolating from the NHANES survey sample to the general U.S. population. Our results are slightly lower than the NHANES results. One possible reason for the difference is that our modeling is focusing on methylmercury only while NHANES may be capturing some inorganic mercury in addition to methylmercury. Another possibility may be that our modeling screens out more of the methylmercury contribution from recreational fishing than does NHANES. NHANES is unlikely to capture unusual, localized patterns of recreational consumption but it does not actively screen out recreational consumption. Our modeling does some screening by using the NMFS data on commercial fish supplies, for example.

Age of First Walking: The model predicts that without any contribution by methylmercury to the net effect, the age of first walking would range from 6.3 months through 17.8 months, with a median estimate of 10.4 months. This timeframe provides a frame of reference for the size of the methylmercury contribution.

As with the table for age of first talking, Table V-5 provides a median estimate and a 95 percent confidence interval for the size of the methylmercury contribution at various percentiles of U.S. exposure (the 10<sup>th</sup> percentile through the 99.9<sup>th</sup> percentile). The table shows that for age of first walking, the most likely delays are less than a day through the 90<sup>th</sup> percentile of exposure. Above that, the median estimate is about a day-and-a-half at the 95<sup>th</sup> percentile, 3.5 days at the 99<sup>th</sup> percentile, and 4.6 days at the 99.5<sup>th</sup> percentile. As with age of talking, the delay nearly doubles to 7.4 days at the 99.9<sup>th</sup> percentile, commensurate with the increase in exposure between the 99.5<sup>th</sup> and the 99.9<sup>th</sup> percentiles.

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When compared to the size of an IQ point in the far right column of Table V-5, the delays are equivalent in size to a fraction of an IQ point through the 99.5<sup>th</sup> percentile of exposure (median estimates), and slightly exceed one IQ point in size at the 99.9<sup>th</sup> percentile.

The confidence intervals for the age of first walking model are notably wider than they are for the age of talking model. At one end, the confidence limit is always zero, i.e., no adverse contribution to the net effect, suggestive of a possible threshold of effect for methylmercury that is above all U.S. exposures to it through the 99.9<sup>th</sup> percentile of exposure. By comparison, the age-of-talking model predicts that a possibility of no adverse contribution only exists through the 50<sup>th</sup> percentile of exposure. The reason for this difference is that the individual data points (i.e., the results from specific individuals in the study populations in the Seychelles and Iraq) include one individual with relatively low exposure but a significant delay in age of talking. This data point reduces the threshold of effect in that model. By contrast, the age of walking model does not contain a similar data point. Suffice it to say that both the age of first talking and age of first walking models predict the possibility of a threshold of effect but differ as to where it might be; and, in any case, these predictions do not reflect a median, or “best” estimate in either model.

**Table V-5: Methylmercury’s adverse contribution to the net effect on fetal neurodevelopment as measured by delay in age of first walking. The effects are expressed as delays in both days and hours. These delays are also expressed in terms of changes in both Z-Scores and “IQ Size Equivalents (IQse).”**

<b>Hg Dose (ppm in maternal hair)</b>	<b>Percentile of U.S</b>	<b>Delay in walking (days)</b>	<b>Delay in walking (hours)</b>	<b>Change in Z-Score</b>	<b>Change in IQse</b>
0.02	10 <sup>th</sup>	<b>-0.0259</b> (-0.0930, 0.0000)	<b>-0.6225</b> (-2.2308, 0.0000)	<b>-0.0003</b> (-0.0011, 0.0000)	<b>-0.0047</b> (-0.0168, 0.0000)
0.04	25 <sup>th</sup>	<b>-0.0656</b> (-0.2368, 0.0000)	<b>-1.5748</b> (-5.6830, 0.0000)	<b>-0.00008</b> (-0.0029, 0.0000)	<b>-0.0119</b> (-0.0429, 0.0000)
0.12	50 <sup>th</sup>	<b>-0.1823</b> (-0.6530, 0.0000)	<b>-4.3744</b> (-15.6714, 0.0000)	<b>-0.0022</b> (-0.0079, 0.0000)	<b>-0.0330</b> (-0.1183, 0.0000)
0.30	75 <sup>th</sup>	<b>-0.4461</b> (-1.5908, 0.0000)	<b>-10.7057</b> (-38.1797, 0.0000)	<b>-0.0054</b> (-0.0192, 0.0000)	<b>-0.0808</b> (-0.2882, 0.0000)
0.63	90 <sup>th</sup>	<b>-0.9920</b> (-3.4041, 0.0000)	<b>-23.8073</b> (-81.6994, 0.0000)	<b>-0.0120</b> (0.0411, 0.0000)	<b>-0.1797</b> (-0.6167, 0.0000)
0.98	95 <sup>th</sup>	<b>-1.5640</b> (-5.2607, 0.0000)	<b>-37.5360</b> (-126.2561, 0.0000)	<b>-0.0189</b> (-0.0635, 0.0000)	<b>-0.2833</b> (-0.9530, 0.0000)
2.16	99 <sup>th</sup>	<b>-3.5134</b> (-11.5457, 0.0000)	<b>-84.3207</b> (-277.0978, 0.0000)	<b>-0.0424</b> (-0.1394, 0.0000)	<b>-0.6365</b> (-2.0916, 0.0000)
2.83	99.5 <sup>th</sup>	<b>-4.6147</b> (-15.1282, 0.0000)	<b>-110.7534</b> (-363.0763, 0.0000)	<b>-0.0557</b> (-0.1827, 0.0000)	<b>-0.8360</b> (-2.7406, 0.0000)
4.37	99.9 <sup>th</sup>	<b>-7.4767</b> (-24.2005, 0.0000)	<b>-179.4416</b> (-580.8112, 0.0000)	<b>0.0903</b> (-0.2923, 0.0000)	<b>-1.3545</b> (-4.3841, 0.0000)

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The IQ Model (Axelrad et al., 2007) and the Battery of Tests Model (Cohen et al., 2005b): The decrements estimated by the Axelrad et al. (2007) and Cohen et al. (2005b) models are shown in Table V-6. Because the results from both models were expressed as decrements in IQ points, we present them the same way. Moreover, since the results are close to each other, we show them as essentially one result.

**Table V-6. IQ loss from methylmercury predicted by Axelrad et al. (2007) and Cohen et al. (2005b)**

Percentile of exposure (Hg in hair): U. S. women of child-bearing age	Change in IQ (central estimates)
10 <sup>th</sup>	0.00 of an IQ point*
50 <sup>th</sup>	0.02 of an IQ point
90 <sup>th</sup>	0.13 of an IQ point
95 <sup>th</sup>	0.20 of an IQ point
99 <sup>th</sup>	0.43 of an IQ point
99.9 <sup>th</sup>	0.87 of an IQ point

\* This number is actually higher than zero, but is low enough to “round” to zero when only two digits to the right of the decimal point are shown.

The results from these models are close to the results from our age-of-first talking model and similar to the results from our age of first walking model in terms of size of effect. (Compare the “IQ Size Equivalents” in Tables V-4 and 5 to the results in Table V-6.) This consistency occurs despite the differences in study populations, age of children, outcome measures, and differences in the analytical approaches. It helps obviate concerns that our model has too narrow a focus relative to a broad range of potential measures of neurodevelopment, as well as the very young age of the children, could limit its ability to provide valid results.

#### Beneficial Fish Contribution to the Net Effect

Table V-7 reports the results from this model. The model essentially predicts the amount of improvement on the language components of the MacArthur Communicative Development Inventory at 15 months and the Denver Developmental Screening Test at 18 months as a consequence of maternal fish consumption. The table expresses these results as changes in Z-Scores. In the right column, the Z-Scores are converted to “IQ Size Equivalents.” The fish consumption column, i.e., the number of grams of fish eaten per day, reflects consumption of a variety of fish over time because the model does not differentiate among types of fish from a nutritional standpoint. Each estimate of fish consumption is associated with an estimated hair-mercury level in the box to the left of it. This hair-mercury level represents what a person’s exposure would be if each fish he or she ate contained 0.086 ppm of methylmercury, i.e., the average amount of

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methylmercury in commercial fish weighted for popularity. In this model, these hair-mercury levels are provided primarily for context since the model only measures the beneficial contribution of the fish independent of methylmercury.

As Table V-7 shows, when consumption involves a variety of fish containing, collectively, the average amount of methylmercury in commercial fish weighted by popularity, the neurodevelopmental effects predicted by the “beneficial fish effect” model are larger than the adverse effects predicted for methylmercury by the ages of first talking and walking models (median estimates) at every percentile of fish consumption and corresponding exposure to methylmercury. Even so, the beneficial effects do not exceed the size of one IQ point until consumption exceeds 44.2 grams of fish per day. Consumption beyond that amount produces benefits that are equivalent in size to just under two IQ points at 97.5 grams of fish per day; equivalent in size to 2.4 IQ points at 127 grams of fish per day; and equivalent in size to just under four IQ points at 205.7 grams of fish per day. At this highest level of fish consumption examined by the model, the upper limit of the confidence interval shows a small possibility of benefits equivalent in size to 7.5 IQ points.

**Table V-7: Fish’s beneficial contribution to the net effect on fetal neurodevelopment as measured by improvements in verbal scores on the MacArthur Communicative Development Inventory and the Denver Communication Test. The improvements are expressed in terms of changes in both Z-Scores and “IQ Size Equivalents (IQse).” Because the assessment did not measure the differences in beneficial contributions from species to species, these results essentially reflect eating a variety of fish over time.**

<b>Hg Dose (ppm in maternal hair) Estimated for a Corresponding Amount of Fish/ Day</b>	<b>Amount of Fish Consumed (grams of fish/day)</b>	<b>Change in Z-Score</b>	<b>Change in IQse</b>
0.02	0.8	<b>0.0010</b> (0.0003, 0.0020)	<b>0.0152</b> (0.0049, 0.0293)
0.04	2.0	<b>0.0025</b> (0.0008, 0.0048)	<b>0.0376</b> (0.0121, 0.0724)
0.12	5.5	<b>0.0069</b> (0.0022, 0.0133)	<b>0.1033</b> (0.0333, 0.1991)
0.30	13.3	<b>0.0168</b> (0.0054, 0.0324)	<b>0.2518</b> (0.0812, 0.4854)
0.63	28.6	<b>0.0360</b> (0.0116, 0.0694)	<b>0.5403</b> (0.1741, 1.0414)
0.98	44.2	<b>0.0557</b> (0.0179, 0.1073)	<b>0.8348</b> (0.2691, 1.6091)
2.16	97.5	<b>0.1229</b> (0.0396, 0.2369)	<b>1.8437</b> (0.5943, 3.5538)

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2.83	127.8	<b>0.1610</b> (0.0519, 0.3104)	<b>2.4155</b> (0.7786, 4.6561)
4.37	205.7	<b>0.2600</b> (0.0838, 0.5013)	<b>3.9007</b> (1.2573, 7.5188)

The Net Effect on Fetal Neurodevelopment from Commercial Fish: In order to estimate the net effect on fetal neurodevelopment from maternal consumption of commercial fish, we developed this model by combining the results from age of talking in Iraq and Seychelles (representing “methylmercury”) with early age verbal comprehension results from the United Kingdom (representing “fish”). The results were combined by converting them all into a common metric of Z-Scores and then adding them together. We converted these Z-Scores into “IQ Size Equivalents.”

“Average Commercial Fish” Results: As with the other models, we present results in a table that predicts effects at specific levels of fish consumption and methylmercury exposure (Table V-8). The disadvantage in this presentation is that, by necessity, it is limited to people who eat a variety of fish that, over time, contain both an average amount of methylmercury for commercial fish (0.086 ppm) and an average amount of nutrients that contribute to a beneficial net effect for fetal neurodevelopment.

There is also an advantage in this presentation, however, because it can estimate whether exposure to methylmercury through the 99.9<sup>th</sup> percentile of exposure from eating a lot of “average” commercial fish -- which are toward the low end of the spectrum in terms of methylmercury concentrations<sup>18</sup> – could result in a net adverse effect.

The results, as presented in Table V-8, are beneficial through the 99.9<sup>th</sup> percentile of exposure to methylmercury. This level of exposure requires the consumption of 205.7 grams of “average” commercial fish per day. For purposes of comparison, the current FDA/EPA consumption advisory recommends eating no more than 50 grams of fish per day. Neither the median estimates nor the confidence intervals surrounding each median estimate predict the possibility of an adverse effect.

Benefits tend to increase as both fish consumption and exposure to methylmercury increase. The benefits are the size of a fraction of an IQ point through the 95<sup>th</sup> percentile of exposure to methylmercury (involving the consumption of 44.2 grams of fish per day), but then increases to the size of about 1.5 IQ points at the 99<sup>th</sup> percentile of exposure (involving the consumption of about 98 grams of fish per day), and to the size of about three IQ points at the 99.9<sup>th</sup> percentile of exposure (involving 205.7 grams of fish per day). At this highest level the model also predicts a low possibility that the benefit could be as high as about 6.8 IQ points (the highest confidence limit of the confidence interval

<sup>18</sup> As stated previously, the “average” commercial fish weighted for popularity contains about an order of magnitude less methylmercury than the commercial species with the highest concentrations of methylmercury on average.

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surrounding the median estimate). Note that these predicted benefits are all slightly lower than those predicted for the beneficial contribution from fish. We attribute the difference to the adverse contribution of methylmercury to the net effect.

**Table V-8: The net effect on fetal neurodevelopment from eating commercial fish that, collectively, contain an average amount of methylmercury and an average amount of beneficial nutrients. Eating a variety of commercial fish over time should achieve this outcome. The results are expressed in terms of changes in both Z-Scores and “IQ Size Equivalent (IQse).”**

<b>Hg Dose (ppm in maternal hair) Estimated for a Corresponding Amount of Fish/ Day</b>	<b>Amount of Fish Consumed (grams of fish/day)</b>	<b>Change in Z-Score</b>	<b>Change in IQse</b>
0.02	0.8	<b>0.008</b> (0.0001, 0.0018)	<b>0.0126</b> (0.0018, 0.0268)
0.04	2.0	<b>0.0021</b> (0.0003, 0.0044)	<b>0.0310</b> (0.0043, 0.0660)
0.12	5.5	<b>0.0057</b> (0.0008, 0.0121)	<b>0.0851</b> (0.0115, 0.1813)
0.30	13.3	<b>0.0137</b> (0.0018, 0.0293)	<b>0.2054</b> (0.0276, 0.4389)
0.63	28.6	<b>0.0292</b> (0.0037, 0.0627)	<b>0.4373</b> (0.0561, 0.9405)
0.98	44.2	<b>0.0448</b> (0.0058, 0.0969)	<b>0.6714</b> (0.0866, 1.4531)
2.16	97.5	<b>0.0985</b> (0.0121, 0.2139)	<b>1.4778</b> (0.1816, 3.2090)
2.83	127.8	<b>0.1291</b> (0.0156, 0.2803)	<b>1.9361</b> (0.2345, 4.2044)
4.37	205.7	<b>0.2078</b> (0.0253, 0.4526)	<b>3.1177</b> (0.3788, 6.7895)

“Baseline” Results: We also modeled results from actual U.S. consumption of commercial fish by women of childbearing age, including diets involving fish that are both lower and higher in methylmercury. Because this version of the model involves fish that 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. Consequently, we present these results in terms of percentiles of the population that are likely to experience a particular effect, without associating these percentiles to specific levels of exposure or consumption. Table V-9 arrays these percentiles from adverse (lower population percentiles) to beneficial (higher population percentiles).

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The effects are presented as changes in Z-Score and “IQ Size Equivalents.” In summary, the model estimates that one-tenth of one percent of the population is likely to experience an adverse effect and that most of the remainder of the population is likely to experience a beneficial effect (although some may experience no effect one way or the other). These are the median estimates of effect. The confidence intervals surrounding these estimates include a small possibility of no adverse effect for anyone but also a small possibility of an adverse effect through 10 percent of the population. It is this probability of a net adverse effect for a small segment of the population that differentiates the “baseline” results from results involving identical exposures from methylmercury but only from the consumption of “average commercial fish,” e.g., from eating a variety of commercial fish over time.

**Table V-9: The net effect on fetal neurodevelopment on a population basis as a result of “baseline” consumption of commercial of fish, i.e., what women of childbearing age actually eat (as of about 2005). The population percentiles are arrayed from most adverse net effect (at the top) to most beneficial net effect (at the bottom). The results are expressed in terms of changes in both Z-Scores and “IQ Size Equivalents (IQse).”**

<b>Population Percentile</b>	<b>Change in Z-Score</b>	<b>Change in IQse</b>
0.1 Percentile	-0.003 (-0.046, 0.000)	-0.04 (-0.69, 0.000)
0.2 Percentile	-0.000 (-0.028, 0.000)	-0.00 (-0.41, 0.00)
0.3 Percentile	0.000 (-0.024, 0.000)	0.00 (-0.36, 0.01)
0.4 Percentile	0.000(-0.019, 0.000)	0.00 (-0.29, 0.01)
0.5 Percentile	0.000 (-0.018, 0.000)	0.00 (-0.27, 0.01)
1 <sup>st</sup> Percentile	0.000 (-0.011, 0.001)	0.00 (-0.17, 0.01)
5 <sup>th</sup> Percentile	0.001 (-0.002, 0.003)	0.02 (-0.03, 0.04)
10 <sup>th</sup> Percentile	0.002 (-0.001, 0.005)	0.03, (-0.01, 0.08)
25 <sup>th</sup> Percentile	0.004 (0.000, 0.010)	0.06 (0.00, 0.15)

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50 <sup>th</sup> Percentile	0.009 (0.001, 0.021)	0.14 (0.02, 0.31)
75 <sup>th</sup> Percentile	0.020 (0.003, 0.045)	0.30 (0.05, 0.67)
90 <sup>th</sup> Percentile	0.039 (0.007, 0.082)	0.58 (0.11, 1.23)
95 <sup>th</sup> Percentile	0.055 (0.011, 0.118)	0.82 (0.17, 1.77)
99 <sup>th</sup> Percentile	0.105 (0.022, 0.226)	1.58 (0.33, 3.39)
99.5 <sup>th</sup> Percentile	0.140 (0.028, 0.299)	2.10 (0.42, 4.49)
99.9 <sup>th</sup> Percentile	0.221 (0.048, 0.540)	3.32 (0.72, 8.09)
Most Adverse	-0.027 (-0.138, 0.000)	-0.41 (-2.07, 0.00)
Most Beneficial	0.311 (0.088, 0.788)	4.67 (1.32, 11.82)

“What-If” Scenarios: We modeled several “what-if” scenarios in addition to the recent “baseline” in order to predict how changes in fish consumption by women of childbearing age could affect their children’s neurodevelopment.

The results are presented as population shifts above or below the “baseline.” For purposes of these “what if” scenarios, we calculated the average individual effect on neurodevelopment for all children at the “baseline” as compared to what the average effect would be if their mothers ate no fish and were essentially exposed to no methylmercury during pregnancy. The “baseline” represents an average improvement in Z-Score of 0.017 (equivalent in size to an average improvement of 0.255 of an IQ point) from maternal fish consumption during pregnancy as compared to maternal consumption of no fish.<sup>19</sup> A change against the “baseline” is an increase or decrease in this average individual effect.

A summary of the results is presented in Table V-10.

**First “What If” Scenario: Women of Childbearing Age Limit Their Consumption to 12 Ounces a Week.** Under this scenario, women who consume 12 ounces or less of fish per week would not alter the amount or types of fish they eat. Those who are eating more than 12 ounces per week would reduce their consumption to exactly 12 ounces but would not change the types of fish they eat. (The third and fourth scenarios involve changes in types of fish.)

On an overall national basis, the average change against baseline is predicted to be a loss per child of 0.001 Z-Score (equivalent to the size of 0.015 of an IQ point) even though most children would not be affected one way or another (because roughly 95 percent of pregnant women do not eat over 12 ounces of fish per week). The change against “baseline” reflects the reduction in fish consumption by roughly five percent of pregnant women. (However, children whose mothers had to reduce their consumption of fish that were high in methylmercury could experience an improvement.) Again, an average for

<sup>19</sup> This is so even though at the “baseline,” a small fraction of the population will probably experience a net adverse effect. Because the overwhelming majority of people will experience a beneficial effect, the overall population average at the “baseline” is beneficial.

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all children shows how this scenario would affect the national average relative to the “baseline.”

**Second “What If” Scenario: Women of Childbearing Age All Consume 12 Ounces a Week.** Under this scenario, all women of childbearing age eat exactly 12 ounces of commercial fish per week. This scenario would require changes in consumption by most people. Twelve ounces of fish per week is about 40 pounds per year while per capita fish consumption is only around 16 pounds per year. Most people would have to increase their fish consumption substantially in order to maintain 12 ounces per week. Only a small minority (about five percent) would have to reduce consumption.

On an overall national basis, the predicted average change against “baseline” is a neurodevelopmental improvement per child of 0.038 Z-Score (equivalent to the size of 0.57 of an IQ point). This is the greatest average per-child gain in all of our scenarios due to the substantial national increase in fish consumption that would be needed for most people to achieve 12 ounces per week.

Children born to mothers who had to increase their fish consumption (most children) would generally experience increased benefits. However, if their mothers increased their fish consumption by eating a lot of fish that were relatively high in methylmercury, their benefits could be decreased to the point where the net effect for them could become adverse.

For children whose mothers had to reduce consumption down to 12 ounces per week (a minority), the model predicts they would generally experience a reduction in benefits. However, if their mothers’ reduced fish consumption involved eating less fish that were relatively high in methylmercury, an opposite result could occur.

**Third “What If” Scenario: Women of Childbearing Age Limit Their Consumption to 12 Ounces a Week of “Low Methylmercury Fish”:** As a modification to the first scenario, we estimated the impact if women of child-bearing age were to limit their weekly consumption to no more than 12 ounces of fish that are low in methylmercury.<sup>20</sup> Those who already eat 12 ounces or less of fish per week would continue to eat the same amount but would only eat fish that are low in methylmercury. Those who already eat over 12 ounces of fish per week would reduce to exactly 12 ounces and would eat only fish that are low in methylmercury. This scenario is more protective than the current FDA/EPA consumption advice because the advice allows consumption of all commercial species that average below 0.73 ppm (the average for king mackerel, one of the four commercial species that should be avoided during pregnancy per the consumption advice).

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<sup>20</sup> For purposes of this scenario, we used 0.12 ppm to represent fish that are low in methylmercury. This concentration is slightly higher than the average for all commercial fish weighted for popularity. Table AA-2 in Appendix A provides a list of species with their average mercury concentrations.

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On an overall national basis, the predicted average change against “baseline” would be a loss per child of 0.0004 Z-Score (equivalent to the size of 0.006 of an IQ point). The reductions in fish consumption within the population would produce losses that exceeded the gains from all the switches to fish that are low in methylmercury. Most commercial fish, including most the more popular species, are toward the low end of the spectrum in terms of methylmercury concentration, in that they contain from 5 – 10 times less methylmercury than the highest commercial species on average. Switching to fish that are low in methylmercury would not involve substantial changes in exposure to methylmercury for most people. On the other hand, the switch to fish that are low in methylmercury produces an average loss against “baseline” that is slightly smaller than the loss in the first scenario, in which women of childbearing age do not exceed 12 ounces of fish per week but eat any fish regardless of methylmercury content.

Specifically, children born to mothers who did not have to reduce their fish consumption or change the types of fish they ate would be unaffected. The model predicts that children born to mothers who did not have to reduce their fish consumption but did have to change at least some of the types of fish they ate would likely experience a benefit.

For children whose mothers had to reduce their fish consumption but did not have to change the types of fish they ate, the model predicts they would generally experience reduced benefits. Children whose mothers had to reduce their fish consumption and had to change the types of fish they ate could experience either reduced or an increased benefits depending upon the nature of the change.

**Fourth “What If” Scenario: Women of Childbearing Age Eat Only “Low Methylmercury Fish” with No Limit on Consumption:** This scenario enables a comparison of the 12 ounce per week limitation on fish consumption in the previous scenario against no limitation on consumption. In both scenarios, women of childbearing age are limited to fish that are low in methylmercury.

The only change against “baseline” in this scenario is a reduction in the concentrations of methylmercury in fish consumed by some people. Otherwise, the scenario is identical to the “baseline.” On an overall national basis, the predicted average change against “baseline” is a gain per child of 0.0012 Z-Score (equivalent to the size of 0.018 of an IQ point). This predicted gain derives from reduced exposures to methylmercury experienced by children whose mothers had to change at least some of the types of fish they ate.

**Table V-10: “What If” Scenarios for Fetal Neurodevelopment. The results are presented as changes in overall population effects above or below a baseline.**

Scenario	Change in Z-Score	Change Expressed as IQ Size Equivalence
<b>Baseline:</b>	Z-Score: 0.017	

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The effect on fetal neurodevelopment from recent fish consumption and the resulting exposure to methylmercury by women of childbearing age.	(0.002, 0.037)  (Average Z-Score for children is 0.017 higher than it would be if women of childbearing age ate no fish.)	Average improvement over eating no fish is equivalent to the size of 0.225 of an IQ point (0.03, 0.555)
<b>1<sup>st</sup> Scenario:</b>  Women of child-bearing age eat no more than 12 oz. of fish per week	Average Z-Score loses 0.0010 (-0.0001, -0.0036) from baseline.	Average loss is equivalent to the size of 0.0105 of an IQ point (-0.0015, -0.054)
<b>2<sup>nd</sup> Scenario:</b>  Women of child-bearing age eat exactly 12 ounces of fish per week	Average Z-Score gains 0.038 (0.008, 0.076) over baseline.	Average improvement is equivalent to the size of 0.57 of an IQ point (0.12, 1.17)
<b>3<sup>rd</sup> Scenario:</b>  Women of child-bearing age eat no more than 12 oz. of “low MeHg” fish per week	Average Z-Score loses 0.0004 (-0.0010, 0.0025) from baseline.	Average loss is equivalent to the size of 0.006 of an IQ point (-0.015, 0.0375)
<b>4<sup>th</sup> Scenario:</b>  Women of child-bearing age eat only “low MeHg” fish with no limit on consumption	Average Z-Score gains 0.0012 (0.0002, 0.0018) over baseline.	Average improvement is equivalent to the size of 0.018 IQ points (0.003, 0.027)

### **(c) Fatal Coronary Heart Disease (CHD)**

We present results from two models, which we refer to as the “CHD meta-analysis model” and the “CHD pooled analysis model” as described in Section IV.

#### Baseline Results:

The “CHD meta-analysis model” defines a linear relationship between fish consumption and CHD death in which every additional 20 grams of fish per day, on average, leads to seven percent lower risk of CHD mortality (He, et al., 2004a). No model uncertainty is included in this analysis.

In Table V-11, the bottom two rows reflect the “CHD meta-analysis model’s” estimates for the median change in CHD death rate and the median number of deaths due to current levels of fish consumption. Negative numbers in the fourth row indicate reductions in death rates due to fish consumption. The differences in the subpopulations reflect the differences in the overall rates in each subpopulation as well as differences in the amount