Spiller, P., van Wijngaarden, E., Adams, H., Strain, J., McSorley, E., Mulhern, M., Conway, M., Yates, A., Carrington, C., Bolger, P. M., Morgan, K., Taylor, C. M., Ralston, N., Crawford, M., Hibbeln, J., Brenna, J. T., & Myers, G. (2023). Net effects explains the benefits to children from maternal fish consumption despite methylmercury in fish. *NeuroToxicology*, *99*, 195-205. https://doi.org/10.1016/j.neuro.2023.10.010

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10.1016/j.neuro.2023.10.010

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Net Effects Explains the Benefits to Children from Maternal Fish Consumption Despite Methylmercury in Fish

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ABSTRACT:

In 2001 the U.S. Food and Drug Administration (FDA) issued precautionary advice to pregnant women to limit fish consumption over concerns that the methylmercury content might harm their children's neurodevelopment. This concern was based largely on results from an epidemiological study of mothers primarily exposed to methylmercury from consuming pilot whale. Subsequently, FDA and the World Health Organization/Food and Agriculture Organization (WHO/FAO) undertook independent assessments of fish consumption that considered net effects from both fish nutrients, primarily omega-3 fatty acids, as beneficial and methylmercury as harmful. Both assessments estimated that when mothers regularly consume fish during pregnancy, their children are likely to have improved neurodevelopment compared to children of non-fish eaters despite their exposure to methylmercury. These estimated improvements included gains of two to over five full scale IQ points from levels of maternal consumption that are achievable in most of the world. Consistent with those estimates, human research on fish consumption and child neurodevelopment from more than 200,000 mother-child pairs now collectively reports 51 beneficial associations with neurodevelopmental outcomes and three adverse associations, the latter with no discernable pattern. These associations include full scale IQ gains similar to, or somewhat higher than, those estimated by FDA and FAO/WHO. Also consistent with the FDA and FAO/WHO estimates, research has reported beneficial associations with fish consumption when pregnant women are exposed to methylmercury from fish in excess of the U.S. Environmental Protection Agency's (EPA) Reference Dose (RfD). Our analysis evaluates how the net effects approach as utilized by FDA and FAO/WHO provides a holistic explanation for these results with implications for public health policy. This concordance of net effects modeling and empirical scientific evidence supports a clarification of

current public health recommendations to focus on greater fish consumption by pregnant women for their children's neurodevelopment.

Keywords:
fish
methylmercury
net effects
neurodevelopment
omega-3
pregnancy

1. Introduction

Methylmercury (MeHg) is present in fish from natural biologic causes.[1] It is taken up by fish after being converted from mercury in the environment. The developing fetus is particularly susceptible to neurotoxic effects from MeHg based on evidence from industrial poisoning events in Japan and Iraq in the mid-20th century (Marsh, et al., 1987; Bakir et al., 1973; Harada, 1995). In those events exposures to MeHg by pregnant women exceeded typical exposures from fish consumption in the United States by 100 times or greater, causing clinically observable harm to their children. In some cases the children had intellectual deficiencies, cerebral palsy, deafness, and blindness. Since then, no similar events have been reported from anywhere in the world. Nonetheless, these events raised concerns about whether naturally occurring background levels of MeHg in fish might be causing subtle adverse effects in children that had not yet been detected, but that could have substantial public health implications if present.

In 2000 the National Research Council (NRC) of the U.S. National Academy of Sciences issued a report entitled "Toxicological Effects of Methylmercury." The report claimed that more than

[1] MeHg is the organic form of mercury found in fish. Laboratory analyses often test for total mercury because nearly all the mercury in fish is MeHg. In this paper we only use the term "MeHg" for consistency, even when referring to exposures that were measured as total mercury.

60,000 babies born each year in the United States were “at risk” of neurodevelopmental deficits due to their mothers’ consumption of fish during pregnancy (NRC, 2000). The NRC’s claim was derived largely from an epidemiology study in the Faroe Islands involving the consumption of sea mammals containing higher levels of methylmercury (MeHg) than most commercially available fish as well as other neurotoxicants. Epidemiology studies focusing on effects only from fish consumption during pregnancy had yet to be published.

Merriam-Webster defines “at risk” as “a situation where one is likely to meet with harm” (M-W, 2023). When the FDA asked the Chairman of the NRC committee that wrote the toxicology report to explain the derivation of its claim that more than 60,000 babies are born at risk, the Chairman responded that “at risk” referred to children born each year to mothers who had been exposed to MeHg over the Reference Dose (RfD) developed by the United States Environmental Protection Agency (EPA). EPA defines an RfD as “…an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime” (EPA, 1993). The Chairman further noted that it was not possible to estimate whether actual harm might be occurring within that population (personal correspondence of Dr. Goyer to Joseph Levitt, Director of FDA’s Center for Food Safety and Applied Nutrition, dated December 1, 2000, included in the supplemental materials).

Research results germane to this uncertainty were primarily available from two large, high quality epidemiology studies. One study in the Faroe Islands was reporting subtle adverse associations between prenatal exposures to MeHg and neurodevelopmental outcomes when consumption of pilot whale was the primary source of that exposure. The exposures were typically 10 times higher than most exposures in the United States and other toxicant co-exposures were present (Grandjean et al., 1997; Debes et al., 2006). The other study, in the Seychelles Islands, was reporting no consistent adverse associations between similar outcomes and exposures to MeHg that were somewhat higher but were solely from marine fish and there were no toxicant co-exposures (Davidson et al., 1998). There was considerable speculation within the scientific community about why the two studies were reporting different results (NRC 2000, pp. 312-3; IOM 2006, p.128). One possibility was that the marine fish consumed in the Seychelles Islands were in some way offsetting or protective against neurotoxic effects from MeHg due to their nutrient content while pilot whale in the Faroe Islands was not (IOM, 2006, p. 130).

In the face of this scientific uncertainty and in what it considered to be a protective measure, the FDA advised pregnant women in 2001 to limit their consumption of commercially available fish to no more than 12 ounces per week (FDA's 2001 advice provided in the supplemental materials). The advice was precautionary since there was no evidence of harm from consuming fish with naturally occurring levels of MeHg available to support it, but it could not be ruled out. FDA chose 12 ounces per week to avoid recommending consuming less fish than the American Heart Association was then recommending for heart health.[2] Subsequent survey research indicated that this advice caused many pregnant women who were already consuming less than 12 ounces per week to reduce their consumption still further or to eliminate it altogether (Oken et al., 2003). Subsequent survey research by FDA also indicated that pregnant women were eating less fish than non-pregnant women of the same age (Lando et al., 2012). A similar reaction was reported in the United Kingdom in 2023 in response to precautionary consumption

[2] This is based on the recollections of co-authors and former FDA staff P. Michael Bolger and Philip Spiller, who participated in that decision.

advice that emphasized types of fish to limit and avoid for safety (Beasant et al., 2023). Twenty-seven percent of those surveyed ate fish less often during pregnancy and four percent stopped eating fish altogether.

These findings raised questions about whether the advice might be inadvertently harming children since commercially available fish are known to contain omega-3 fatty acids and possibly other nutrients essential for brain development (FAO/WHO 2011, p. 4). Also in question was whether the concentrations of MeHg in those fish were sufficient to harm the nervous system. The balance of this net effect could theoretically vary depending on the quantities of beneficial nutrients and possibly of harmful MeHg.

2. The FDA and FAO/WHO Assessments of Net Effects: A Brief History

FDA's initial attempt to develop a scientific basis for its fish consumption advice focused on quantitative assessment that would estimate the likelihood and magnitude of harm to children's neurodevelopment from MeHg in commercially available fish consumed by their mothers. FDA reconsidered this risk-centric approach when results from the Avon Longitudinal Study of Parents and Children (ALSPAC) in the United Kingdom showed beneficial relationships between fish consumed during pregnancy and children's early language and communication skills (Daniels et al., 2004). The ALSPAC is a study based in the University of Bristol that has followed more than 14,000 parents and children since the 1990's to provide data on environmental and genetic factors that affect health and development (U. of Bristol, 2023). FDA subsequently redesigned its assessment to account for "net effects," i.e., beneficial effects from one or more nutrients in fish in addition to possible adverse effects from MeHg.

FDA initially estimated net effects on early age language development from ALSPAC data and subsequently added full scale and verbal IQ data to the assessment from the ALSPAC (Hibbeln et al., 2007). FDA completed its “Quantitative Assessment of the Net Effects on Fetal Neurodevelopment from Eating Commercial Fish (as Measured by IQ and also by Early Age Verbal Development) in Children” in 2014 (FDA 2014). FDA presumed that the net effects on these endpoints were likely to be reasonably representative of net effects on neurodevelopment generally (FDA 2014, section I(d)).

Meanwhile, in 2010 the FAO/WHO convened an “Expert Consultation” (EC) to compare health benefits of fish consumption during pregnancy against health risks associated with contaminants in those fish, including MeHg. It consisted of scientists from 11 countries with expertise in nutrition, toxicology, epidemiology, dietary exposure, and risk-benefit assessment. The EC focused on full scale IQ after concluding that a causal beneficial relationship between child IQ and the omega-3 fatty acid DHA (docosahexaenoic acid) in fish had been established (FAO/WHO 2011, p. 16). The FAO/WHO issued a “Report of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption” in 2011 (FAO/WHO 2011).

Both assessments estimated net effects from individual species and market types of fish. FDA did so for 47 species and market types that are commercially available in the United States. This focus was in keeping with its statutory mandate relating to the safety and applied nutrition of food in interstate commerce. The FDA assessment did not include recreational and subsistence catch such as from rivers, lakes, and streams nor did it include marine mammals, which are not consumed in most countries. The EC calculated net effects for over 100 species and market types available internationally and also excluded marine mammals.

3. Assessment Methods

3.1. The FDA Assessment of Net Effects

FDA's technical approach for each species and market type was to calculate a beneficial dose/response relationship for nutrients and a separate adverse dose/response relationship for MeHg. FDA theorized that these effects could occur simultaneously and independently of one another. FDA based this theory on an absence of evidence that either affects the existence of the other. FDA then added them together to calculate a dose/response relationship for the overall net effect. A net effect could be either beneficial or adverse depending on which of the two contributions were larger in a particular circumstance involving amounts and types of fish being consumed.

For the FDA assessment, the adverse impact on full scale IQ was represented by a dose/response relationship for MeHg's effect on IQ that had been calculated by a team from EPA and Harvard University (Axelrad et al., 2007). This relationship was a loss of 0.18 of an IQ point in children for each additional part per million of MeHg measured in their mothers' hair. (For context, over 90 percent of women of childbearing age in the US have been estimated to have less than one part per million of MeHg in their hair (FDA 2014, Table V-3). FDA theorized that this decline becomes proportionately smaller down to the lowest exposures, i.e., that MeHg has no threshold of effect below which it is not neurotoxic. Likewise, the adverse associations get proportionately larger with greater exposures as occurred in Japan and Iraq. FDA concluded that a linear dose/response relationship matched the evidence and was a common scientific conclusion per source documents (NRC, 2000, p. 297; Axelrad et al., 2007). FDA also acknowledged that if there were a threshold of effect FDA had no way of knowing where it might be.

Web Table 1 in the supplemental materials provides FDA's key theories, the theoretical basis for them, and their effect on the assessment's modeling.

It should be noted that FDA focused solely on MeHg as the adverse contributor to the net effects and did not take dioxins or polychlorinated biphenyls (PCBs) into account. FDA reasoned that these contaminants are not common in commercially available marine fish or aqua-cultured fish. In addition, FDA concluded that the science relating to dioxins and PCBs was not sufficiently developed to enable calculation of dose/response relationships between these compounds and neurodevelopment.

For the beneficial dose/response relationship, FDA used data from the ALSPAC study that showed a gain of multiple full scale IQ points from maternal consumption of at least eight ounces of fish per week (FDA 2014, figure C-17). Based on evidence from ALSPAC, the FDA theorized that the benefits increase along with consumption until they reach a "plateau," after which they no longer increase regardless of how much additional fish are consumed.

Even with a plateau, FDA estimated from the ALSPAC data that beneficial contributions from nutrients are substantially larger than the adverse contributions from MeHg at and beyond amounts that pregnant women in the United States typically eat. Consequently, the FDA estimated that each of the 47 species and market types is likely to be net beneficial through these amounts. Beyond the beneficial "plateau," however, FDA theorized that the net benefits gradually decrease since the adverse contribution from MeHg continues to increase. Under this theory, a gradual decrease could ultimately cause a beneficial net effect to dissipate completely and be replaced by an adverse net effect, although the amounts of fish necessary for this to occur typically exceed what is possible to consume (see Tables 1 and 2).

FDA modeled net effects twice for each endpoint based on alternative theories about the source of the beneficial contribution. One model was based on the theory that fish contain a "package" of nutrients including omega-3 fatty acids that collectively benefit neurodevelopment. The second model was based on a theory that only the omega-3 fatty acids in fish are the source of the benefits.

The endpoints for which there were adequate data to carry out this assessment were full scale IQ, verbal IQ, and early age language development. FDA presumed that the results for these endpoints would be reasonably representative of neurodevelopment generally because they: (a) occur at early ages (15-18 months for language development) and later ages (through 8 years for IQ); (b) encompass a range of neurodevelopmental skills (full scale and verbal IQ); and (c) also focus on a relatively narrow endpoint (early age language development).

3.2. The FAO/WHO Expert Consultation (EC)

The EC utilized FDA's net effects approach and implicitly incorporated most of FDA's theories. The primary exception was that the EC only modeled omega-3 fatty acids as the source of the beneficial contribution, although it acknowledged that there was emerging evidence that other compounds in fish may contribute to this effect (FAO/WHO 2011, p.3). The EC also quantitatively estimated net effects for individual species and market types although the number was considerably larger to include as many as possible that are internationally available.

The EC incorporated the same calculations for the MeHg contribution from Axelrad et al., 2007 but its estimates for the beneficial contributions from omega-3 fatty acids were somewhat larger than those estimated by FDA. For this reason, the EC's net gains for scale IQ were somewhat larger than those estimated by FDA.

The EC estimated and presented the omega-3 and MeHg contributions to full scale IQ when consumption was one serving per week (3.53 ounces), two servings per week (7.06 ounces), four servings per week (14.12 ounces), and seven servings per week (24.7 ounces). The beneficial contributions increased until they reached plateaus at various amounts depending on the omega-3 content of the particular fish, while the adverse contributions did not stop increasing through seven servings (24.7 ounces).

Because the EC did not estimate the beneficial and adverse contributions beyond 24.71 ounces (seven servings) per week, its primary modeling did not estimate amounts needed for the adverse contributions to become the larger of the two, i.e., for the net effects to become adverse. However, the rate of decline in IQ after benefits reach a plateau suggest that such amounts would be beyond what most people eat or could eat, similar to those estimated by FDA.

4. Assessment Results

4.1. The FDA Assessment of Net Effects

Based on the data then available to FDA and the theories it adopted, FDA chose to estimate the following data points for each of 47 commercial species and market types:

1. An amount per week that could produce the largest net benefit for full scale IQ, verbal IQ, and early age language development;
2. The size of the largest net benefit for these endpoints; and
3. An amount per week that could eventually cause the net benefit to become net adverse for these endpoints.

Tables 1 and 2 provide FDA's estimates for full scale IQ for seven of the 47 species and market types it assessed. The average MeHg and omega-3 concentrations for these seven species and market types range from relatively high to relatively low (FDA 2014, table V-8). Haddock is the exception, with a MeHg concentration that is close to the mean for commercial species and market types in the United States weighted for consumption, although its omega-3 concentration is relatively low (FDA 2014, section 2(c)).

Table 1 shows FDA's estimates when it theorized that a "package" of nutrients cause the beneficial effects. Because FDA could not identify with certainty which nutrients actually contribute to the benefits or in what proportions, FDA estimated what would happen if the "package" were the same for all species and market types. In this model, differences in net effects among species and market types are due solely to differences in average MeHg concentrations.

Table 2 shows the estimates when FDA theorized that the omega-3 fatty acids in fish are the sole source of the beneficial effects. In this model, differences in net effects are due to variations in omega-3 content in addition to variations in MeHg content. As a result, this model produced greater variation, particularly in amounts needed to obtain the most net benefits. For example, when the omega-3 content is relatively large, e.g., salmon, that amount can be considerably less than in the "package" model (4 ounces per week compared to 10 ounces per week). The opposite can also be true when the omega-3 content is relatively low, e.g., haddock, which requires 29 ounces per week to obtain the most net benefit as compared to 9 ounces per week in the "package" model.

FDA also conducted a sensitivity analysis in which it estimated how these outcomes would be affected if the toxicity of MeHg were 20 percent greater than in Tables 1 and 2. When FDA increased the toxicity by 20 percent, the direction of effect remained beneficial for all species and market types.

--- INSERT TABLES 1 AND 2 HERE ---

4.2. The FAO/WHO Expert Consultation

Table 3 contains the EC's estimates from its primary modeling for full scale IQ for the same species and market types that are in our Tables 1 and 2. The EC estimated that the beneficial contributions from omega-3 fatty acids reach a plateau at 5.8 IQ points while the adverse contributions from MeHg continue to increase. For that reason, the net benefits increase with consumption but then decline after the contributions from omega-3 fatty acids reach 5.8 IQ points. Even with that decline, the EC estimated that virtually all fish are net beneficial through at least 24.71 ounces per week (roughly the 99.9th percentile of consumption for women of childbearing age in the United States (FDA, 2014, table V-7). For ease of comparison, the largest beneficial net effect for each fish in the 5th column of Table 3 can be compared to FDA's estimates of these fish in the 5th column of Table 2.

The greatest net benefits in the FAO/WHO assessment are somewhat larger than in the FDA assessment but they might be smaller than what actually occurs. An analysis of data from the ALSPAC study showed that children of mothers who ate fish during pregnancy had full scale IQ scores slightly more than six points higher than children of mothers who ate no fish when all the mothers' exposures to MeHg had been essentially the same (Golding et al., 2022).

In secondary modeling which was essentially a sensitivity analysis, the EC estimated how these outcomes would be affected if the MeHg contribution were increased by nearly 400 percent. In this analysis eight fish with the highest concentrations of MeHg became net adverse (four immediately and four by 24.71 oz/wk) while the nearly 100 remaining fish continued to be net beneficial.

--- INSERT TABLE 3 HERE ---

5. Research on Fish Consumption during Pregnancy and Children's Neurodevelopment

Research on fish consumption during pregnancy and children's neurodevelopmental outcomes has flourished since the two assessments were initiated and continues to the present day. We examined this literature to determine how it matches the assessments' estimates.

We found five systematic reviews of the evidence for whether fish consumption during pregnancy affects children's neurodevelopment (Avela-Garcia & Julvez, 2014; Starling et al., 2015; Hibbeln et al., 2019; Snetselaar et al., 2020; VKM, 2022). These reviews were published from 2014 to 2022 and focused on outcomes from fish consumption studies. As a rule, they did not consider studies that examined nutrients or toxicants individually or from sources other than fish. We identified 30 high quality studies in which amounts of fish consumed by pregnant women were the independent variables and specific neurodevelopmental outcomes in their children were the dependent variables. These were published in peer reviewed scientific journals in the English language after 2000. Collectively, they included over 200,000 mother-child pairs in the United States, eight European countries, Japan, China, and the Republic of the Seychelles and included children whose ages ranged from infancy through 14 years (Williams et al., 2001; Daniels et al., 2004; Oken et al., 2005; Butz-Jørgensen et al., 2007; Hibblen et al., 2007; Gale et al., 2008; Lederman et al., 2008; Oken et al., 2008a & b; Mendez et al., 2009; Suzuki et al., 2010; Sagiv et al., 2012; Deroma et al., 2013; Valent et al., 2013; Hu et al., 2016; Julvez et al., 2016; Oken et al., 2016; Steenweg de-Graaff et al., 2016; Xu et al., 2016; Hisada et al., 2017; Mesirow et al., 2017; Furlong et al., 2018; Vejrup et al., 2018; Normia et al., 2019; Hamazaki et al., 2020; Julvez et al., 2020; Vecchione et al., 2021; de Lauzon-Guillan et al., 2022; Vejrup et al., 2022; Conway et al., 2023).

These studies inherently reflect “net effects” from the totality of the food’s contents, including beneficial nutrients and any environmental toxicants in the fish. By contrast, outcomes that have been associated with individual components of fish, e.g., MeHg or omega-3 fatty acids (Grandjean et al., 1997; AHRQ, 2016), have not always been consistent with outcomes from the whole food.

The fish consumption studies are primarily observational epidemiological. Although a clinical-type study would be the “gold standard” for research, a controlled study that dictated how much or what types of fish the pregnant participants could eat over an entire pregnancy would raise serious ethical questions as well as have other significant implementation concerns. For those reasons, controlled studies over entire pregnancies have not been conducted and these observational studies are the best results that can be obtained.

The absence of controls in observational studies raise uncertainties, however, including whether neurodevelopmental test scores appear to be related to amounts of fish but are really because of other factors, such as socio-economic advantages or disadvantages. To minimize this type of uncertainty, researchers have typically adjusted their outcome models in order to diminish possible confounding effects of other variables and ensure that the observed effects are likely to be due to fish consumption. Our analysis reports these adjusted outcomes.

6. The Assessments of Net Effects Provide a Holistic Explanation for the Research Results

6.1 Direction of Effect

The assessments estimated that each commercially available species and market type is likely to be net beneficial for children’s full scale IQ (FDA and FAO/WHO), children’s verbal IQ (FDA), and early age language development (FDA) through amounts beyond what most people consume or could consume. The theoretical basis for these estimates was net effects in which beneficial contributions from nutrients are substantially larger than adverse contributions from MeHg.

FDA presumed that this theoretical basis would apply to neurodevelopment generally. We are now able to examine whether that has been the case. Thirty studies provided 54 statistically significant outcomes (out of a total of 108 outcomes) in nine of 10 neurodevelopmental domains (identified here by a Pediatric Neuropsychologist (HRA), including those addressed by FDA and FAO/WHO. Fifty-one of the 54 statistically significant outcomes were beneficial while three were adverse. They measured differences in children's performance when pregnant women consumed some fish (amounts as decided by the study designers) versus when pregnant women consumed no fish or close to no fish.

Many studies reported multiple outcomes from different tests and at different ages. We focus on outcomes with children at their oldest ages in each study in order to capture results from the most sophisticated tests possible and provide an indicator for whether associations from maternal consumption during pregnancy remain over time. Even so, these ages could still be quite young, with roughly 30 percent of outcomes occurring at 18 months and less (Daniels et al., 2004; Oken et al., 2005; Hibbeln et al., 2007; Oken et al., 2008b, Valent et al., 2013; Hu et al., 2016; Julvez et al., 2016; Hisada et al., 2017; Hamazaki et al., 2020). The remaining outcomes ranged through 14 years of age, the oldest age tested in any of the studies. These age ranges closely match the earliest and latest ages in the relatively limited data available to FDA when it conducted its assessment. As stated previously, benefits at both early and later ages were one reason why FDA presumed that its results would be reasonably representative of neurodevelopment generally.

- <u>IQ</u>:
    - Full Scale IQ: Three outcomes were statistically significantly beneficial (Hibbeln et al., 2007; Gale et al., 2008; Lederman et al., 2008); none were statistically significantly adverse. The average per study gain was 5.15 full scale IQ points.
    - Verbal IQ: Five outcomes were statistically significantly beneficial (Hibbeln et al., 2007;Gale et al., 2008; Lederman et al., 2008; Mendez et al., 2009; Julvez et al., 2016); none were statistically significantly adverse. The average per study gain was 6.29 verbal IQ points. The greater gain for verbal over full-scale IQ suggests that the gains in full scale IQ are largely due to the gains in the verbal subset of full scale IQ. This difference matches the FDA assessment, which estimated greater gains for verbal IQ than for full scale, and also matches the results from the first study to analyze the relationship between maternal fish consumption and IQ (Hibbeln et al., 2007). By contrast, performance/non-verbal IQ does not appear to contribute substantially to the gains from full scale IQ.
    - Performance/Non-Verbal IQ: One outcome was statistically significantly beneficial (Furlong et al., 2018) and one was statistically significantly adverse (Deroma et al., 2013).
- <u>Processing Speed</u>: , No statistically significant outcomes in only two studies that included this domain (Sagiv et al., 2012; Furlong et al., 2018).

- Vocabulary/Language Development: Eight outcomes were statistically significantly beneficial (Daniels et al., 2004; Oken et al., 2008b; Valent et al., 2013; Furlong et al., 2018; Vejrup et al., 2018); none were statistically significantly adverse.
- Motor Development: Eight outcomes were statistically significantly beneficial (Butz-Jørgensen et al. 2007, Hibbeln et al., 2007; 2007; Lederman et al., 20008; Oken et al., 2008b; Mendez et al., 2009; Julvez et al., 2016; Xu et al., 2016; Hamazaki et al., 2020); none were statistically significantly adverse.
- Cognitive Milestones/Early Cognitive Development: Five outcomes were statistically significantly beneficial (Lederman et al., 2008; Oken et al., 20008b; Mendez et al., 2009; Valent et al., 2013; Julvez et al., 2016; Hisada et al., 2017; de Lauzon-Guillain et al., 2022) and one was statistically significantly adverse (Mendez et al., 2009).
- Visual Perception/Visuomotor/Spatial: Two outcomes were statistically significantly beneficial (Butz-Jørgensen et al., 2007; Oken et al., 2008a); none were statistically significantly adverse.
- Attention and Working Memory: Two outcomes were statistically significantly beneficial (Julvez et al., 2020); none were statistically significantly adverse.
- Learning and Memory: Four outcomes were statistically significantly beneficial (Oken et al., 2005; Mendez et al., 2009; Sagiv et al., 2012; Julvez et al., 2016) and one outcome was statistically significantly adverse (Oken et al., 2016).
- Social/Emotional/Behavioral Development: Eight outcomes were statistically significantly beneficial (Daniels et al., 2004; Hibbeln et al., 2007; Gale et al., 2008; Hu et al., 2016; Julvez et al., 2016; Mesirow et al., 2017; Vecchione et al., 2021; Vejrup et al., 2022); none were statistically significantly adverse.

- <u>Other Miscellaneous Outcomes (e.g. executive function, visual function, counting & sorting)</u>: Five outcomes were statistically significantly beneficial (Williams et al., 2001; Julvez et al., 2016; Hamazaki et al., 2020); none were statistically significantly adverse.

These domains are defined in Web Table 2 in the supplemental materials. Among other things, Web Table 2 describes in detail the studies that examined each domain and outcomes within each domain.

The number of statistically significant beneficial outcomes at the 5% significance level was 10 times greater than what would be expected if no association were truly present (five or six statistically significant outcomes would be expected). For that reason, there is a substantial likelihood that these outcomes represent actual improvements. Sixty-five percent of these outcomes spanned domains of IQ, vocabulary/language development, motor development, and social/emotional/behavioral development. It is possible that this clustering reflects the fact that a greater number of studies have examined these domains.

The three adverse outcomes were in different domains. One of them was an adverse effect when consumption was below 12 oz/wk but it lost statistical significance when consumption exceeded 12 oz/wk (Oken et al., 2016). The authors acknowledged that this outcome was contrary to what they would have expected. The other two were in subsets of small study populations and involved adverse outcomes in subsets of those populations. In one, consumption of shellfish and squid was adverse while consumption of fresh fish was not (Mendez et al., 2009), an outcome that puzzled the authors and was not reported in any other study. In the other, canned fish generally without specification of species was reported to be adverse while consumption of fresh fish was not (Deroma et al., 2013).

In addition to these studies we consider a recent study conducted in the Seychelles Islands that compared performance when pregnant women ate large amounts of fish relative to other locations against performance when they ate less but still relatively large amounts of fish (Conway et al., 2023). This study is addressed in section 6.3 below.

Beneficial outcomes through multiple domains are generally consistent with FDA's prediction. The assessments' beneficial estimates are not perfectly representative, however, due to three adverse outcomes and to a remainder with differences in performance that were not statistically significant. These outcomes may be due to factors that the assessments could not take into account, possibly including:

- Variability of results from the large number of test instruments and the timing and manner of their administration used in the 30 studies;
- Variability in the studies' power to detect effects due to size of study;
- Variability in the genetics of the study populations that possibly affect the time it takes to excrete MeHg;
- Variability in dietary patterns in addition to fish. For example, it has been postulated that consuming greater amounts of omega-6 fatty acids from certain foods relative to amounts of omega-3 fatty acids from fish could reduce benefits from fish or possibly negate them. Omega-6 and omega-3 fatty acids compete with each other for the same enzymes in the body in order to be metabolized (Blasbalg et al., 2011; Simopoulos 2011). Although they were not fish outcomes per se, three studies found higher omega-6 to omega-3 ratios were associated with more child autistic traits (Steenweg de-Graaff et al., 2016), poor communication development (Strain et al., 2015), and motor development (Llop et al., 2016).

6.2 Beneficial Effects Beyond Amounts that People Eat or Could Eat

As shown in Tables 1 and 2, the FDA assessment estimated that commercial fish in the United States are net beneficial though at least 24 oz/wk (e.g., swordfish) and into hundreds (e.g., haddock) and even the thousands of oz/wk (e.g., salmon). The FAO/WHO assessment estimated that virtually all of the internationally available fish it assessed are net beneficial through and implicitly beyond 24.71 ounces per week, the highest amount considered by the EC. The theoretical basis for these estimates was that the size of the beneficial contribution is so much bigger than the adverse contribution that the net effects remain beneficial through large amounts of fish even as the adverse contribution gradually reduces them.

Here we review the extent to which studies reported beneficial associations beyond 12 oz/wk, consistent with that theoretical basis. We chose this amount (and many of the studies examined whether there were differences in outcomes above and below 12 oz/wk) because U.S. advice recommends that pregnant women not exceed 12 oz/wk for safety (FDA/EPA, 2022a). As described previously, this amount was adopted in 2001 as a precautionary measure and it remains in U.S. advice to this day.

Twelve of the 30 studies reported one or more statistically significantly beneficial associations above 12 oz/wk (Daniels et al., 2004; Oken et al., 2005; Hibbeln et al., 2007; Gale et al., 2008; Oken et al., 2008a & b; Sagiv et al., 2012; Valent et al., 2013; Julvez et al., 2016; Vejrup et al., 2018; Hamazaki et al., 2020; Julvez et al., 2020). In these studies the highest amounts of fish pregnant women consumed ranged to over 100 oz/wk, with highs over 30, 40, 70, and 90 oz/wk. Whether the FDA assessment of net effects was correct that net benefits can extend into the several hundreds of oz/wk and beyond will likely remain theoretical given the implausibility of anyone eating that much fish (FDA calculated that 55 oz/wk represented the 99.9th percentile of consumption for U.S. women of childbearing age (FDA, 2014, Table V-1)), but these studies indicate that net benefits extend to the maximum that people have been reported to eat.

6.3 Optimum Amounts of Fish

As shown in Tables 1-3 for full scale IQ, the assessments estimated amounts for each species and market type at which net benefits rise to a peak, after which they gradually decline. These peaks represent optimum amounts of fish consumption during pregnancy for neurodevelopment. The theoretical basis for them was a dose/response relationship for net effects that takes the rough shape of "an inverted 'U', with the greatest net benefit at the high point of the 'U'. This dose/response is the product of a beneficial contribution that plateau's and an adverse contribution that does not.

In the FDA "package of nutrients" model for full scale IQ, these net beneficial peaks occur from 8-10 oz/wk with a mean of 9.1 oz/wk for the 47 species and market types that FDA assessed. In FDA's "omega-3" model the net beneficial peaks occur over a range that extends beyond 20 oz/wk for some fish, with an overall mean of 12.3 oz/wk. In the FAO/WHO assessment net beneficial peaks typically occur between 14.1 oz/wk (4 servings) and 24.7 oz/wk (7 servings).

The study results are generally consistent with the assessments' estimates for beneficial peaks in so far as they reported amounts in each study population where the greatest benefits began. The greatest benefits began at 8 oz/wk in some studies (Oken et al., 2008a; Mendez et al., 2009; Sagiv et al., 2012) and began at 12 oz/wk and greater in other studies (Daniels et al., 2004; Butz-Jørgensen et al., 2007; Hibbeln et al., 2007; Gale et al., 2008; Oken et al., 2008a & b; Mendez et al., 2009; Sagiv et al., 2012; Julvez et al. 2016; Vejrup et al., 2018; Hamazaki et al., 2020; Julvez et al., 2020; Vejrup et al., 2022).

This consistency between the assessments and the study results indicates that a substantial gap may exist between amounts associated with the greatest benefits and amounts that pregnant women actually eat on a population-wide basis. A survey of pregnant women conducted by FDA reported a median of 1.8 oz/wk (Lando et al., 2012). FDA subsequently calculated a population-wide median of 1.9 oz/wk with a mean of 3.7 oz/wk for women of childbearing age for its assessment (FDA 2014, see Table V-1). We are not aware of evidence that would indicate these amounts have changed significantly.

Only two studies, however, had consumption categories at high enough amounts to show whether a decline occurred at some point beyond the greatest benefit. One of these reported a slight decline after 13.5 oz/wk (Daniels et al., 2004). The other reported a slight decline after 16.2 oz/wk on one test and after 21.2 oz/wk on another test (Julvez et al., 2016). While results from only two studies are not strongly corroborative, they are consistent with the assessments on this point. More evidence is needed, however. If there is no decline, that would raise questions about whether an underlying adverse effect exists, at least at these amounts.

A third study, from the Seychelles Islands, compared outcomes between a consumption category with a median of 38.3 oz/wk and a category with a median of 13.7 oz/wk (Conway et al., 2023), both of which are beyond the 99.5^{th} and 95^{th} percentiles of U.S. consumption respectively. The Seychelles Islands present a unique situation in that residents eat large amounts of marine fish relative to other locations. In this study with 222 mother-child pairs, none of the outcomes were statistically significant, suggesting that the direction of effect did not change to an appreciable extent beyond 13.7 oz/wk. This interpretation is consistent with the theory that all benefits plateau at some point. If there were a decline, it was too gradual to be clear from these results.

6.4 Adverse Contribution from MeHg

The FDA and FAO/WHO assessments theorized that MeHg in fish is neurotoxic to the fetus down to the lowest possible exposure, although the effect becomes extremely small.

In addition to this theory, two other possible explanations for the dominance of beneficial outcomes in the studies are:

(a) MeHg may have a threshold of effect below which it is not neurotoxic; the studies essentially involve exposures below that threshold, or

(b) MeHg has a unique ability to chemically bond with selenium and induce a selenium deficiency in brain tissues that might result in neurodevelopmental deficits (Ralston, 2021). Because commercially available fish tend to be rich in selenium, eating them can enable the brain to build a selenium "reserve" that the MeHg in the fish cannot deplete. Since the brain will have plenty of surplus selenium to fall back on, the result will be no adverse neurodevelopmental effects (Ralston et al., 2019).

These competing explanations matter. If there is an underlying effect from MeHg, fish lower in MeHg can be more net beneficial than fish higher in MeHg, and vice versa (as shown in Tables 1-3). Moreover, an underlying MeHg effect would typically cause beneficial net effects to be somewhat smaller than they would otherwise be if there were no underlying effect from MeHg. By contrast, if there is no effect from MeHg at levels of consumption reported in the studies, then the various MeHg concentrations in fish become irrelevant for estimating net effects and do not influence the size of net benefits regardless of amounts of fish being consumed.

Evidence in the studies for an underlying effect from MeHg (in addition to the three outcomes with adverse directions of effect) is as follows:

(1) In seven studies that treated MeHg as an independent variable in addition to fish, MeHg showed an adverse direction of effect while fish showed a beneficial direction of effect on the same outcomes (Butz-Jørgensen et al., 2007; Lederman et al., 2008; Oken et al., 2005; Oken et al., 2008a; Suzuki et al., 2010; Sagiv et al., 2012;Deroma et al., 2013). A possible explanation for these contradictory directions is that these studies showed both beneficial net effects from fish and an underlying adverse contribution to those net effects from MeHg.

(2) Three studies that adjusted their fish results by statistically removing any contribution from MeHg found that this adjustment caused the fish benefit to become larger (Oken et al., 2005; Oken et al., 2008a; Sagiv et al., 2012). These outcomes fit the assessments' theory that an underlying MeHg effect reduces the size of a net benefit. Similarly, one study that adjusted its MeHg results by statistically removing the beneficial effects from fish found that this adjustment caused the MeHg association to become stronger (Lederman et al., 2008). Again, this outcome fits the assessments' theory.

As one study author observed, these results suggest that beneficial and adverse effects occur simultaneously (Oken et al., 2005) and that net beneficial effects from fish would be greater if MeHg were not present (Oken et al., 2008a).

The evidence in the studies goes both ways on this, however. Evidence for no underlying effect from MeHg is:

(1) In five studies that treated MeHg as an independent variable in addition to fish, the MeHg had beneficial directions of effect along with the fish, or it was not statistically significant (Daniels et al., 2004; Valent et al., 2013; Oken et al., 2016; Xu et al., 2016; Vejrup et al.,

2018). These outcomes suggest that MeHg was having no effect on its own and thus was not contributing to the net effects.

(2) One study that adjusted its fish results by statistically removing any contribution from MeHg found that doing so did not affect the size of the beneficial effect from fish (Daniels et al., 2004). This outcome suggests that MeHg was not reducing the size of the net benefit, i.e., that it was having no effect. The authors noted, however, that MeHg exposures in this population were low.

In summary, the assessments provide an explanation for some of the evidence but not for all of it.

6.5 Benefits and No Harm When Exposures to MeHg Exceed the EPA RfD

Federal advice now recommends that pregnant women limit fish consumption to 12 oz/wk in order to keep their exposures to MeHg below EPA's RfD (FDA/EPA, 2022a & b). Like the recommended 12 ounce per week limit, the RfD for MeHg was first developed before beneficial associations from fish had been reported in the scientific literature (EPA, 2001). The RfD is quantified as 5.8 parts per billion in cord blood (NRC, 2000, see p. 29) which is commonly translated to 1.2 parts per million (ppm) of MeHg in hair **(**NRC, 2000; Oken et al., 2005; Oken at al., 2016).

The FDA and FAO/WHO assessments estimated benefits and no harm from eating fish when exposures from the MeHg in fish exceed the RfD. It is now possible to evaluate those estimates as well as the RfD itself against a body of evidence from the fish consumption studies. Twelve studies reported maternal exposures above the RfD value of 1.2 ppm. These exposures ranged from 2 ppm through 18.5 ppm (Oken et al., 2005; Lederman, et al., 2008; Oken et al., 2008a;

Suzuki et al., 2010; Sagiv et al., 2012; Deroma et al., 2013; Valent et al., 2013; Oken et al., 2016; Xu et al., 2016; Vejrup et al., 2018; Vejrup et al., 2022; Conway et al., 2023). None of them had outcomes that were statistically significantly adverse when exposures exceeded the RfD while seven of them had one or more statistically significantly beneficial outcomes (Oken et al., 2005; Lederman et al., 2008; Sagiv et al., 2012; Valent et al., 2013; Xu et al., 2016; Vejrup et al., 2018; Vejrup et al., 2022).

These outcomes essentially corroborate the assessments' estimates. Consistent evidence of benefits and no harm above the RfD also confirm that it is an exposure without appreciable risk over time, as EPA defines it, when commercial species of fish are consumed, and that it could be considerably higher and still meet that definition for commercial fish. In that respect the evidence further confirms that at virtually any level at which it could be set, the RfD would not be a single exposure to methylmercury that causes commercial fish to transform from safe from unsafe, a common misperception that the Institute of Medicine of the National Academies of Science pointed out as early as 2007 (IOM, 2007, p. 177). The RfD for Hg contains an "uncertainty factor" set at one-tenth of the lowest exposure possibly associated with adverse associations reported from the Faroe Islands study of consumption of pilot whale. By design, the RfD cannot provide information about the likelihood of adverse net effects from consuming commercial fish at or above the RfD or about MeHg's contribution to those net effects (Axelrad et al., 2007), or about amounts of fish that could maximize benefits. Both the FDA and FAO/WHO assessments were developed to address those questions.

7. Research Recommendations

FDA observed that its assessment of net effects could point scientists to areas where additional research would be useful since, like all quantitative assessments, it had to rely on theories to fill gaps in the empirical data then available to it (FDA 2014, see Executive Summary). The FAO/WHO assessment also addressed research priorities and data gaps (FAO/WHO 2011, see Section 4). Here we make research recommendations about gaps that would be useful to fill.

To the extent possible, a better understanding is needed on whether the beneficial associations with children's neurodevelopment come solely from omega-3 fatty acids or from multiple nutrients in fish acting synergistically. There is a strong logic for the importance of the omega-3 fatty acids in fish as follows: (a) they are known to be important for brain development; (b) fish is their primary dietary source; and (c) there is compelling evidence that fish eaten as a whole food during pregnancy is beneficial for neurodevelopment. Evidence for the significance of omega-3 fatty acids comes from a Randomized Controlled Trial in Norway in which the children whose mothers ate a mix of fish species had higher scores on a cognitive scale than children whose mothers had substituted fish relatively low in omega-3 fatty acids (cod) for some portion of the overall mix of fish they had been eating (Markhus et al., 2021). However, omega-3 supplements taken during pregnancy in Randomized Controlled Trials have not been consistently beneficial (AHRQ, 2016), suggesting the possibility that other nutrients present in fish are needed along with the omega-3 fatty acids.

Further research is needed on the extent to which omega-6:omega-3 fatty acid ratios affect neurodevelopmental outcomes from eating fish during pregnancy. There is some evidence that higher ratios of omega-6 relative to omega-3 fatty acids reduce the net benefits from fish by limiting availability of the omega-3 fatty acids from fish. Research could also help resolve questions about whether increasing levels of omega-6 fatty acids in western diets compared to relatively stable levels of omega-3 fatty acids are meaningful in this regard or whether there is an overall deficiency of omega-3 fatty acids unrelated to levels of omega-6 fatty acids (Harris, 2018).

Evidence is needed on whether the effects on neurodevelopment extend into adulthood. Such evidence would have a bearing on their ultimate significance.

Similarly, analysis is needed on the extent to which the gains in neurodevelopment associated with fish consumption are sufficient to affect people's lives or be meaningful on a population-wide basis. The effects appear to be significant for IQ but gains on test scores in the other domains need to be analyzed for their significance.

Given that a surplus in selenium, as mentioned in Section 6.4, is a possible explanation that the assessments did not consider for the relative paucity of adverse directions of effect in the studies, direct evidence in humans would be highly useful in confirming this explanation. There is confirmatory laboratory and animal evidence but the scientific community has been hesitant to embrace the selenium explanation without direct evidence from human studies.

8. Conclusion

The FDA and FAO/WHO assessments estimated effects on neurodevelopment for a substantial number of individual species and market types of fish that are commercially available in the United States and internationally. These assessments were based on a "net effects" theory that took both risks and benefits into account. Both assessments estimated that net effects on the endpoints available when they were carried out were beneficial and currently available evidence confirms the beneficial association with numerous other neurodevelopmental outcomes.

We conclude that “net effects” theory as utilized by these assessments offers a holistic explanation for the research results in most of their particulars. Consumption of commercially available fish during pregnancy is likely to benefit children’s neurodevelopment across multiple neurodevelopmental domains. Current evidence also supports benefits to neurodevelopment beyond amounts of fish that most people eat or even could eat. Those benefits are likely related to omega-3 fatty acids for which fish is the primary dietary source, possibly with other nutrients in fish acting in combination.

Fish consumption advice that emphasizes these benefits could be highly impactful since pregnant women may be consuming substantially less than the assessments and the studies both associated with the most benefits. Considerable evidence supports consuming amounts near and above 12 oz/wk although pregnant women typically consume well below those amounts. Conversely, the evidence does not support treating the EPA RfD as a “bright line” that should not be exceeded for purposes of safety. Advice that continues to emphasize precautionary limitations to fish consumption developed at the beginning of this century no longer matches the science.

CRediT Authorship Contribution Statement

Philip Spiller: Conceptualization, Data curation, Investigation, Methodology, Project Administration, Visualization, Writing – original draft; **Gary J. Myers:** Conceptualization, Project Administration, Visualization, Writing – review and editing; **Heather R. Adams:** Conceptualization, Methodology, Data Curation, Writing – review and editing; **J.J. Strain:** Project Administration, Writing – review & editing; **Emeir M. McSorley:** Writing – review and editing; **Maria S. Mulhern:** Writing – review and editing; **Marie C. Conway:** Writing – review and editing; **Allison J. Yeates:** Writing – review and editing; **Clark Carrington:** Conceptualization, Methodology, Formal analysis, Writing – review and editing; **P. Michael Bolger:** Conceptualization, Supervision, Writing – review and editing; **Caroline M. Taylor:** Writing – review and editing; **Nicholas V.C. Ralston:** Conceptualization, Writing – review and editing; **Michael A. Crawford:** Conceptualization; **Joseph R. Hibbeln:** Conceptualization, Writing – review and editing; **J. Thomas Brenna:** Conceptualization, Writing – original draft, Writing – review and editing; **Edwin van Wijngaarden:** Conceptualization, Visualization, Writing – review and editing.

Declaration of Competing Interest

Author Nicholas R.V. Ralston received funding from the Seafood Industry Research Fund in 2019 to publish research findings from a study performed for the United States Environmental Protection Agency (U.S. EPA) National Center for Science to Achieve Results (STAR) grant RD834792-01: Fish Selenium Health Benefit Values in Mercury Risk Management. Costs to present findings of these EPA studies at meetings were provided by Conxemar in 2020, and InterFish Espana in 2021. No funding agency has had any input in the decision to submit this article for publication.

All remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

A**cknowledgements**

We express our deep appreciation to the following individuals who reviewed the manuscript during development and offered suggestions and encouragement: Jean Golding, Emeritus Professor of Paediatric and Perinatal Epidemiology, Center for Academic Child Health, Bristol Medical School, University of Bristol, U.K. and Founder of the Avon Longitudinal Study of Parents and Children; Susan E. Carlson, A.J. Rice Professor of Nutrition and University Distinguished Professor, Department of Dietetics and Nutrition, University of Kansas Medical Center, Kansas City, MO, USA; Sonja L. Connor, Research Associate Professor, Endocrinology, Diabetes and Clinical Nutrition, Oregon Health Science University, Portland OR, USA; William S. Harris, Professor, Department of Internal Medicine, University of South Dakota, SD, USA; Penny M. Kris-Etherton, Even Pugh University Professor of Nutritional Sciences, Distinguished

Professor of Nutrition, Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA, USA; Michael Landa, retired former Director, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration. Author Caroline M. Taylor acknowledges that she was supported by a Medical Research Council (MRC) Career Development Award (grant number MR/T010010/1) and author Edwin van Wijngaarden is funded by NIH grant R24 ES029466. Authors Philip Spiller, P. Michael Bolger, and Clark Carrington acknowledge that they were involved in the development of the FDA assessment of net effects. Additionally J.J. Strain chaired the Expert Consultation that developed the FAO/WHO risk and benefit assessment and P. Michael Bolger and Clark Carrington participated in that assessment.

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TABLE 1: Full IQ If Benefits Come from an Identical "Package" of Nutrients: FDA's results for seven of the 47 species and market types. The numbers within the parentheses are 95% confidence limits that reflect a range of possible outcomes above and below the central estimates.

Species or Market Type	Mean MeHg Level	Oz/ Week to Reach Maximum Net Benefit	Size of Maximum Net Benefit in Full IQ Points	Oz/Week to Become Net Adverse	Percent of U.S. Consumption At or Below the Amount That Becomes Net Adverse*
Swordfish	1.00 ppm	8 (7, 13)	2.0 (0.7, 3.0)	24 (12, 43)	Slightly below 99
King Mackerel	0.73 ppm	8 (7, 13)	2.4 (1.4, 3.2)	32 (16, 59)	99.5
Tuna, Albacore Canned	0.35 ppm	9 (8, 13)	2.8 (2.2, 3.7)	67 (35, 123)	Above 99.9
Halibut	0.22 ppm	9 (8, 13)	3.0 (2.4, 3.9)	95 (49, 175)	Above 99.9
Tuna, Light Canned	0.12 ppm	9 (8, 13)	3.1 (2.6, 4.1)	196 (101, 360)	Above 99.9
Haddock	0.07 ppm	9 (8, 14)	3.2 (2.6, 4.2)	351 (181, 644)	Above 99.9h
Salmon	0.02 ppm	10 (8, 14)	3.2 (2.7, 4.2)	1,024 (528, 1,876)	Above 99.9

- **"ppm" = parts per million of MeHg in hair.**
- **Percentages of U.S. consumption are from Table V-1, FDA Assessment of Net Effects.**

TABLE 2: Full IQ if Benefits Are Solely from Omega-3 Fatty Acids: FDA's results for the same species and market types. The numbers within the parentheses are 95% confidence limits that reflect a range of possible outcomes above and below than the central estimates.

Species or Market Type	**Mean MeHg Level**	**Mean Omega-3 Fatty Acid Level** (grams per 100 grams of fish)	**Oz/ Week to Reach Maximum Net Benefit**	**Size of Maximum Net Benefit in Full IQ Points**	**Oz/Week to Become Net Adverse**	**Percent of U.S. Consumption At or Below the Amount that Becomes Net Adverse***
Swordfish	1.00 ppm	0.90	5 (4, 8)	2.5 (1.7, 3.4)	24 (12, 43)	Slightly below 99
King Mackerel	0.73 ppm	0.40	11 (9, 17)	2.0 (0.8, 3.0)	32 (16, 59)	99.5
Tuna, Albacore Canned	0.35 ppm	0.86	5 (5, 8)	3.0 (2.4, 4.0)	67 (35, 123)	Above 99.9
Halibut	0.22 ppm	0.71	7 (6, 10)	3.1 (2.5, 4.0)	95 (49, 175)	Above 99.9
Tuna, Light Canned	0.12 ppm	0.27	17 (15, 26)	3.0 (2.4, 3.9)	196 (101, 360)	Above 99.9
Haddock	0.07 ppm	0.16	29 (26, 43)	3.0 (2.4, 4.0)	351 (181, 644)	Above 99.9
Salmon	0.02 ppm	1.18	4 (4, 6)	3.3 (2.7, 4.3)	1,080 (546, 2,023)	Above 99.9

- **"ppm" = parts per million of MeHg in hair.**
- **Percentages of U.S. consumption are from Table V-1, FDA Assessment of Net Effects.**

TABLE 3: Selected Results from the FAO/WHO Expert Consultation: These are from the FAO/WHO's primary modeling. The 2nd column provides percentile of U.S. consumption for context. The 3rd and 4th columns provide the EC's estimates for the adverse and beneficial contributions to the net effects. In the 5th column, we add them together to show the net effects. For salmon, the table includes wild caught and aquaculture salmon separately; FDA did not differentiate between the two. Also, since the EC did not estimate net effects for canned light tuna per se, the table includes the EC's estimates for skipjack, which can be found in canned light tuna.

Amount in Ounces and Servings Per Week	Percent of U.S. Consumption At or Below This Amount*	Decline in IQ Points from MeHg	Gain in IQ Points from Omega-3 Fatty Acids	Net Effects: (The Overall Change in IQ when Decline & Gain are Added Together)
SWORDFISH				
3.53 (1 serving)	Between 50 & 75	-0.6	+2.1	+1.5
7.06 (2 servings)	Between 75 & 90	-1.2	+4.2	+3.0
14.12 (4 servings)	Between 95 & 99	-2.4	+5.8	+3.4
24.71 (7 servings)	Slightly below 99	-4.2	+5.8	+1.6
KING MACKEREL				
3.53 (1 serving)	Between 50 & 75	-0.3	+2.1	+1.8
7.06 (2 servings)	Between 75 & 90	-0.6	+4.2	+3.6
14.12 (4 servings)	Between 95 & 99	-1.2	+5.8	+4.6
24.71 (7 servings)	Slightly below 99	-2.1	5.8	+3.7
TUNA, ALBACORE				
3.53 (1 serving)	Between 50 & 75	-0.12	+2.10	+ 1.98
7.06 (2 servings)	Between 75 & 90	-0.20	+4.20	+4.00
14.12 (4 servings)	Between 95 & 99	--0.48	+5.80	+5.32
24.71 (7 servings)	Slightly below 99	-0.84	+5.80	+4.96
HALIBUT				
3.53 (1 serving)	Between 50 & 75	-0.12	+4.40	+4.28
7.06 (2 servings)	Between 75 & 90	-0.20	+5.80	+5.60
14.12	Between	-0.48	+5.80	+5.32

(4 servings)	95 & 99			
24.71 (7 servings)	Slightly below 99	-0.84	+5.80	+4.96
TUNA, SKIPJACK (surrogate for canned light tuna)				
3.53 (1 serving)	Between 50 & 75	-0.12	+4.40	+4.28
7.06 (2 servings)	Between 75 & 90	-0.20	+5.80	+5.60
14.12 (4 servings)	Between 95 & 99	-0.48	+5.80	+5.32
24.71 (7 servings)	Slightly below 99	-0.84	+5.80	+4.96
HADDOCK				
3.53 (1 serving)	Between 50 & 75	-0.02	+0.77	+0.75
7.06 (2 servings)	Between 75 & 90	-0.04	+1.5	+1.46
14.12 (4 servings)	Between 95 & 99	-0.08	+3.1	+3.02
24.71 (7 servings)	Slightly below 99	-0.14	+5.14	+5.26
SALMON (WILD CAUGHT)				
3.53 (1 serving)	Between 50 & 75	-0.02	+4.4	+4.38
7.06 (2 servings)	Between 75 & 90	-0.04	+5.8	+5.76
14.12 (4 servings)	Between 95 & 99	-0.08	+5.8	+5.72
24.71 (7 servings)	Slightly below 99	-0.14	+5.8	+5.66
SALMON (AQUACULTURE)				
3.53 (1 serving)	Between 50 & 75	-0.02	+5.8	+5.78
7.06 (2 servings)	Between 75 & 90	-0.04	+5.8	+5.76
14.12 (4 servings)	Between 95 & 99	-0.08	+5.8	+5.72
24.71 (7 servings)	Slightly below 99	-0.14	+5.8	+5.66

- **Percentages of U.S. consumption are from Table V-1, FDA Assessment of Net Effects.**