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Scientific foundations of fish-consumption advice for pregnant women: Epidemiological evidence, benefit-risk modeling, and an integrated approach

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ABSTRACT

Background: Pregnant women need fish consumption advice that increases seafood intake and simultaneously reduces methylmercury (MeHg) exposure. Two disciplines, epidemiology and benefit-risk modeling, can support such advice. Some current models suggest that fish consumption during pregnancy has only net beneficial effects. In contrast, many recent epidemiological studies have associated adverse effects on cognitive development with ordinary fish intake and MeHg doses routinely encountered by up to one in six US women of childbearing age. Proposed federal fish-consumption advice is based solely on a benefit-risk model. A more complete assessment integrating both types of evidence is needed.

Objectives and methods: The goal of this paper is to use a model to rank seafood items by their relative benefits and risks, producing consumer seafood choice recommendations that are also consistent with epidemiological observations. Recent epidemiological studies and benefit-risk models are reviewed, and model results are compared with one another and with epidemiological observations to identify commonalities that support inter-calibration.

Results and conclusions: Both approaches quantify MeHg doses at which harm slightly exceeds benefit. A model from the US Food and Drug Administration (FDA) predicts adverse effects at fish intakes containing, on average, more than 16 times the the US Reference Dose (RfD) for MeHg. Epidemiological results indicate that the RfD itself approximates a minimal adverse dose. This conceptual similarity allows FDA's model to be calibrated with the epidemiological results to generate fish intake recommendations that both the model and the epidemiology suggest should have substantially positive public health impacts.

1. Introduction

Fish consumption by women of childbearing age, especially during pregnancy, is a matter of substantial public health concern. (In this paper the terms “fish” and “seafood” are used interchangeably to encompass marine and freshwater finfish and shellfish.) Seafood is the principal dietary source of the omega-3 (n-3) polyunsaturated fatty acids (PUFAs), primarily Docosahexaenoic Acid (DHA) and Eicosapentaenoic Acid (EPA), essential for prenatal nervous system development (Hibbeln et al., 2007). But fish is also a source of methylmercury (MeHg), formed in the environment from inorganic mercury (Hg) emitted by natural and anthropogenic sources, and accumulated in aquatic food webs. MeHg is neurotoxic, and even mildly elevated exposure during gestation can damage the developing brain (Karagas et al., 2012).

Fish consumption during pregnancy thus poses significant benefit-risk tradeoffs for prenatal brain development. While nutritional guidelines urge 2–3 seafood meals (about 8-12 ounces) per week (DGA, 2015), the average American woman of childbearing age currently eats less than half that amount (FDA, 2014a). Concerns about MeHg appear to be one factor discouraging greater consumption (Lando and Lo, 2014).

An analysis of data from the National Health and Nutrition Examination Survey (NHANES) from 1999 through 2010 found that seafood intake among women of childbearing age remained stable, while blood Hg levels decreased moderately (Birch et al., 2014), which suggests that recent fish consumption advice has helped American women reduce MeHg exposure. On the other hand, the possible methylmercury exposure consequences of efforts to increase seafood consumption need careful assessment.

While advice simply to eat *more* seafood is important, *which types* of seafood women choose to eat also can affect health outcomes (Mahaffey et al., 2011). As Table 1 illustrates, popular fish

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Table 1
Omega-3 and mercury content of selected popular fish and shellfish varieties.[a]

Seafood Item	n-3 s, mg/100 g	Hg, μg/100 g
Sardines	1190	2
Salmon	1180	2
Herring, Anchovies	2020	5
Shrimp	350	1
Pollock	530	4
Clams	200	2
Tilapia	90	1
Flounder, Sole	300	8
Tuna, Canned Albacore	860	35
Tuna, Canned Light	270	13
Cod	160	9
Lobster	200	11
Swordfish	900	100
Shark	690	98
Orange Roughy	30	57

[a] Source of data, US FDA (2014a, Table V-8).

and shellfish types vary widely in both n-3 and MeHg content. In practical terms, a woman who doubles her fish intake without changing her seafood selections will double her doses of both beneficial n-3 s and potentially harmful MeHg. But a woman who switches from eating, for example, 100 g/week each of cod and canned light tuna to 100 g/week each of salmon and shrimp would almost quadruple her n-3 intake, from 430 to 1530 mg. She would also reduce her MeHg dose from 22 to 3 μg, and substantially increase the benefit-risk ratio of her seafood meals. Fish consumption advice can thus improve health outcomes most effectively not only by persuading women to eat fish more often but also by guiding them to choose varieties with more n-3 s and less MeHg, and to avoid or limit consumption of varieties with the opposite profile.

Advice for pregnant women on how much seafood of which varieties to eat should rest on scientific understanding of the comparative benefits and risks of consuming different seafood choices. Two types of evidence can support such recommendations: epidemiological studies of benefits and risks of fish consumption during pregnancy, and benefit-risk models.

Each type of evidence has advantages, disadvantages and limitations. Epidemiology deals only with associations between environmental exposures (e.g., to n-3 s and MeHg) and outcomes, and repeated concordant findings from similar studies are generally required to establish and quantify any particular relationship. Studies of neurodevelopmental effects of fish consumption during pregnancy are subject to mutual negative confounding; i.e., beneficial and harmful effects tend to offset or obscure each other, making it more difficult to measure outcomes in either direction (Budtz-Jørgensen et al., 2007). Further, it is not feasible in an epidemiological study to record in detail what fish varieties women ate at various points during a pregnancy, or to associate positive or negative developmental outcomes with any particular seafood choices.

Models, on the other hand, incorporate some epidemiological data and use assumptions and data about seafood constituents and intakes to estimate the benefits, harm and net effects of different fish consumption choices. They can be powerful tools for comparing and contrasting relative benefits and risks of consuming different fish varieties in different scenarios. However, a model is only as good as the data and assumptions fed into it by the modelers, decisions that are quite subjective and often arbitrary. While policymakers may be tempted to overlook the uncertain nature of model results, practitioners of the discipline are certainly aware of its limitations. The statistician George Box, an early modeler, famously quipped, “All models are wrong, but some models are also useful” (see Box and Draper, 1987).

Ideally, epidemiological evidence and benefit-risk modeling would be used complementarily to provide the fullest and most balanced evidentiary basis for fish consumption advice, but that has not been the case. Simply stated, the different approaches have led to different conclusions, and advice based on the two disciplines has also varied markedly.

For example, two prominent recent models (FAO/WHO, 2011; FDA, 2014a) both suggest that eating any amount of any fish during pregnancy almost always has only net beneficial effects on neurodevelopment. Fish consumption advice for pregnant women recently proposed by four US agencies is based only on results of these models; the proposed advice stresses increasing fish intake and downplays the need to manage MeHg exposure (DGAC, 2015; FDA, 2014b).

In contrast, more than a dozen epidemiological studies published since 2005 (enumerated in the next section) indicate that for a substantial minority of children, adverse neurodevelopmental effects of prenatal MeHg exposure can outweigh beneficial nutritional effects of maternal fish consumption. The same evidence suggests that even for children with net benefits, the beneficial effect is significantly larger when MeHg exposure is minimized. Consequently, many research teams have urged pregnant women to eat more fish, but have also stressed the importance of choosing low-Hg varieties (e.g., Ginsberg and Toal, 2009; Karagas et al., 2012; Lederman et al., 2008; Oken et al., 2005, 2008a; Orenstein et al., 2014; Sagiv et al., 2012).

In short, results of population studies and prominent models have differed; epidemiological evidence contradicts the models, and advice based on the different approaches has diverged. To ground fish consumption advice more soundly on science, it is essential to resolve this conflict between modeling and epidemiology, to weigh both types of evidence in a balanced and integrated way.

2. Methods

A review of evidence from both disciplines was conducted to identify commonalities that support a synthesis. A crucial concept in both approaches is the “minimal adverse dose” (MAD) of methylmercury. In epidemiology, the MAD is the exposure level above which adverse effects are first observed. One model, the FDA's, predicts an intake for each seafood variety (and thus, the MeHg dose it contains) above which adverse effects just begin to outweigh beneficial effects, i.e., a model-derived MAD. By comparing results of both approaches quantitatively, the model can then be re-calibrated with MAD estimates from epidemiology.

FDA's model also identifies weekly intakes of each seafood variety above which net adverse effects first occur; these can be taken as maximum permissible intakes for each fish type. After recalibrating the model with an epidemiologically-derived MAD, new maximum weekly intakes were calculated for each seafood item. Those results were then arrayed in a seafood-choice chart for pregnant women, sorting varieties in terms of permissible weekly servings.

The step-by-step analysis leading to that end point is presented in the sections that follow. The epidemiological evidence is first reviewed and summarized. Four benefit-risk models are then reviewed and compared with each other and with the epidemiological data. The quantitative re-calibration of the FDA model by comparing its MADs with those from epidemiology is then carried out to produce the consumer choice chart. Finally, results of this analysis are discussed and compared with other seafood-choice advice based only on risk-benefit models.

3. Review of epidemiological evidence

The objective of this review is not to explore evidence in detail nor to assess the strengths and weaknesses of individual studies. Instead it provides an overview of quantitative estimates of beneficial effects of fish consumption during pregnancy, adverse effects of prenatal MeHg exposure, or net effects on cognitive development, for later comparison with estimates of those effects generated by benefit-risk models. Therefore, only studies that observed beneficial or adverse outcomes are included.

3.1. Early studies

Neurotoxic effects of MeHg in fish and the heightened vulnerability of the developing nervous system were first observed in the 1960s in severe industrial pollution incidents in Japan (Sakamoto et al., 2004; Yorifuji et al., 2013). Later research has explored whether MeHg exposure associated simply with seafood consumption, i.e., without localized pollution, may have similar if subtler adverse effects. Studies of populations with high-fish diets in New Zealand and the Faroe Islands (where the residents also eat high-Hg pilot whale meat) associated deficits in several cognitive developmental outcomes with prenatal MeHg exposure (Crump et al., 1998; Grandjean et al., 1997; Kjellstrom et al., 1986, 1989). A study in the Seychelles initially failed to associate any adverse effects with MeHg exposure (Davidson et al., 1998; Myers et al., 2003).

In exploring why their results differed, the Faroes and Seychelles research teams zeroed in on the possibility that beneficial effects on cognitive development from nutrients in fish and adverse effects of MeHg might have partially or fully obscured each other. Both groups developed improved statistical methods to adjust for this mutual negative confounding, and both subsequently reported that substantial confounding had in fact been present in their earlier data (Budtz-Jørgensen et al., 2007; Davidson et al., 2008; Strain et al., 2008).

3.2. Meta-analyses

A decade ago, two research teams did meta-analyses of data on cognitive developmental effects of MeHg (Axelrad et al., 2007; Cohen et al., 2005a); see results in Table 2. Cohen et al. (2005b) also developed a meta-analysis for cognitive benefits of maternal n-3 intake. No epidemiological data on the latter were then available, so Cohen et al. used data from clinical trials in which pregnant or lactating women were given n-3 supplements, which at best offer relatively weak, indirect evidence of possible benefits of eating fish.

Both meta-analyses of adverse cognitive developmental effects of prenatal MeHg exposure used the New Zealand data and early reports from the Faroes and Seychelles studies. Both of the latter data sets were subsequently shown to be seriously confounded by beneficial effects of fish consumption (Budtz-Jørgensen et al., 2007, Davidson et al., 2008; Strain et al., 2008); thus, both meta-analyses probably significantly underestimated the size of MeHg's adverse effects.

3.3. Recent studies: beneficial effects

Table 3 summarizes data on the neurodevelopmental benefits of maternal fish consumption during pregnancy. The number of studies is relatively small and all were published in the past decade or so.

The Avon Longitudinal Study of Parents and Children (ALSPAC), a large prospective cohort study in the United Kingdom, examined multiple factors that can affect neurodevelopment. Daniels et al. (2004) associated higher verbal development scores with maternal intake of 1–3 fish meals per week during pregnancy when compared with no fish consumption. The largest gains were associated with eating any fish meals per week compared to none, and no greater benefit was found with 4 or more seafood meals weekly, suggesting that beneficial effects reached a plateau at about 3 meals per week. Hibbeln et al. (2007) observed an odds ratio of 1.48 for low verbal IQ score in children whose mothers ate no fish or less than 12 ounces of fish per week, compared to children whose mothers ate more than 12 ounces weekly during pregnancy; improvements on other cognitive developmental outcomes were also associated with higher maternal fish consumption. Odds of having a low IQ decreased as maternal seafood intake increased across all three consumption levels, with no obvious plateau.

Oken et al., (2008b) analyzed data from the Danish National Birth Cohort and reported odds ratios of 1.25 at age 6 months and 1.29 at age 18 months of scoring higher on various developmental milestones for children of mothers in the highest quintile of fish intake during pregnancy, compared with the lowest quintile. This analysis also found continuous improvement in developmental status as fish consumption rose, i.e., no plateau of beneficial effects.

Gale et al. (2008), Lederman et al. (2008), Oken et al. (2005, 2008a), Sagiv et al. (2012) and Suzuki et al. (2010) have also reported beneficial effects of maternal fish consumption during pregnancy, in much smaller studies than the ALSPAC or Danish cohorts. These studies offer additional corroboration that maternal fish consumption during pregnancy has beneficial effects on cognitive development. No meta-analysis of data from these studies has yet been published.

3.4. Recent studies: MeHg effects

During the past decade the focus of research has shifted to whether MeHg exposure from eating ordinary amounts and types of fish might adversely affect cognitive development. Table 4 summarizes recent evidence on this topic.

The question, at what level of MeHg exposure are adverse effects (that is, either net adverse effects, or a substantial diminution of beneficial effects) likely to occur is obviously a key one for fish consumption advice. A reference point is therefore useful to define how much MeHg intake is deemed “acceptable,” or conversely, “excessive.” The US has established a Reference Dose (RfD) for MeHg for that purpose, and it is used here to help interpret results in Table 4. The RfD is described and explained in Sidebar A.

Studies summarized in Table 4 come from many countries and examine diverse cognitive outcomes in children ranging in age

Table 2
Meta-analyses of effects of omega-3 s and methylmercury on neurodevelopment: slopes for beneficial and adverse effects.

Authors/date	Slope, beneficial effect	Slope, adverse effect
Cohen et al. (2005a, 2005b)	+0.13 IQ point per 100 mg/day maternal intake of n-3 s	Central Estimate: −0.7 IQ point per 1 μg/g Hg in maternal hair Low estimate: −0.2 IQ point (Range: 0 to −1.5)
Axelrad et al. (2007)	not included in analysis	−0.18 IQ point per 1 μg/g Hg in maternal hair (Range: −0.009 to −0.378)

Table 3
Recent studies of beneficial effects of maternal fish consumption during pregnancy.

Authors/Date	Country	N=	Ages	Exposure Index, Break Point (s)	% w/ intake	Outcome Measure (s)	Results					
							Raw Scores			Slope or β Coefficient [95% CI]	Odds Ratio [95% CI]	p value	Adjust for Hg?
Daniels et al. (2004)	UK	7,421	15 & 18 mo	fish meals/wk		1. MacArthur Communicative	Fish/ Wk	MCDI/ Vocab	DDST		Top 15% vs. bottom 15% fish intake		
				rare/none	12	Development Inventory @15 mo	0	68	7.1		OR for High Test Score		
				< 1 per wk	18	2. Denver Developmental	< 1	71	7.4		MCDI Vocabulary 1.5 [1.1, 2.0]	0.05	no
				1–3 per week	31	Screening Test @18 mo	1–3	73	7.4		MCDI Social 1.8 [1.4, 2.2]	0.02	no
				4+ per week	39		4+	72	7.4		DDST Language 1.3 [1.0, 1.8]	0.03	no
Oken et al. (2005)	US	135	6 mo	fish meals/wk		Visual Recognition Memory	mean 59.8, range 10.9–92.5			+4.0 VRM pts per fish meal			yes
				mean 1.2			low Hg, low fish, 60			[1.3, 6.7]			
				hi (> 2), n=9	7		low Hg, high fish, 72						
				lo (< 2), n=126	93		high Hg, low fish, 53						
							high Hg, high fish, 55						
Hibbeln et al. (2007)	UK	5,449	6, 18,	fish, g/wk		Primary Outcome: IQ at age 8					OR for Lowest Quartile Verbal IQ		
			30, 42,	none	12	measured with					no fish 1.48 [1.16, 1.90]	0.0041	no
			81 mo,	1–340	65	Wechsler Intelligence Scale					1–340 g/wk 1.09 [0.92, 1.29]		
			8 yr	> 340	23	for Children, 3rd Ed. (WISC-III)					> 340 g/wk 1.0 (referent)		
(Oken et al., 2008a)	US	341	3 yr	fish meals/wk		1. Peabody Picture	Mean scores [± SD]:			β, > 2 vs. ≤ 2 meals/ wk			
				mean 1.5 ± 1.4		Vocabulary Test	PPVT, 105.7 ± 13.8			2.2 [−2.6, 7.0], PPVT			yes
				never, n =47	14		WRAVMA Drawing, 99.9 ± 10.3			6.4 [2.1, 10.7], WRAVMA Drawing			yes
				≤ 2/wk, n =201	74	2. Wide Range Assessment	WRAVMA Pegboard, 99.8 ± 10.3			6.4 [2.0, 10.8] WRAVMA Total			yes
				> 2/wk, n =40	12	of Visual Motor Abilities	WRAVMA Matching, 107.8 ± 14.1						
							WRAVMA Total, 103.2 ± 10.5			no benefit, ≤ 2 meals/wk vs. 0			
Oken et al. (2008b)	Denmark	25,446	6 mo	fish, g/wk		19 Developmental Milestones	Range of scores at 18 mo, 5–12			Change in OR for high score	OR for high developmental score,		
			18 mo	mean 186		at 18 mo and 13 DMs at 6 mo	85% of scores betw 6 and 9			at age 18 months	highest vs. lowest fish intake quintiles		
				none	3	scored by mothers on a				1.49 [1.33, 1.66]	1.29 [1.20, 1.38] at age 18 mo		no
				1–340	86	questionnaire via interview				per added fish meal/ wk	1.25 [1.17, 1.34] at age 6 mo		no
				> 340	11								
Gale et al. (2008)	UK	217	9 yr	fish meals/wk		1. Wechsler Abbreviated							
				never	9	Scale of Intelligence	+7.55 [0.75, 14.4] Verbal IQ				OR of "hyperactive" child, eating oily		
				≤ 1 per wk	25	2. Strengths & Difficulties	if mothers ate any fish during				fish in early pregnancy vs. no fish		
				1–2 per wk	47	Questionnaire (Focus on	late pregnancy, vs. no fish				OR 0.34 [0.15, 0.78]		no
				3+ per wk	19	Hyperactivity, 1 of 6 indices)							
Lederman et al. (2008)	US	280	12, 24,	types of fish		1. Bayley Scales of Infant	Ate fish vs. no fish:						
			36, 48	0, n =67	32	Development, 2nd Ed.,	BSID Psychomotor Devel						

Table 3 (*continued*)

Authors/Date	Country	N=	Ages	Exposure Index, Break Point (s)	% w/ intake	Outcome Measure (s)	Results				
							Raw Scores	Slope or β Coefficient [95% CI]	Odds Ratio [95% CI]	p value	Adjust for Hg?
			mo	1, n =46	22	at ages 1, 2 and 3 yr	Index @36 mo,+8.7			0.002	yes
				2, n =42	20	2. Wechsler Preschool and Primary	WPPSI Full IQ @48 mo,+5.64			<0.001	yes
				≥3, n =57	27	Scale of Intelligence at age 4 yr	WPPSI Verbal IQ @48 mo,+5.60			<0.001	yes
Suzuki et al. (2010)	Japan	498	3 days	fish, g/wk		Neonatal Behavioral		Pearson Product-Moment			
				mean, 357		Assessment Scale:		Correlation Coefficient			
				S. D. ± 244		28 behavioral and 18 reflex		betw. fish intake and			
				median, 306		items scored in 7 clusters		Motor Cluster score, 0.102		0.03	yes
				range, 0.3–2,185		Focus on Motor Cluster					
Sagiv et al. (2012)	US	421	8 yr	fish meals/wk		Diagnosis of Attention Deficit			>2 vs. ≤2 fish meals/week		
				mean, 3.7 ± 3.9		Hyperactivity Disorder @ age 8,			OR of score above 86th percentile on		
				median, 2.3		Inattentive component &			Connors Rating Scale Components:		
				range, 0−22.6		Impulsive/Hyperactive component;			Inattentive, OR 0.6 [0.4, 0.9]		yes
				≤2, n =248	48	Based on computer lab evaluations,			Impuls/Hyperact, OR 0.4 [0.2, 0.6]		yes
				>2, n =267	52	WISC-III Hyperactivity Scales, and Connors (teacher) ratings			Total ADHD, OR 0.6 [0.4, 0.9]		yes

Table 4
Recent studies of adverse effects of prenatal methylmercury exposure.

Authors/date	Country	N =	Ages	Exposure index, Break Points	% w/exp	Outcome Measures	Results: Raw Scores	Results: Slope or β Coefficient [95% CI]	Results: Relative Risk/OR [95% CI]	Results: p value	Results: Adjust for ben?
Oken et al. (2005)	US	135	6 mo	Maternal hair Hg		Visual Recognition Memory	mean 59.8, range 10.9 – 92.5	− 7.5 [− 13.7, − 1.2] per μg/g hair Hg			yes
				mean 0.55 μg/g			low Hg, low fish, VRM = 60				
				min 0.02 μg/g			low Hg, high fish, VRM = 72				
				max 2.38 μg/g			high Hg, low fish, VRM = 53				
				low, < 1.2 μg/g	90		high Hg, high fish, VRM = 55				
				high, ≥ 1.2 μg/g	10						
Jedrychowski et al. (2006)	Poland	233	1 yr	Maternal blood Hg		Bayley Scales of Infant	15% scored "Delayed" on BSID		RR for "delayed" score		
				GM 0.55 μg/L		Development, 2nd Ed. (BSID-II)	MDI, 92.6 ± 11.6 vs. 102.6 ± 8.7		3.58 [1.40, 9.14] for cord blood		
				S. D. ± 0.06 μg/L		Two sub-indices:	PDI, 83.0 ± 9.4 vs. 99.6 ± 10.1		Hg > median, 0.80 μg/L		
				median 0.50 μg/L		Mental Development Index (MDI)	Hg, normal, 0.52 [0.46, 0.58] μg/L		2.82 [1.17, 6.79] for maternal	0.0101	no
				min 0.10 μg/L		Psychomotor Devel. Index (PDI)	Hg, delayed, 0.75 [0.59, 0.94] μg/L		blood Hg > median, 0.50 μg/L		
				max 3.4 μg/L							
				low, ≤ 1.0 μg/L	75						
				high, > 1.0 μg/L	25						
Gao et al. (2007)	Zhoushan, China	384	3 days	Cord blood Hg		Neonatal Behavioral Neurological	Maximum NBNA score is 40		OR for decreased Behavior		
				GM 5.58 μg/L		Assessments (NBNA)	94% of subjects scored ≥ 37		score if cord Hg > 5.8 μg/L,	< 0.001	no
				high, > 5.8 μg/L	70	Five clusters: Behavior, Passive	Behavior scores of boys were		1.235 [1.078, 1.414]		
				maternal hair Hg		Tone, Active Tone, Reflexes,	associated with Hg exposure				
				GM 1.25 μg/g		and General Assessment	(no other clusters, none in girls)				
Oken et al. (2008a)	US	341	3 yr	Maternal rbc Hg		1. Peabody Picture Vocabulary Test	Effect Estimates,	− 0.4 PPVT pts per ng/g Hg			yes
				mean 3.8 ng/g		2. Wide Range Assessment	Top decile Hg vs. lower 90%:	− 0.06 WRAVMA pts per ng/g Hg			yes
				S. D. ± 3.8 ng/g		of Visual Motor Abilities	PPVT, − 4.5 [− 8.5, − 0.4]				yes
				range 0.03 – 21.9			WRAVMA, − 4.6 [− 8.3, − 0.9]				yes
				low, < 9.1 μg/g	90						
				high, ≥ 9.1 μg/g	10						
Lederman et al. (2008)	US	280	12, 24,	Cord blood Hg		1. Bayley Scales of Infant	Mean (± S. D.) outcome scores:	β, Ln Cord Hg vs. outcome:			
			36, 48	mean 7.82 μg/L		Development, 2nd Ed.,	BSID MDI, 24 mo, 96.1 ± 12.6	− 2.76		0.035	
			mos	S. D. 9.71 μg/L		at ages 1, 2 and 3 yr	BSID PDI, 36 mo, 98.4 ± 13.1	− 4.16		0.007	yes
				min 0.10 μg/L		2. Wechsler Preschool	Perf IQ, 48 mo,	− 3.45		0.023	

Table 4 (*continued*)

Authors/date	Country	N =	Ages	Exposure index, Break Points	% w/exp	Outcome Measures	Results: Raw Scores	Results: Slope or β Coefficient [95% CI]	Results: Relative Risk/OR [95% CI]	Results: p value	Results: Adjust for ben?
						and Primary	100.7 ± 13.9				
				max 63 μg/L		Scale of Intelligence at age 4 yr	Verbal IQ, 48 mo, 95.7 ± 13.2	−2.92		0.023	
				GM 4.44 μg/L			Total IQ, 48 mo, 97.6 ± 12.7	−3.76		0.002	
Suzuki et al. (2010)	Japan	498	3 days	Maternal hair Hg		Neonatal Behavioral Assessment		1. Pearson product-moment			
				mean 2.22 μg/g		Scale, 28 behavioral items		correlation coefficient, hair Hg			
				S. D. ± 1.16 μg/g		and 18 reflex items, 7 clusters		& motor cluster score: −0.126		0.01	yes
				median 1.96 μg/g		Motor Cluster includes muscle		2. β coefficient, adjusted multiple			
				min 0.29 μg/g max 9.35 μg/g		tone and movement		regression model: −0.116		< 0.05	yes
Sagiv et al. (2012)	US	421	8 yr	Maternal hair Hg		Diagnosis of Attention Deficit	Scores dichotomized at 86th		RR, Hair Hg ≥ 1 μg/g vs. < 1 μg/g		
				mean 0.62 μg/g		Hyperactivity Disorder @ age 8,	percentile of Connors scale;		(fully adjusted model)		
				S. D. ± 0.57 μg/g		Inattentive component &	RR's calculated of score above				
				median 0.45 μg/g		Impulsive/Hyperactive component;	86th percentile (i.e., ADHD)		Inattentive, 1.3 [1.0, 1.7]		yes
				range 0.03 – 5.14		Based on computer lab evaluations,			Impuls/Hyperact 1.6 [1.1, 2.4]		yes
				high = ≥ 1.0 μg/g	16	WISC-III Hyperactivity Scales,			Total ADHD Score 1.5 [1.1, 2.0]		yes
				low = < 1.0 μg/g	84	and Connors (teacher) ratings					
Lam et al. (2013)	Hong Kong, China	608	8 yr	Cord blood Hg		1. Hong Kong Version of Weschsler	1. Picture arrangement, HK-WISC				
				mean 10.0 μg/L		Intelligence Scale for Children	low Hg 11.83, high Hg 11.53	β = −0.944 ± 0.479		0.049	no
				S. D. ± 4.8 μg/L		2. Hong Kong List Learning Test	2. Short-delay word recall, *HKLLT*				
				median 9.2 μg/L		3. Tests of Everyday Attention	low Hg −0.83, high Hg −1.40	β = −1.087 ± 0.399		0.007	no
				max 36.9 μg/L		for Children	3. Long-delay word recall, *HKLLT*				
				low, ≤ 5.8 μg/L	19	4. Boston Naming test	low Hg −0.85, high Hg −1.36	β = −1.161 ± 0.415		0.005	no
				high, > 5.8 μg/L	81	5. Grooved Pegboard Test					
Wu et al. (2014)	Zhoushan, China	418	3 days	Maternal blood Hg		Neonatal Behavioral Neurological	Hg exposure associations				
				mean 5.68 μg/L		Assessments (NBNA)	with decreased score for:				
				S. D. ± 4.04 μg/L		Five clusters: Behavior, Passive	Active muscle tone	β = 0.06 ± 0.02	OR 1.06 [1.01, 1.11]	0.017	no
				75%ile 8.19 μg/L		Tone, Active Tone, Reflexes,	Passive muscle tone	β = 0.07 ± 0.03	OR 1.07 [1.02, 1.13]	0.0071	no
				low, ≤ 5.8 μg/L	44	and General Assessment	Primary reflexes	β = 0.09 ± 0.05	OR 1.11 [1.02, 1.21]	0.0662	no

				high, > 5.8 μg/L	56		Total NBNA score	β=0.03 ± 0.01		0.0409	no
Orenstein et al. (2014)	US	393	7–11 yr	Maternal hair Hg		Wide Range Assessment		Each 1 μg/g Hg in maternal hair			yes
			ave. 8	mean 0.60 μg/g		of Memory and Learning	Mean scores (n =393)	is associated with:			
				S. D. ± 0.60 μg/g		9 subtests, 3 indices:					
				min 0.03 μg/g		1. Visual Memory Index	88.3 ± 13.2, Visual Memory	−2.8 [−5.0, −0.6] Visual Memory		0.01	yes
				max 5.1 μg/g		2. Verbal Memory Index	91.2 ± 13.0, Verbal Memory	−1.7 [−3.9, 0.6] Verbal Memory		0.14	yes
				low, ≤ 1.0 μg/g	~85	3. Learning Index	97.4 ± 14.0, Learning	−2.2 [−4.6, 0.2] Learning		0.08	yes
				high, > 1.0 μg/g	~15						
Ng et al. (2015)	Taiwan, China	166	2 yr	Cord blood Hg		Chinese Version of Child behavior	Results in ε4 APOE carriers,	β (SE), ε4 APOE carriers w/ high			
				mean 14.7 μg/L		Checklist (100 items in 7 domains)	Scores for affected domains,	Hg vs. non-carriers w/ low Hg			
				S. D. ± 8.7 μg/L		(only affected domains listed)	mean ± S. D., (range)				
				median 12.0 μg/L		Internalizing	12.0 ± 7.3 (0 − 32)	5.6 (2.1)		0.01	yes
				min 1.53 μg/L		Externalizing	15.8 ± 7.7 (0 − 39)	4.1 (2.2)		0.06	yes
				max 47.1 μg/L		Emotionally Reactive	3.1 ± 2.5 (0 − 11)	1.8 (0.7)		0.02	yes
				low, < 12.0 μg/L	50	Anxious/Depressed	3.7 ± 2.3 (0 − 12)	2.1 (0.7)		< 0.01	yes
				high, ≥ 12.0 μg/L	50	Aggressive Behavior	12.8 ± 6.4 (O −32)	3.6 (1.8)		0.05	yes
						Total Problems	46.6 ± 21.3 (6 − 109)	14.3 (6.1)		0.02	yes
Jacobson et al. (2015)	Nunavik, Canada	279	11 yr	Cord blood Hg		Childhood IQ, using Wechsler	Full IQ Scores, mean ± S. D.:	β, effect of cord Hg on IQ:	Relative Risk of IQ < 80		
				mean 21.8 μg/L		Intelligence Scale for Children	Hg < 7.5 μg/L, IQ 95.8 ± 11.7	−0.17 [−0.31, −0.02]	17.2% if Hg ≥ 7.5 μg/L	0.021	yes
				S. D. ± 17.5 μg/L		4th Ed. (WISC-IV) and additional	Hg > 7.5 μg/L, IQ 91.0 ± 11.0		4.3% if Hg < 7.5 μg/L		
				min 1.0 μg/L		culturally-adapted tests for			RR =4.0		
				max 99.3 μg/L		verbal ability					
				low, < 7.5 μg/L	17						
				high, ≥ 7.5 μg/L	83						
Vejrup et al. (2016)	Norway	46,750	3 yr	Maternal Hg daily		Language Development,	Indices of Speech Development		OR's, high Hg vs. low Hg		
				dose in diet (est.)		rated on a 5-point scale for use	(best to worst ratings):				
				median 1.3 μg		of grammar, full sentences,	Full sent., good gram, n =36,177				
				min 0.00 μg		speaking clearly	Full sent., bad gram., n =8,719		1.01 [0.93, 1.10]		yes
				max 14.45 μg			Short sentences, n =1,486		1.06 [0.88, 1.26]		yes
				high, > 90th %ile,			Unintelligible Speech, n =102		2.22 [1.31, 3.72]		yes
				> 2.6 μg	10		Did not talk/single words, n =266		1.04 [0.69, 1.57]		yes
						Ability to Communicate	Normal skills, n =44,757				
							Weak skills, n =595		1.33 [1.03, 1.70]		yes

Sidebar A–: The U. S. Reference Dose

The U. S. Environmental Protection Agency (EPA) establishes *Reference Doses* for toxic substances. A Reference Dose (RfD) is an estimated level of long-term exposure likely to pose no appreciable risk of adverse effects. RfDs are set by the USEPA to define tolerable exposures against which estimated actual exposures of populations can be compared to assess whether risk management measures may be called for.

In 2000 the USEPA set a RfD for MeHg (Rice et al., 2003). The agency began with the Faroes study (Grandjean et al., 1997), which associated several significant adverse cognitive outcomes with an average blood Hg level of 58 μg/L. Using that as a Benchmark Dose, EPA applied a 10-fold Uncertainty Factor (UF) to account for variation in individual sensitivity to toxic effects and other uncertainties in the risk assessment. The 10X UF produced a target blood Hg level of 5.8 μg/L, which a pharmacokinetic model associated with a dietary MeHg dose of 0.1 μg/kg of body weight per day. EPA thus set the RfD at 0.1 μg/kg/day.

That RfD can be used to estimate exposures at the RfD level for individuals of various body weights and various times. For example, the RfD for a 60-kg woman is 60 kg × 0.1 μg/kg/day = 6 μg/day. Since fish consumption advice typically focuses on weekly intake, MeHg intake at the RfD for one week for that standard 60-kg woman can be calculated as 42 μg (i.e., 7 days × 6 μg/day).

The equilibrium blood Hg level associated with long-term intake at the RfD, 5.8 μg/L, is sometimes called the "reference level" of Hg in blood, a term used in this paper. A hair Hg level of 1.0 μg/kg corresponds approximately to a blood level of 5.8 μg/L, and is sometimes referred to as the "reference level" of Hg in hair.

from 3 days to 11 years. A meta-analysis of data from these studies has not been feasible, in large part because of this heterogeneity. The primary aims of Table 4 are to display the array of cognitive outcomes MeHg may affect and to compare levels of exposure associated with cognitive decrements in recent low-dose studies.

Several studies appear in both Tables 3 and 4; i.e., those studies observed both beneficial effects of maternal fish consumption and adverse effects of MeHg on the same cognitive outcomes in the same children. Those studies (and a few that looked for beneficial effects but found no statistically significant ones) generally controlled effectively for mutual confounding between benefits and harm, and their estimates of each effect have been adjusted to account for any confounding that was present; these methodological strengths enhance confidence in their quantitative results. For those studies in Table 4 that did not assess beneficial effects or adjust for mutual confounding, the cognitive decrements reported are, by default, net adverse effects.

Most studies in Table 4 divided their study populations into high- and low-MeHg exposure groups and compared outcomes for the two subsets. Gao et al. (2007), Lam et al. (2013) and Wu et al. (2014) each used the US reference blood Hg level, 5.8 μg/L (see Sidebar A) as their dividing line, and observed adverse effects in subjects with exposure > 5.8 μg/L. Jacobson et al. (2015) divided their subjects at a cord blood Hg level of 7.5 μg/L, or slightly above the US reference level. Oken et al., 2005, 2008a used the 90th percentile of Hg exposure in their cohort as their dividing line; their 2005 high-Hg subjects had a hair Hg level of ≥ 1.2 μg/g, or slightly above the US reference hair Hg level of 1 μg/g. In 2008 they used maternal red blood cell Hg as their exposure index. NHANES data for the Northeast show a 90th percentile whole blood Hg level of 5.2 μg/L (Mahaffey et al., 2009), which is probably a reasonable estimate for the 90th percentile whole blood level (not reported) in this study. Sagiv et al. (2012) defined elevated exposure in their cohort as maternal hair Hg > 1 μg/g.

Two studies, Lederman et al. (2008) and Orenstein et al. (2014), developed continuous dose-response functions spanning the full range of exposure in their cohort. Lederman et al.'s subjects had a mean maternal blood Hg level of 1.6 μg/L, while Orenstein et al.'s had a mean maternal hair Hg level of 0.60 μg/g. In both populations, the applicable US reference level fell within the exposure distribution, and higher-exposed individuals (those more likely to experience adverse outcomes) had blood or hair Hg values around or above those same reference levels. In summary, these nine studies all have associated adverse neurodevelopmental effects of MeHg exposure with exposures around or only slightly above about 5.8 μg/L in blood or 1 μg/g in hair, exposure levels that correspond roughly to the US RfD.

Two other studies in Table 4 associated cognitive deficits with prenatal MeHg exposures substantially below the US RfD. Jedrychowski et al. (2006) found developmental delays in children with a geometric mean cord blood Hg level of 1.05 μg/L and maternal GM 0.55 μg/L. Vejrup et al. (2016) associated delays in language development with maternal Hg doses above 2.6 μg/day, i.e., less than half the US RfD for a 60-kg woman. Though still low-dose studies, Suzuki et al. (2010) and Ng et al. (2015) each examined populations with higher fish intake and Hg exposure than in the US. The mean maternal hair Hg in Suzuki et al.'s Japanese cohort was 2.22 μg/g, while the median cord blood level in Ng's Taiwanese subjects was 12 μg /L; each value is about twice the corresponding US reference level.

3.5. Discussion: epidemiological evidence

The studies in Table 3 form a small but cohesive body of evidence that shows fairly convincingly that fish consumption during pregnancy has substantial benefits for children's cognitive development. Several issues remain unresolved. The strongest evidence is from the ALSPAC study, which has not been replicated, and may have controlled inadequately for some important confounding factors (Hattis, 2011). It is also unclear whether ALSPAC findings would apply for other populations with different seafood diets.

It is still somewhat uncertain whether benefits reach a plateau, although some analysts have concluded that they do. Specific constituents of fish that benefit prenatal cognitive development have also not been definitively identified. The n-3 PUFAs are known to be essential for brain development, and target intakes for n-3 s during pregnancy have been set (see DGA, 2015). Some clinical trials have reported beneficial effects of n-3 supplementation during pregnancy or lactation (see Cohen et al., 2005b), while other more recent trials have been negative (Makrides et al., 2009, 2010; Smithers et al., 2010, 2011). The studies in Table 3 for the most part reported seafood consumption (fish meals or grams per week during pregnancy), rather than quantifying n-3 intake. Thus significant uncertainty remains as to whether observed neurodevelopmental benefits can be attributed specifically to the n-3 content of seafood diets or just to "fish" as a package of nutrients.

Recent studies associating adverse effects on cognitive development with fish consumption during pregnancy, summarized in Table 4, mostly involve low-dose MeHg exposures, with dividing lines between high and low exposure clustered rather tightly around the US RfD. On the whole this evidence suggests that the RfD, which when established was thought to incorporate a 10-fold margin of exposure below the benchmark (i.e., clearly harmful) dose, may now be more accurately regarded as a dose level at or only slightly above which adverse effects can be observed.

In qualitative terms, several studies in Table 4 report neurodevelopmental deficits that cannot readily be converted to IQ scores (as was necessary for the meta-analyses in Table 2 and most benefit-risk models discussed in the Section 4); many of these

effects also were not previously linked to Hg. Some of these findings are supported by other evidence; for instance, Sagiv et al.'s 2012 report linking low-level MeHg exposure with Attention Deficit/Hyperactivity Disorder is similar to a study in a highly-exposed Inuit population associating a 4-fold increased risk of ADHD diagnosis with elevated prenatal MeHg exposure (Boucher et al., 2012). Three studies in Table 4 (two in China and one in Japan) have associated mildly impaired neuromotor functions in newborn infants with elevated maternal Hg exposure from fish consumption.

Several studies, starting with Murata et al.(2004), have associated low-level MeHg exposure with delayed transmission of nerve signals in the brain. Murata et al. examined auditory signals, while Boucher et al. (2014) and Ethier et al. (2012) linked MeHg with delayed transmission of signals in the visual cortex. Oken et al. (2005), Lam et al. (2013), Orenstein et al. (2014) and others have flagged visual memory development as a specific cognitive domain that may be particularly sensitive to disruption by MeHg exposure. On the whole, the literature now suggests that MeHg exposure can affect development of a wide variety of neurobehavioral and cognitive functions, some just beginning to be identified. There is no clear consensus as to what outcome or domain is "critical" or most sensitive to possible MeHg effects during brain development.

Both the quantitative magnitude of observed cognitive deficits and the fraction of the cohort with elevated exposure varied widely across the studies in Table 4, but the evidence as a whole suggests that MeHg effects are neither rare nor minimal and cannot be regarded as negligible compared to beneficial effects of fish intake. Decrements in relative performance on various outcome measures are greater than 25% of scoring scales in some studies; relative risks of adverse outcomes are up to 3–4 times as great in some higher-exposed subjects. These differences are as large as or in some cases greater than beneficial effects associated with fish consumption in Table 3.

The Hg doses associated with cognitive decrements in different studies also vary. The high fish and Hg intake of the Japanese, Hong Kong and Taiwan cohorts occur in only about 2% of US women, according to the FDA (2014a). The fraction of women with exposure above US Reference Levels (used as the definition of elevated exposure in several studies) varies from region to region in the US but averages about 4–5% (Mahaffey et al., 2009). In some subpopulations, such as Sagiv et al. (2012)'s New Bedford subjects or the Asian-American subset of Lederman et al.'s (2008) cohort, the fraction is much higher; 17% of Sagiv et al.'s mothers exceeded the hair reference level, and Lederman et al.'s Asian children had 4 times the average cord blood Hg level of non-Asians. The low dose (less than half the US RfD) associated with language delays in Norway is exceeded by about 17% of US women (FDA, 2014a). Overall, the evidence summarized in Table 4 associates frequently non-negligible cognitive deficits with prenatal MeHg exposure from fish intake. The doses involved are comparable to those routinely encountered by from a few percent to up to one in six US women of childbearing age.

There are many data gaps and differences and inconsistencies among studies, and many questions need more research. Some studies observed effects in very young subjects but not in the same cohorts when they were older (e.g., Jedrychowski et al., 2006, 2007; Oken et al., 2005, 2008a, 2014; Suzuki et al., 2010 and Tatsuda et al., 2014). In contrast, Lederman et al. (2008) found stronger associations in 3- and 4- year olds than in younger children, and Jacobson et al. (2015), Lam et al. (2013), Orenstein et al. (2014) and Sagiv et al. (2012), examined only older children but still associated deficits with prenatal exposure. Overall, the evidence suggests that effects of MeHg are highly domain-specific; as yet, neither IQ (often used to integrate results of different studies) nor any other outcome measure(s) can be defined as the most appropriate indicator of MeHg toxicity to the developing brain. While the existence and importance of variation among individuals in sensitivity to toxic effects has long been recognized, only recently has research begun to explore some specific genetic variations that affect susceptibility to MeHg (see Basu et al., 2014; Julvez and Grandjean, 2013; Julvez et al., 2013; Lee et al., 2010; Ng et al., 2013, 2015).

4. Benefit-risk models

The focus here is on models designed for or useful for comparing different seafood items to support consumer advice on which fish to choose or to avoid. Some benefit-risk models have also been used to estimate aggregate effects on neurodevelopment of all children, but that topic is outside the scope of this discussion. Four recent models are suitable for supporting seafood-choice advice. Their developers have combined epidemiologically-derived functions for benefits of nutrients and adverse effects of MeHg with seafood consumption scenarios to estimate net effects on cognitive development from eating different fish. Although the absolute values of the estimated outcomes differ widely based on differences in the data and assumptions fed into each model, the relative results for and rankings of different fish varieties offered by the models are generally quite informative and useful.

Benefit-risk models are valuable tools precisely because modelers can plug in any data and assumptions that seem reasonable and examine how those choices affect outcomes of interest. That same flexibility is also the most important limitation on modeling: Essentially, the results of modeling depend on subjective, often arbitrary choices, and the value of exploring multiple scenarios is offset by the need to interpret any quantitative model results cautiously.

Table 5 compares the projected net effects on neurodevelopment for 22 seafood varieties included in most or all models examined ("n.a." indicates that a particular variety was not included in that model.) Two of the models, FAO/WHO (2011) and FDA (2014a), include multiple versions and scenarios and appear in more than one column of the table. Three models expressed their results in terms of projected net effects on child IQ, while Ginsberg and Toal (2009) used Visual Recognition Memory (VRM) data from Oken et al.'s 2005 study, described in Tables 3 and 4 above. VRM, like IQ, is scored on a 100-point scale. Values in standard font in the table are net beneficial effects (i.e., IQ or VRM points gained), while values shown in parentheses and bold font (in parentheses) are net adverse effects (IQ or VRM points lost).

As the table makes clear, results of the different models vary a great deal. Ginsberg and Toal (2009) considered 16 popular seafood choices in Connecticut, USA and assumed a pregnant woman ate one 6-ounce (170-g) serving of one item per week. Their model projects effects that range from net gains of 10–12 VRM points for salmon, herring or anchovies, to net losses of 25–26 VRM points for swordfish and shark. Zeilmaker et al. (2013) used dose-response functions from Cohen et al., (2005a, (2005b, see Table 2) and assumed a "worst-case scenario" in which a woman ate 100 g of one seafood variety every day (700 g/week) before and throughout pregnancy to compare 33 popular European seafood items. Their model also projected a broad range of outcomes, from net gains of 0.5-2 IQ points for half a dozen fish varieties to net IQ losses of 8-12 IQ points for higher-Hg items like albacore tuna, pike and swordfish.

In contrast, the US FDA (2014a) and FAO/WHO (2011) models project net beneficial effects from consuming essentially any amount of any fish during pregnancy. The FDA modelers used a benefits slope derived using data from Daniels et al. (2004, see

Table 5
Net effects on neurodevelopment of consuming various popular seafood items while pregnant, as estimated by recent risk-benefit models.

	Benefit-Risk Models (cited publications)							
Authors & Date	Ginsberg and Toal (2009)	Zeilmaker et al. (2013)	FAO/WHO (2011)	FAO/WHO (2011)	FAO/WHO (2011)	FAO/WHO (2011)	FDA (2014a)	FDA (2014a)
Weekly Fish Intake	170 g/week	700 g/week	200 g/week	200 g/week	700 g/week	700 g/week	Optimal[a]	Optimal
Model Version			Central Est	Upper Bound	Central Est	Upper Bound	Fish	Omega-3 s
Outcome Measure	**VRM**	**IQ**	**IQ**	**IQ**	**IQ**	**IQ**	**IQ**	**IQ**
Seafood Item								
Sardines	n.a.	0	5.8	5.6	5.7	5.3	3.2	3.3
Salmon, Atlantic	12	2	5.8	5.6	5.7	5.3	3.2	3.3
Herring, Anchovies	10	0.5	5.8	5.6	5.7	5.3	3.2	3.3
Trout, Freshwater	5	0.3	5.8	5.6	5.7	5.3	3.2	3.2
Mackerel, Atlantic	n.a.	1	5.8	5.6	5.7	5.3	3.2	3.2
Shrimp	2	0	1.5	1.3	5.3	4.9	3.3	3.3
Pollock	1.2	n.a.	1.5	1.3	5.3	4.9	3.2	3.2
Clams/Mussels/ Oysters	n.a.	0	1.5	1.3	5.3	4.9	3.3	3.3
Tilapia	0.5	0.5	1.5	1.3	5.3	4.9	3.3	3.2
Catfish	n.a.	**(−1.5)**	1.5	1.3	5.3	4.9	3.3	3.2
Flounder, Sole	1.4	**(−2)**	1.5	1.3	5.3	4.9	3.2	3.1
Halibut	**(−4)**	**(−4)**	5.6	4.9	5	2.5	3	3.1
Tuna, Canned Albacore	**(−6)**	**(−8)**	4	3.3	3.4	0.9	2.8	3
Tuna, Canned Light	**(−2)**	n.a.	n.a	n.a.	n.a	n.a	3.1	3
Tuna, Fresh	**(−8)**	**(−8)**	1.3	0.6	4.6	2.1	2.8	2.9
Sea Bass	**(−5)**	n.a.	5.6	4.9	5	2.5	3	3.1
Cod	**(−2.5)**	**(−1)**	1.5	1.3	5.3	4.9	3.2	2.9
Lobster	**(−5)**	n.a.	1.3	0.6	4.6	2.1	3.2	2.9
Pike	n.a.	**(−11)**	1.5	1.3	5.3	4.9	n.a	n.a.
Swordfish	**(−25)**	**(−12)**	3	**(−0.5)**	1.6	**(−10.5)**	2	2.5
Shark	**(−26)**	n.a.	3.6	1.9	3.7	**(−2.4)**	2	2.4
Orange Roughy	n.a.	n.a.	0.9	**(−0.8)**	3.3	**(−2.8)**	2.6	0

[a] "Optimal" intake in the FDA model varies by seafood type; it is the weekly intake at which the excess of benefit over risk is maximum.

Table 3), and the adverse effects slope from Axelrad et al. (2007), shown in Table 2. The model has a version in which benefits are attributed to n-3 s, and one in which they are associated simply with "fish" as a nutrient package. MeHg reduces the size of beneficial effects in this model, but overall it predicts strong net beneficial effects for virtually all seafood varieties and likely consumption scenarios. The model identifies an optimal intake for each variety, defined as the weekly serving at which the excess of benefit over adverse effect is maximized. Optimal servings are all 8-10 ounces (227–284 g) per week in the fish-as-a-package version of the model, but range from 3 to 53 ounces 85-1,504 g) in the n-3 s version, reflecting the wide differences in n-3 content of seafood items. At optimal intakes in either version the model projects net IQ gains of 2.0-3.3 points for most seafood choices, with only small differences by type of fish.

The FAO/WHO model is largely based on an earlier iteration of FDA's model (FDA, 2009). The expert consultation that produced this modeling report sorted 96 seafood varieties into a 4×4 matrix, stratified by n-3 and MeHg content, then projected beneficial and adverse effects on neurodevelopment using average n-3 and Hg values for each matrix cell. For example, herring, anchovies, Atlantic mackerel, trout, sardines and farmed Atlantic salmon all fall in the group with highest n-3 and lowest Hg content, and as the table shows, all are projected by the model to have identical large net beneficial effects on IQ.

The FAO/WHO modelers ran multiple scenarios, assuming a woman would eat 1, 2, 4 or 7 100-g servings of seafood per week while pregnant; for simplicity, they assumed she would always choose items from the same matrix cell. Two of those scenarios (200 and 700 g/week intake) are shown in Table 5. This model also includes two versions in which different slopes were used for the effect of prenatal MeHg exposure on child IQ; the table displays results using the "central estimate" slope (from Axelrad et al., 2007, see Table 2), and "upper bound" slope (from Cohen et al., 2005a, Table 2) for each intake scenario.

As Table 5 shows, the FAO/WHO model using the upper bound slope for Hg effects predicts net adverse effects on child IQ for a few highest-Hg fish at both consumption rates. But the FAO/WHO report focuses only on the central estimate results, concluding that "maternal fish consumption lowers the risk of suboptimal neurodevelopment in their offspring compared with the offspring of women not eating fish in most circumstances evaluated" (FAO/WHO, 2011).

Differences in results of these different models have led to parallel differences in seafood consumption advice from the modelers. Ginsberg and Toal (2009) and Zeilmaker et al. (2013) stressed both the benefits of maternal fish intake and the need to minimize prenatal MeHg exposure, and advised women to choose higher n-3, lower Hg seafood items. On the other hand, the US FDA and EPA relied almost exclusively on the FDA model when issuing updated draft joint fish consumption advice (FDA, 2014b); the advice urges pregnant women to eat more fish and treats seafood variety and Hg content as relatively minor concerns. The Dietary Guidelines Advisory Committee, advising HHS and USDA on the 2015 update to the Dietary Guidelines for Americans, cited only the FAO/WHO model as its basis for recommending that pregnant women increase their fish intake and that MeHg concerns should be de-emphasized (DGAC, 2015).

4.1. *Discussion: benefit-risk models*

The results in Table 5 not only differ greatly from each other, but some also differ strikingly from the epidemiological evidence, particularly on the risk side summarized in Table 4. At minimum, divergence between epidemiological observations and modeling results suggests that model results need to be interpreted cautiously. Because the FDA and FAO/WHO models are a proposed basis for US fish consumption advice, it is worth exploring in some detail why model results differ so much from each other and from epidemiological observations.

Table 6
Slopes for benefit and risk functions used in different models.

	FDA (2014a)	FAO/WHO Central Est.	FAO/WHO Upper Bound	Ginsberg and Toal (2009)	Zeilmaker et al. (2013)
	(IQ points)	(IQ points)	(IQ points)	(VRM points)	(IQ points)
DHA Benefit per 100 mg/day	2.8	4	4	2	0.13 (0.08, 0.18)
Benefit plateau?	Yes	Yes	Yes	No	No
Mercury Harm per μg/g in hair	−0.18	−0.18	−0.7	−7.5	−0.2 (0, −1.5)

The simplest and most obvious reason for the disparities in model results in Table 5 is that the modelers in each case used different dose-response coefficients to estimate beneficial and adverse effects. Table 6 shows the slopes chosen for those coefficients in the different models. Slopes used in the models can also be compared with the slopes observed for various beneficial and adverse effects in epidemiological studies shown in Tables 3 and 4.

Zeilmaker et al. (2013) used slopes from Cohen et al., (2005a, 2005b, see Table 2); the slope for n-3 benefits, from clinical trials with supplements, was far smaller than the slope for MeHg effects derived from the Faroes, Seychelles and New Zealand studies. Thus their model projected modest net benefits for some species and larger net adverse effects for other varieties.

FDA (2014a) incorporated data shared with them by the ALSPAC research team into their model and estimated the slope for benefits to be 2.8 child IQ points gained per 100 mg/day of maternal n-3 intake. The FAO/WHO modelers had data from two ALSPAC reports, Daniels et al. (2004) and Hibbeln et al. (2007), and estimated a combined average slope of 4 IQ points gained per 100 mg/day of n-3 s. Both the FDA and FAO/WHO models include an assumption that beneficial effects plateau at about 12 ounces per week of fish intake; consequently, the maximum IQ gain possible from eating any amount of any fish is 3.3 points in the FDA model and 5.8 points in the FAO/WHO model.

To estimate adverse effects of MeHg, both the FDA model and the "central estimate" version of the FAO/WHO model used the slope from Axelrad et al.'s (2007) meta-analysis, −0.18 IQ points per 1 μg/g Hg in maternal hair (see Table 2). Given the very large slopes for beneficial effects and this much smaller slope for MeHg effects, these models' predicted excess of benefits over harm for essentially all plausible seafood intake scenarios is a foregone conclusion. The "upper bound" version of the FAO/WHO model uses a steeper slope, −0.7 IQ points per 1 μg/g hair Hg, Cohen et al.'s (2005a) "central estimate," (see Table 2), but there, too, the difference between slopes for beneficial and adverse effects is about 6-fold, and the model projects net IQ gains for consumption of all but a few very high-Hg fish.

Ginsberg and Toal's (2009) model uses dose-response data showing both strong benefits and strong adverse effects on VRM, measured in the same study by Oken et al. (2005). This model predicts large beneficial effects from eating high n-3, low-Hg fish, and very large adverse effects from eating high-Hg varieties. While this approach avoids uncertainties that arise when data from different studies are combined and converted to IQ, Oken et al.'s data set is quite small, and VRM may not adequately represent many other cognitive functions affected by seafood nutrients and/or MeHg. Ideally, other modelers will follow Ginsberg and Toal's approach and use data from other studies in Tables 3 and 4 to model the benefits and risks of various seafood choices.

A central question is whether any of these models, but especially the FDA and FAO/WHO models, are scientifically sound enough to be the primary basis for government fish consumption advice. Two concerns suggest that the models need to be critically re-examined before they are accepted as the basis for such important policy applications.

The first concern is the contrast between these models and the epidemiological evidence. Fig. 1 illustrates differences in MeHg doses associated with adverse effects by the two approaches. The RfD is shown (green line near the bottom) as a reference point. The FAO/WHO "central estimate" model (highest red line) predicts a net beneficial effect at a weekly swordfish intake of 700 g, containing 25 times the weekly MeHg RfD for a 60-kg woman, while the FDA model predicts zero net effect for almost the same swordfish intake, 681 g/week, containing 16 times the RfD (the models use different values for the MeHg content of swordfish.) In contrast, the much lower MeHg doses associated with cognitive deficits in 13 epidemiological studies fall within the blue-shaded box near the bottom of the figure.

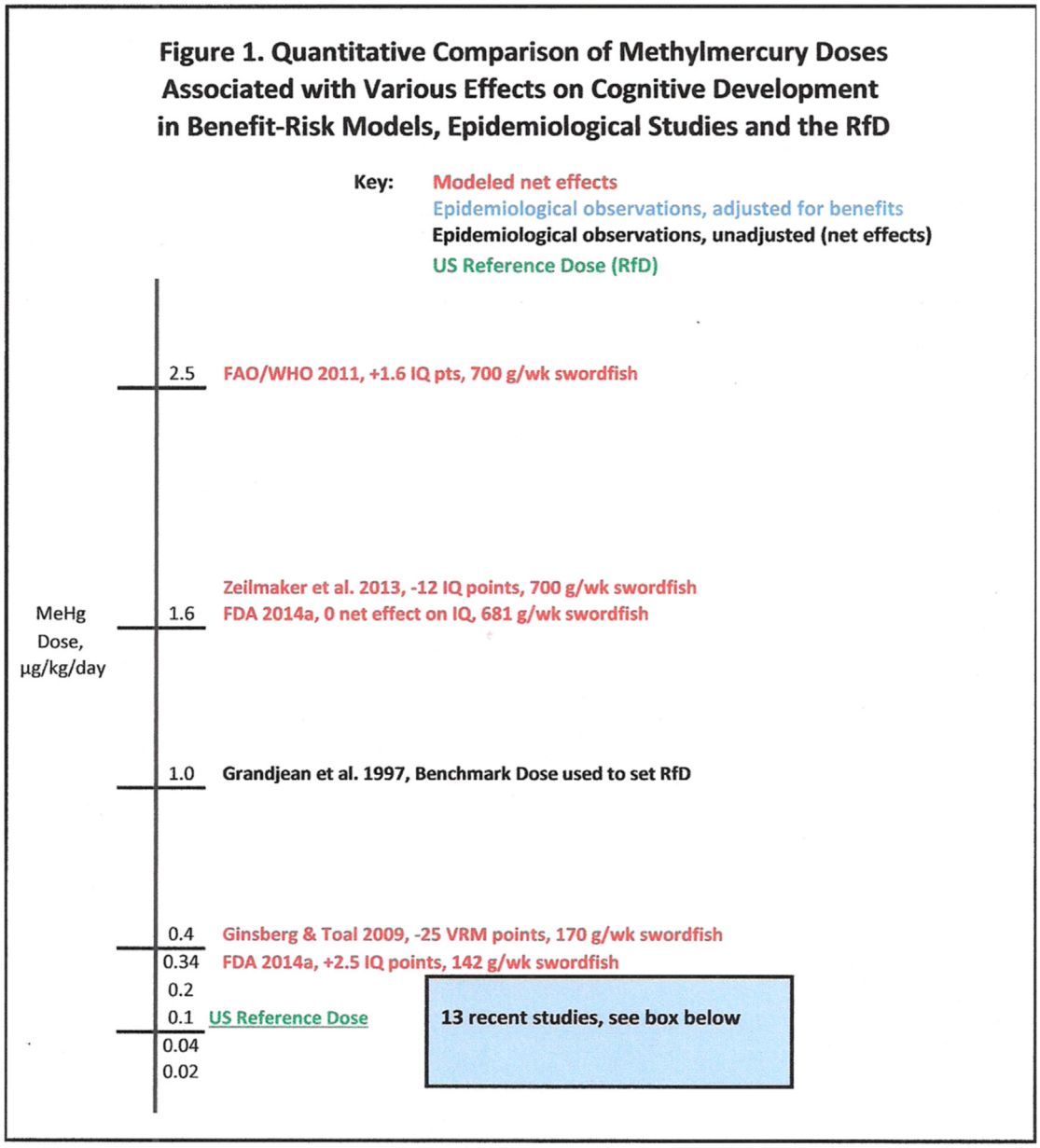
A second fundamental concern is that benefit-risk modeling is subject to unavoidable, well known limitations and uncertainties. Modeling benefits and risks of fish intake is still in its early evolution, with no consensus best approach yet, and all models reviewed here are subject to those limitations (see Sidebar B).

4.2. An integrated approach

Can differences between benefit-risk models and epidemiological data be reconciled, such that both types of evidence can be used in a balanced, integrated way to support fish consumption advice? Calibrating a model quantitatively against epidemiological evidence would support using the model's capacity to discriminate the relative benefits and risks of different seafood varieties to generate fish consumption recommendations consistent with risk and benefit estimates derived from recent epidemiology.

One way to inter-calibrate the two approaches is to replace dose-response functions used in the models with those generated in studies summarized in Tables 3 and 4, as Ginsberg and Toal (2009) have done with Oken et al.'s (2005) VRM data. This would require extensive effort and collaboration but should be encouraged. A second, simpler way to make models more congruent with epidemiology is to examine quantitative outcomes estimated by each, seeking common measures that can be compared to align model results with observed outcomes.

The FDA model (FDA, 2014a) identifies two points of particular interest on the net effects curve, illustrated generically in Fig. 2. At optimal intake, the excess of benefits over harm is maximized, and at crossover intake, the net effect is zero, i.e., the beneficial effects of fish nutrients are exactly cancelled out by the adverse effects of MeHg. Because modeled beneficial effects reach a plateau while adverse effects increase as fish and Hg intake rise, once past the optimal peak the net effects curve falls until it eventually crosses zero, and intakes greater than the crossover amount have net adverse effects. These concepts are clear, simple, reasonable, and major steps forward from vague generalities often used in the past (e.g., "the benefits outweigh the risks"). This is not to say the FDA model is established science; for instance, the assumption that benefits plateau, although perhaps sensible, is still uncertain, and many other critical open issues are enumerated in Sidebar B.



Recent studies showing adverse effects at/around the RfD/Reference Levels (see Table 4):

Gao et al. 2007, ≥ 5.8 µg/L Hg in cord blood
Jacobson et al. 2015, > 7.5 ug/L Hg in cord blood
Jedrychowski et al. 2006, > 0.80 µg/L blood
Lam et al. 2013, ≥ 5.8 µg/L Hg in cord blood
Lederman et al. 2008, continuous dose, GM 1.6 µg/L Hg in maternal blood
Ng et al. 2015, 12 µg/L blood
Oken et al. 2005, ≥ 1.2 µg/g Hg in maternal hair
Oken et al. 2008, > 5.2 µg/L Hg in maternal blood
Orenstein et al. 2014, continuous dose, mean 0.60 µg/g Hg in maternal hair
Sagiv et al. 2012, > 1. 0 µg/g Hg in maternal hair
Suzuki et al. 2010, 2.2 µg/g hair;
Vejrup et al. 2016, 2.6 µg/day dietary intake
Wu et al. 2014, ≥ 5.8 µg/L Hg in cord blood

Fig. 1. Quantitative comparison of methylmercury doses associated with various effects on cognitive development in benefit-risk models, epidemiological studies and the RfD. Mercury dose increases linearly along the Y axis from 0 to > 2.5 µg/kg/day. The US Reference Dose (RfD), 0.1 µg/kg/day, is shown in green near the bottom. Model results are shown in red font, positioned by the mercury dose associated with the outcome indicated. Aside from the 1997 Faroes study, the epidemiological studies shown here examined doses that cluster around the RfD. Their positions on the figure fall within the blue-shaded box. The 13 individual studies are listed in the box below the figure, and study details are summarized in Table 4. Studies in blue font included adjustment for confounding by fish nutrients.

Sidebar B–: Critical Limitations and Uncertainties in the FDA and FAO/WHO Benefit-Risk Models

All benefit-risk models share fundamental, unavoidable limitations: gaps and uncertainties in available data, the need to make often arbitrary data choices and assumptions, the need to combine data from different studies and to convert diverse outcomes to common measures. The FDA and FAO/WHO models are by no means uniquely flawed, and are in many ways useful analytical tools. However, when considering the results of these models, these important limitations should be kept in mind:

- The slopes used for beneficial effects of fish consumption come only from the ALSPAC study, which has not been replicated.
- IQ is far from the only, and not necessarily the best, measure of cognitive benefits.
- The assumed plateau of beneficial effects, while plausible, is not fully supported by available studies and if it exists, the fish intake at which it occurs has not been well quantified.
- The question of whether n-3 intake adequately represents beneficial exposures is unresolved.
- The slopes used in both models for adverse effects of MeHg on cognitive development come from meta-analyses of data later shown to be substantially confounded by fish benefits, and therefore appear to underestimate adverse effects, perhaps by a wide margin.
- IQ is far from the only cognitive outcome affected adversely by MeHg, and may not be the most sensitive or most appropriate measure. Several studies in Table 4 suggest that other outcomes may be more sensitive.
- The FDA and FAO/WHO models are "blind" to effects not convertible to IQ.
- The models use average slopes for beneficial and adverse effects and treat all women and fetuses as average in sensitivity. No uncertainty factors are applied to account for variation among individuals in sensitivity to beneficial or adverse effects, and the results thus likely understate effects (perhaps in both directions, but probably in different individuals in each case) in sensitive sub-populations.
- FDA's exposure model predicts mean and 95th percentile blood Hg levels much lower than those observed in several of the studies in Table 4. The model does not accurately represent geographic and ethnic subpopulations (such as Asian-Americans) with high-fish diets and thus, significantly above-average MeHg exposure.
- The FDA's data on mercury levels in different fish are limited by small sample sizes for some species, and FDA's reported averages for many items differ from average levels in the same species reported elsewhere in the literature (see Karimi et al., 2012).

FDA's model includes two versions, fish-as-a-package and n-3 s, described in Table 5 and the accompanying text. This analysis uses the n-3 s version, not because it is certain that n-3 s are the driving beneficial nutrient in fish but because that version of the model draws distinctions among different fish and shellfish by incorporating a wider range of values for both beneficial and harmful components.

While the model is conceptually sound, its quantitative results need to be squared with recent epidemiological observations. That can be accomplished by comparing estimates generated by each approach of the "minimal adverse dose" (MAD) of MeHg, discussed earlier. The MAD can be estimated three ways:

(1) The RfD, described in Sidebar A, applies an uncertainty factor of 10X to a clearly harmful Benchmark Dose, BMD. By convention, the MAD is presumed to be below the BMD but higher than the RfD, which aims to provide a margin of exposure below the MAD. The RfD of 0.1 μg/kg/day corresponds to a blood Hg level of 5.8 μg/L and a hair level of about 1 μg/g. The RfD therefore indicates, rather imprecisely, that the MAD is associated with more than 5.8 μg/L Hg in blood or 1 μg/g Hg in hair, but less than 10X those exposures.
(2) An epidemiology-derived MAD (eMAD) can be estimated from data summarized in Table 4. Those 13 studies associated adverse effects on cognitive development with prenatal MeHg doses at or slightly above or below the RfD. Overall this evidence places the eMAD very close to the RfD, i.e., considerably lower than the MAD was perceived to be when the RfD was set in 2000. For this analysis, the eMAD is defined as equal to the RfD.
(3) MADs are also estimated by the FDA model. The "crossover" point in Fig. 2 is the intake of any fish (and thus the MeHg dose) at which beneficial effects and adverse effects exactly cancel out; intakes slightly greater than the crossover amount have net adverse effects. This exposure point is conceptually analogous to MADs derived from other approaches, i.e., it is a model-derived MAD (mMAD).

Using mMADs from the FDA model and the eMAD described in (2) above as starting points, the FDA model's crossover serving sizes were re-calculated to bring them more in line with observations from population studies.

The data and calculations used for this recalibration analysis are displayed in Table 7. FDA estimated crossover intakes for 47 seafood categories (FDA, 2014a, Table V-8). The table lists 60 varieties, because FDA lumped similar species together—for example, haddock, hake and monkfish are a single category in FDA's database—while each variety is listed individually in Table 7.

5. Results

As Table 7 shows, FDA's crossover intakes range from 16 ounces (454 g) per week for Gulf tilefish to 3,364 ounces (95,454 g) per week for scallops, and for 43 of the 60 items, crossover intake exceeds 100 ounces/week. Crossover intake reflects the modeled net effect (on child IQ) of n-3 benefits and MeHg adverse effects; however, these intakes are driven primarily by MeHg content of the fish, because benefits plateau at about 8-12 ounces of fish per week on average (full range, 3-53 ounces), while Hg effects increase linearly with dose until benefits are cancelled out and net adverse effects appear.

FDA data on the MeHg content of each seafood item (FDA, 2014a, Table V-8) were used to calculate MeHg doses in crossover servings or mMADs, also shown in Table 7, which range from 514 to 891 μg/week (mean 671 μg/week). The mMADs vary from one fish type to another because amounts of n-3 s, which affect the benefits peak and thus the vertical distance from optimal to crossover intake in Fig. 2, also vary widely among seafood types.

FDA's crossover servings were then recalculated using the eMAD. Since the eMAD is equal to the RfD and weekly MeHg exposure at the RfD for a 60-kg woman is 42 μg, the weekly mMAD for each seafood item was divided by 42 μg, yielding the number of eMADs in each crossover serving. Serving sizes were then divided by the number of eMADs they contain to calculate servings for each seafood item, shown in the next-to-last column of the table,

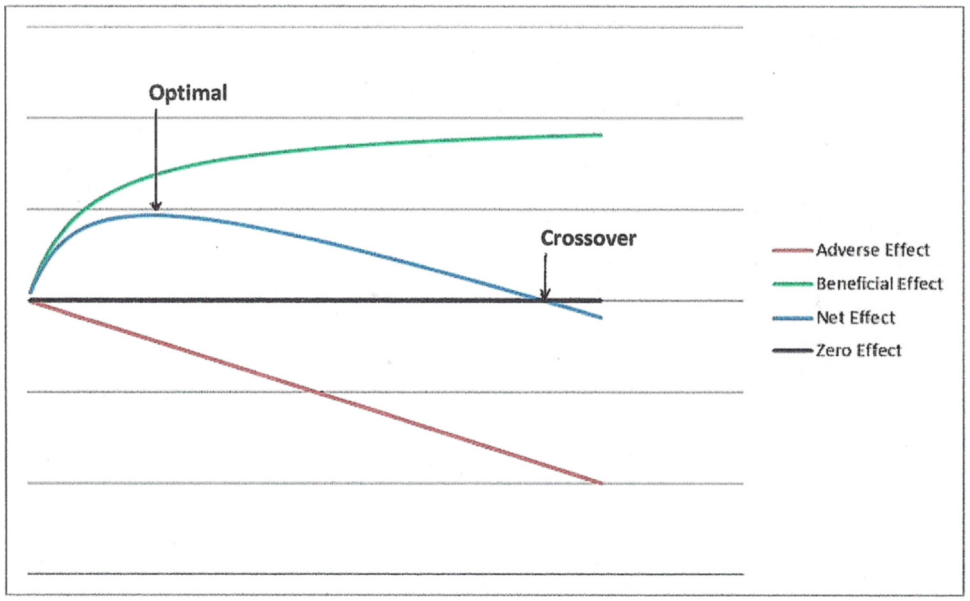


Fig. 2. *FDA's Generic Benefit-risk Model.* The figure (from Spiller, 2014) depicts the interaction between beneficial and harmful effects on cognitive development for any seafood variety consumed during pregnancy. Fish intake increases along the X axis; changes in IQ increase or decrease along the Y axis, with 0 effect at the X axis. Beneficial effects (the uppermost, green line) increase steeply at low fish intakes then level off, because the model assumes these effects reach a plateau. Methylmercury adverse effects (the bottom, red line) increase linearly with dose, in proportion to the amount of fish eaten. Positive effects (IQ gain) and adverse effects (IQ loss) combine to produce net IQ effects, shown by the central, blue curve.

that contain 1 eMAD of MeHg. They range from 1 ounce for Gulf tilefish to 210 ounces for scallops.

One further adjustment was needed. From a risk-management perspective, exposure at the eMAD is probably not acceptable. Estimates of benefits and risks are not precise enough to lay to rest the reasonable concern that exposure around the RfD/eMAD might fall within the range of net adverse effects, at least for sensitive individuals. In addition, the "crossover" point is where nutritional benefits are cancelled out by MeHg harm; a preferable goal of policy would be to aim for intakes whose benefits exceed possible harm by a significant margin. Consumer advice should therefore aim to keep MeHg intake well below the RfD/eMAD, a sensible precautionary approach supported by a fairly broad consensus.

How and where to draw the line below the RfD/eMAD is an admittedly subjective expert judgment with a substantial value component. An uncertainty factor of 2 was applied at this step, with the following rationale: A 2X exposure margin below the eMAD provides some cushion against uncertainties, yet most of the serving sizes that contain 0.5 eMAD fall well within the range of typical intakes. Thus advice based on these results should encourage, not discourage, consumption of the large majority of seafood items.

Final adjusted serving sizes containing 0.5 of the RfD/eMAD are shown in the last column of Table 7, and color-coded to support consumption advice. Because risk management for MeHg exposure from fish depends primarily on risk communication (i.e., consumer advice), the ultimate product of this analysis is a seafood choice chart, Fig. 3. The criteria used to generate the chart from the last column of Table 7 are shown in Table 8. The 60 seafood items fall into five choice categories based on recommended frequency of consumption: Eat All You Like (19 varieties); Eat Often (14 varieties); Eat Occasionally (11 varieties); Eat Rarely (11 varieties); and Do Not Eat (5 varieties).

6. Conclusions and final discussion

Wide differences between results of benefit-risk models and health outcomes observed in epidemiological studies have complicated the task of crafting consistent, science-based fish consumption advice. Many risk communicators have found that when the public perceives that experts cannot agree, consumers tend to be risk-averse. This may be especially true for pregnant women, a notably risk-averse subpopulation, who have not significantly increased fish consumption despite advice from many sources that they should do so. One primary reason for this dilemma seems to be that most consumers do not have enough information about differences in the comparative benefits and risks of seafood choices (Lando and Lo, 2014; Oken, 2014; Oken et al., 2013).

Conflicts between modeling and epidemiology can also undermine the scientific foundations of government fish-consumption advice. Simply put, it is not a sound policy approach to choose to believe a model and ignore the epidemiological evidence, as the US FDA and EPA have recently proposed to do (FDA, 2014b). Disparities between models and epidemiology need to be resolved, so that both types of evidence can be integrated to provide more comprehensive, coherent and scientifically defensible advice.

Some such integration may occur if the research community continues the iterative improvement of benefit-risk models, replacing older dose-response coefficients derived from confounded data used in most models to date with data from recent epidemiological studies.. However, this approach requires extensive resources and collaboration and is likely to proceed slowly, if at all.

A simpler approach, taken here, is to try to align FDA's model results with recent epidemiological evidence. This analysis leads to recommended weekly servings for 60 seafood varieties ranging from 0.5 to 105 ounces. Those serving sizes reflect biologically meaningful differences in the n-3 and MeHg contents of different fish and shellfish, which underlie parallel differences in FDA's crossover servings used as the starting points. The final serving sizes take advantage of the model's discriminatory ability but are also consistent with recent epidemiology-based risk and benefit estimates.

The proposed updated FDA/EPA advice (FDA, 2014b) includes a recommendation that pregnant women eat 8–12 oz of fish per week. Women are advised to choose "lower-Hg" fish, but only a

Table 7
FDA's crossover servings adjusted to generate recommended servings.

Seafood Item	Hg, µg/g	Crossover Serving, Oz/week,	Crossover Serving, g/week,	Hg dose in Serving, µg/week	MADs in Crossover Serving	Adjusted Serving, Oz/week	Half of Adjusted Serving
Tilefish, Gulf	1.45	16	454	658	16	1	0.5
Swordfish	1.00	24	681	681	16	1.5	0.75
Shark	0.98	24	681	667	16	1.5	0.75
King Mackerel	0.73	32	908	663	16	2	1
Orange Roughy	0.57	0	0	0	0	0	0
Grouper	0.46	51	1,447	666	16	3.2	1.6
Fresh Tuna	0.39	60	1,703	664	16	3.8	1.9
Spanish Mackerel	0.37	64	1,816	672	16	4	2
Sablefish	0.37	64	1,816	672	16	4	2
Bluefish	0.35	64	1,816	636	15	4.3	2.2
Canned Albacore Tuna	0.35	67	1,901	665	16	4.2	2.1
Pacific Croaker	0.30	78	2,213	664	16	4.9	2.5
Lingcod	0.29	82	2,327	675	16	5.1	2.6
Scorpionfish	0.29	82	2,327	675	16	5.1	2.6
Sea Trout	0.26	91	2,582	671	16	5.7	2.9
Sea Bass	0.25	95	2,696	674	16	5.9	2.9
Halibut	0.22	95	2,696	593	14	6.8	3.4
Carp	0.17	139	3,944	670	16	8.7	4.4
Buffalofish	0.17	139	3,944	670	16	8.7	4.4
Snapper	0.16	147	4,171	667	16	9.2	4.6
Porgy	0.16	147	4,171	667	16	9.2	4.6
Sheepshead	0.16	147	4,171	667	16	9.2	4.6
Ocean Perch	0.15	157	4,455	668	16	10	5
Rockfish	0.15	157	4,455	668	16	10	5
Mullet	0.15	157	4,455	668	16	10	5
Skate	0.14	172	4,881	683	17	10	5
Canned Light Tuna	0.13	196	5,562	723	17	12	6
American Lobster	0.11	214	6,072	668	16	13	7
Spiny Lobster	0.11	214	6,072	668	16	13	7
Atlantic Tilefish	0.11	214	6,072	668	16	13	7
Whitefish	0.10	235	6,668	667	16	15	8
Cod	0.09	229	6,498	585	14	16	8
Chub Mackerel	0.09	268	7,605	684	16	17	9
Atlantic Croaker	0.08	302	8,569	686	16	19	10
Sole & Plaice	0.08	310	8,796	704	17	18	9
Flounder	0.08	310	8,796	704	17	18	9
Squid	0.07	336	9,534	667	16	21	11
Haddock	0.07	351	9,960	697	17	21	11
Hake	0.07	351	9,960	697	17	21	11
Monkfish	0.07	351	9,960	697	17	21	11
Smelt	0.07	351	9,960	697	17	21	11
Crabs	0.06	374	10,612	636	15	25	13
Butterfish	0.06	406	11,520	691	16	25	13
Anchovies	0.05	471	13,365	668	16	29	15
Herring	0.05	471	13,365	668	16	29	15
Shad	0.05	471	13,365	668	16	29	15
Atlantic Mackerel	0.05	481	13,648	682	16	30	15
Atka Mackerel	0.05	481	13,648	682	16	30	15
Pollock	0.04	636	18,047	722	17	37	19
Crawfish	0.03	693	19,664	589	14	50	25
Freshwater Trout	0.03	736	20,884	627	15	49	25
Salmon (all types)	0.02	1,080	30,645	613	15	72	36
Clams	0.02	1,024	29,056	581	14	73	37
Sardines	0.02	1,177	33,397	668	16	74	37
Catfish	0.02	1,385	39,299	786	19	73	37
Pangasius	0.02	1,385	39,299	786	19	73	37
Oysters & Mussels	0.02	1,570	44,549	891	21	75	38
Tilapia	0.01	1,811	51,387	514	12	151	76
Shrimp	0.01	2,141	60,751	608	14	153	77
Scallops	0.007	3,364	95,454	668	16	210	105

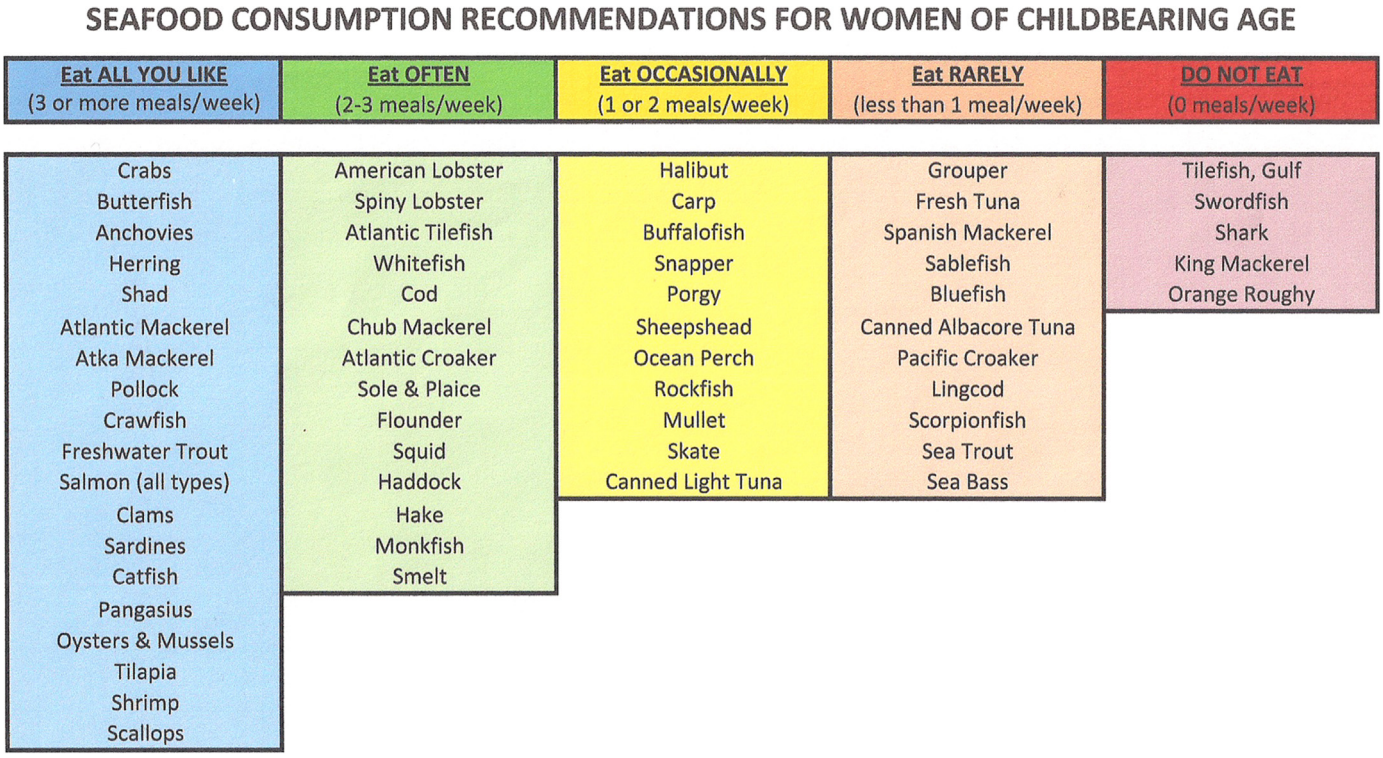


Fig. 3. *Seafood Choice Chart.* Serving sizes for 60 seafood items shown in the final column of Table 7 were sorted into five categories, based on how often they can be consumed by a pregnant woman, using the criteria and color codes in Table 8. The chart headings indicate meals per week, rather than ounces per week, using 4–6 ounces as an approximate standard serving size.

Table 8
Sorting criteria used to create the chart in Fig. 3.

If the adjusted model says a woman can eat	The item goes in this category	And the color code is
≥ 12 ounces per week	Eat All You Like	Blue
6-12 ounces per week	Eat Often	Green
3-6 ounces per week	Eat Occasionally	Yellow
1-3 ounces per week	Eat Rarely	Orange
< 1 ounce per week	Do Not Eat	Red

few items are listed as "lower-Hg choices," and they are all top-selling items in the US seafood market. With no statements to suggest otherwise, it appears that any item not on the FDA/EPA's "do not eat" list (four very high-Hg varieties) is "lower-Hg" and thus an equally acceptable choice. This advice offers little practical guidance for consumers and is unlikely to change either fish consumption patterns or Hg exposure (Groth, 2015).

In 2015 the Dietary Guidelines Advisory Committee recommended to HHS and USDA that updated 2015 guidelines for fish consumption should simply promote increased seafood intake and de-emphasize concerns about MeHg (DGAC, 2015). However, the published 2015 Dietary Guidelines for Americans (DGA, 2015) take a different approach, advising pregnant women to increase consumption of high-n-3, low-Hg seafood varieties and listing nine choices that fit those criteria. While this advice can help pregnant women choose wisely, the 2015 DGA are silent on the benefits and risks of the vast majority of items consumers encounter in the seafood market.

In contrast to the rather limited advice currently available from US agencies, Fig. 3 sorts 60 seafood items into five distinct categories, showing how often each can be eaten by pregnant women. The categories are color-coded and ranked based on relative benefit-risk outcomes in the FDA model, not just on MeHg content, an important distinction. While it remains to be seen whether a robust list of recommended choices will increase fish consumption, possible impacts of following this fish-choice advice on MeHg exposure can be readily examined.

Table 9 uses market share and Hg data from FDA (2014a) to estimate the relative contributions of individual seafood items to the total amount of MeHg in the US seafood supply, and thus, indirectly, to MeHg exposure from commercially-caught seafood among American women of childbearing age. This table updates an earlier analysis (Groth, 2010).

Table 9 shows that the blue, "eat all you like" category of Fig. 3 makes up 60% of the US seafood market, and the green, "eat often" category accounts for another 12%. Nine of the 11 most popular US fish and shellfish varieties (unshaded boxes) fall in those two groups. Women who follow the advice in Fig. 3 will therefore find many widely available, familiar choices recommended, and relatively few changes in consumer behavior would be required for women to "choose wisely" at the seafood market.

On the other hand, the red, "do not eat" and orange, "eat rarely" categories combined make up only 6% of the US seafood market (and more than half of that is one product, canned albacore tuna), but provide more than 40% of total MeHg exposure. If women cut back on consuming these varieties, market impacts, except on canned tuna (see below), should be minimal. FDA/EPA advisories have long warned women not to eat Gulf tilefish, swordfish, shark and king mackerel (see FDA, 2004), and in issuing proposed updated advice (FDA, 2014b) the agencies sought comments on whether to add orange roughy to that list. The red category in Fig. 3 is thus almost perfectly congruent with current and proposed FDA/EPA advice.

Fig. 3 differs most notably from recently issued and proposed

Table 9
Contributions to total mercury in the US seafood supply by individual seafood varieties as sorted in Fig. 3.

Seafood Item	Mercury µg/g	Market Share, %	Hg Input Factor	Percent of Total Hg
Blue Category				
Crabs	0.060	1.57	0.0942	1.462
Butterfish	0.060	0.06	0.0036	0.056
Anchovies, Herring & Shad	0.050	1.55	0.0775	1.203
Mackerel, Atlantic & Atka	0.050	0.57	0.0285	0.443
Pollock	0.040	9.27	0.3708	5.758
Crayfish	0.030	0.53	0.0159	0.247
Freshwater Trout	0.030	0.74	0.0222	0.345
Salmon (all types)	0.020	9.14	0.1828	2.839
Clams	0.020	0.98	0.0196	0.304
Sardines	0.020	0.64	0.0128	0.199
Catfish & Pangasius	0.020	6.16	0.1232	1.913
Oysters & Mussels	0.020	0.59	0.0118	0.183
Tilapia	0.010	7.22	0.0722	1.121
Shrimp	0.010	20.16	0.2016	3.130
Scallops	0.010	0.70	0.0070	0.109
Category Totals:	**0.021**	**59.88**	**1.2437**	**19.312**
Green Category				
American Lobster	0.110	0.72	0.0792	1.230
Spiny Lobster	0.110	0.46	0.0506	0.786
Atlantic Tilefish	0.110	0.01	0.0011	0.017
Whitefish	0.100	0.16	0.0160	0.248
Cod	0.090	4.29	0.3861	5.996
Chub Mackerel	0.090	0.09	0.0081	0.126
Atlantic Croaker	0.080	0.21	0.0168	0.261
Flounder, Sole & Plaice	0.080	2.77	0.2216	3.441
Squid	0.070	1.29	0.0903	1.402
Haddock, Hake & Monkfish	0.070	2.20	0.1540	2.391
Smelt	0.070	0.05	0.0035	0.054
Category Totals:	**0.084**	**12.25**	**1.0273**	**15.952**
Yellow Category				
Halibut	0.220	0.48	0.1056	1.640
Carp & Buffalofish	0.170	0.04	0.0068	0.106
Snapper, Porgy, & Sheepshead	0.160	0.43	0.0688	1.068
Perch, Rockfish & Mullet	0.150	0.83	0.1245	1.933
Skate	0.140	0.40	0.0560	0.870
Canned Light Tuna	0.128	8.87	1.1354	17.632
Category Totals:	**0.135**	**11.05**	**1.4971**	**23.249**

Table 9 (*continued*)

Orange Category				
Grouper	0.460	0.15	0.0690	1.071
Fresh/Frozen Tuna	0.390	1.29	0.5031	7.813
Spanish Mackerel	0.370	0.03	0.0111	0.172
Sablefish	0.370	0.19	0.0703	1.092
Bluefish	0.350	0.06	0.0210	0.326
Canned Albacore Tuna	0.350	3.61	1.2635	19.621
Pacific Croaker	0.300	0.01	0.0030	0.046
Ling Cod & Scorpionfish	0.290	0.02	0.0058	0.090
Saltwater Trout	0.260	0.01	0.0026	0.040
Saltwater Bass	0.250	0.01	0.0025	0.039
Category Totals:	**0.363**	**5.38**	**1.9519**	**30.310**
Red Category				
Gulf Tilefish	1.450	0.02	0.0290	0.450
Swordfish	1.000	0.37	0.3700	5.746
Shark	0.980	0.06	0.0588	0.913
King Mackerel	0.730	0.04	0.0292	0.453
Orange Roughy	0.570	0.30	0.1710	2.655
Category Totals:	**0.833**	**0.79**	**0.6580**	**10.217**

government advice by listing 33 specific recommended choices (the blue and green categories), and by providing tiered, nuanced cautionary advice to limit—not eliminate—intake of 22 other choices (the yellow and orange categories).

Table 9 shows (grey-shaded boxes) the 10 largest sources of MeHg in the US seafood supply. These top 10 items combined account for 75% of US MeHg exposure from commercially-caught seafood. Intuitively, if women ate less of these 10 items, their average exposure to MeHg should decrease. It is actually not quite that simple—5 of the top 10 sources are in fact low or about average in MeHg content, but are top sources because of their large market shares. On the other hand, the three varieties of tuna in Table 9 (canned albacore, canned light and fresh/frozen) are the three largest sources of Hg exposure by a wide margin; combined, these tuna varieties account for over 45% of the Hg total shown in Table 9. If the average American woman is to reduce her MeHg exposure while she also eats more fish, eating less tuna and less of a few other varieties like swordfish, shark and orange roughy, and eating more of low-Hg varieties like salmon, shrimp and herring, should help achieve both goals.

In 2009 FDA estimated that the market-weighted overall average Hg level in the US seafood supply was 0.086 μg/g (FDA, 2009). By 2014, the estimate had dropped to 0.071 μg/g (FDA, 2014a). This trend reflects gains in market share by low-Hg varieties such as salmon, shrimp, catfish and tilapia in recent years, while consumption of larger, predatory, higher-Hg varieties such as swordfish and canned tuna has been declining steadily.

The market-weighted average Hg level of seafood items in the blue column of Fig. 3 is 0.021 μg/g, while the average for the green column is 0.084 μg/g; combined, the average Hg content of the two columns is 0.031 μg/g. If women chose the vast majority of their seafood meals from the blue and green categories, the average Hg content of an average woman's fish meals could be reduced to less than half of the current average for the US seafood supply as a whole. In that scenario, even a woman who doubled her fish consumption could simultaneously markedly reduce her MeHg exposure.

In summary, a few high-Hg seafood varieties account for a very large share of US exposure to MeHg. Consumption advice that guides women away from those varieties, and toward lower-Hg, high n-3 choices, can both foster increased fish consumption and its attendant benefits and reduce MeHg exposure. To meet both goals, advice needs to draw clear distinctions among fish and shellfish varieties, identifying a lengthy list of choices with favorable benefit-risk profiles and cautioning women to limit or avoid consuming other varieties with less favorable profiles. Fig. 3 provides one template for such advice.

This approach has the advantages of simplicity and transparency; some might argue that it is *too* simple, even simplistic. The step-by-step analysis laid out here can be compared with the complexity and frequent lack of transparency of benefit-risk models. Moreover, while agencies relying on the FDA and FAO/WHO models as foundations for advice have largely failed to examine critically the dozens of data gaps, uncertainties and value judgments inherent in the models, many of those limitations are explicitly enumerated in Sidebar B here. Since the starting point is FDA's model, the results of this analysis are subject to those caveats. A key value judgment embedded in adjustments to the model is also explicit.

This approach is limited to examining the well-documented trade-offs between n-3 benefits and MeHg risks for prenatal cognitive development. Other nutrients and contaminants in seafood may affect those and other developmental outcomes, and fish consumption has large cardiovascular benefits that are outside the

scope of the analysis.

In this context, no method for crafting advice is perfect, and iterative improvement should be the goal. The objective of public health policy is to optimize benefits and minimize risks of fish consumption by pregnant women (or to maximize the excess of benefits over risks) for individuals to the extent possible, and for society in general. It is not feasible to tailor fish consumption advice precisely enough to guarantee optimal outcomes for individual consumers. More modest and appropriate goals are to make the best sense possible of the available evidence, to avoid trying to be more definitive than science allows, and to offer general guidance that is reasonably likely to promote both increased benefits and reduced risks.

The integration of modeling with epidemiological evidence developed here comes closer to those objectives than advice based on either approach by itself, and thus, offers a broader and potentially sounder scientific foundation than the proposed basis for recently drafted government advice on this topic. In particular, by calibrating the FDA model against the epidemiological results for MeHg exposures, this analysis tries to resolve the dose-response disparity on the risk side of the equation, arguably the most problematic shortcoming of the model.

Fig. 3 is certainly not the last word on the subject; there is no one "best" way to craft and present seafood consumption advice. But it may contribute to a national conversation on how public health policy can optimize both of these vital objectives.

Conflict of interest declaration

The author declares he has no conflicts of interest.

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