Risk-Benefit Synthesis for Fish Consumption Advisories

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Fish Consumption Advisories Traditionally Focus on Risk

- Mercury, PCBs, Chlordane, Dioxin
- High risk group – WC-BA, young children
- Consumption limits based upon RfD
- Benefits of fish consumption not quantitatively considered
  - FCA encourages consumption while also give warning msg and setting limits

Dueling Epi Studies 1990's to 2000s

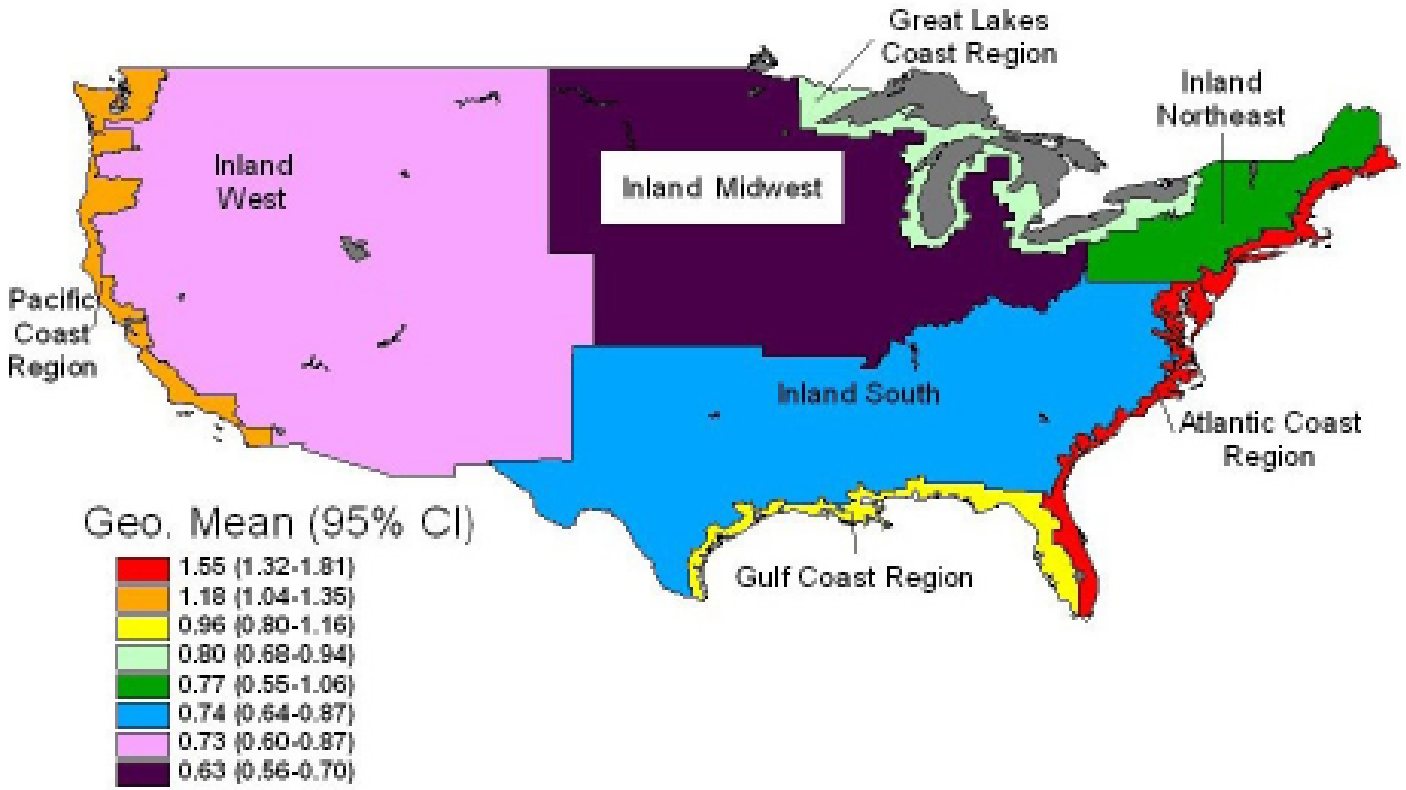
Seychelles Island

NAS Resolved Debate in 2000 – showed how to set RfD

Mahaffey, et al. EHP, 2008

(http://www.ehponline.org/members/2008/11674/11674.pdf)

2A. Blood total mercury concentration (µg/L)



Fish Consumption Debate Not Over

- With RfD, set limits on fish consumption
  - One to two meals/week of commercial seafood
  - No swordfish, shark, tilefish, king mackerel
  - Statewide freshwater advisory – 1 meal/month
- But – lose omega-3 benefits??
  - Brain development
  - Cardiovascular mortality – acute MI
    - Miscellaneous other benefits – eyes, anti-inflamm
  - Benefits really lost if msg too scary
- To eat fish or not to eat fish – Is that the Question?

Possible Risk Benefit Approaches for FCA

- Retain current advisory but improve risk communication – only balance the msg?
- Refocus advisory on individual fish?
- Separate risk-benefit assessment for diff endpoints and types of receptors?

Qualitative Assessment: IOM, 2006

- Qualitative review of fish consumption patterns, benefits,risks, uncertainties
- Recommendations
  - Include seafood in diet
  - Keep consumption w/in federal advice for high risk group for mercury in seafood
  - Increase monitoring
  - Gen pop – eat 2 3oz meals/wk – CV benefit
    - If eat more, choose from a variety of species

Qualitative Evaluation: Mozaffarian and Rimm, 2006

- Reviewed D/R for CV benefits and Hg risks
- Table of nutrients & contams in fish species
- Reviewed costs, supplements, n6:n3 ratio
- Evidence synthesis
  - Benefits outweigh risks – but …..
  - Women of CBA/nursing moms - follow federal advice
  - All others, no limits; if > 5 mls/wk, no high Hg species
  - Don’t worry about cancer risks from organoCl’s

Mozaffarian and Rimm, 2006

Figure 2. Relationship Between Intake of Fish or Fish Oil and Relative Risks of CHD Death in Prospective Cohort Studies and Randomized Clinical Trials

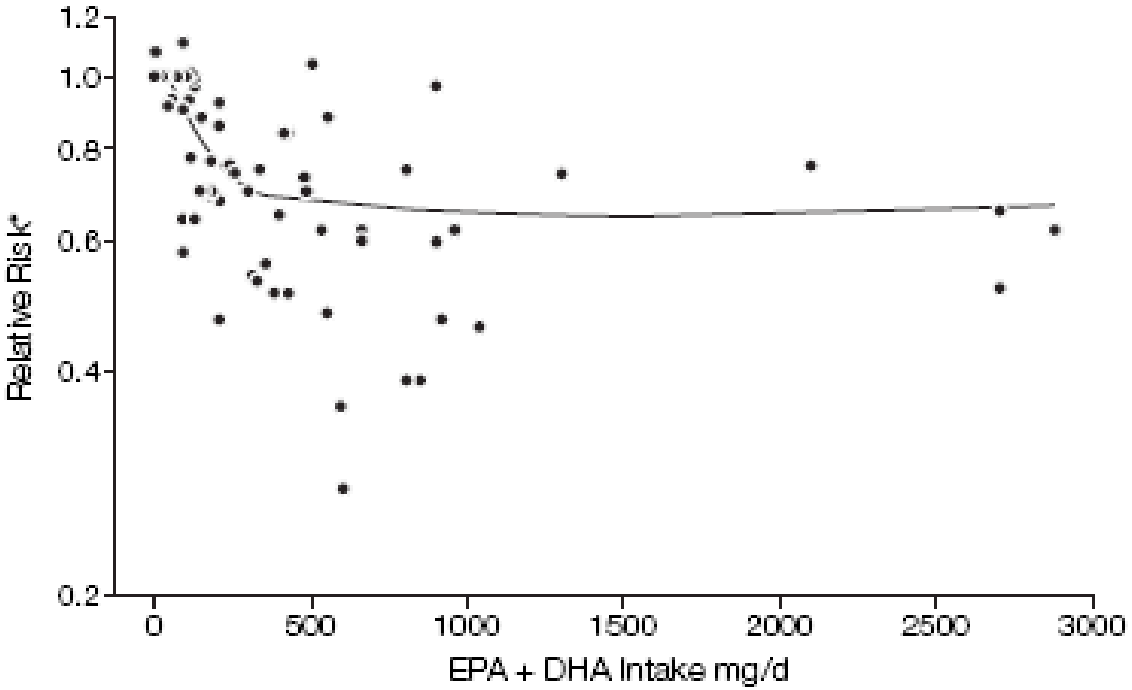
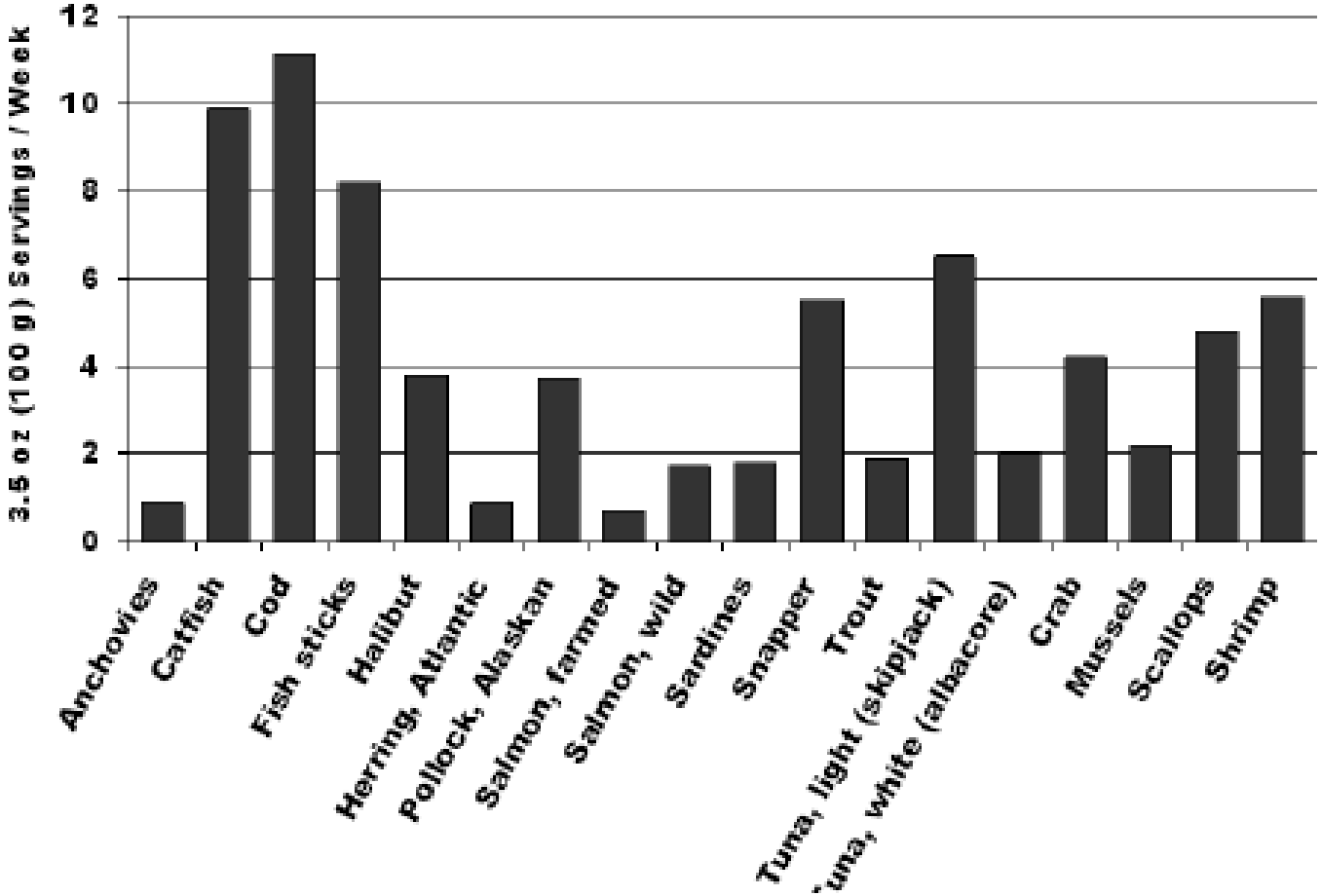


Figure 2. The number of 3.5 oz (100 g) fish servings per week needed to provide an average of 250 mg/day of the marine n-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Based on data from Mozaffarian and Rimm [1].



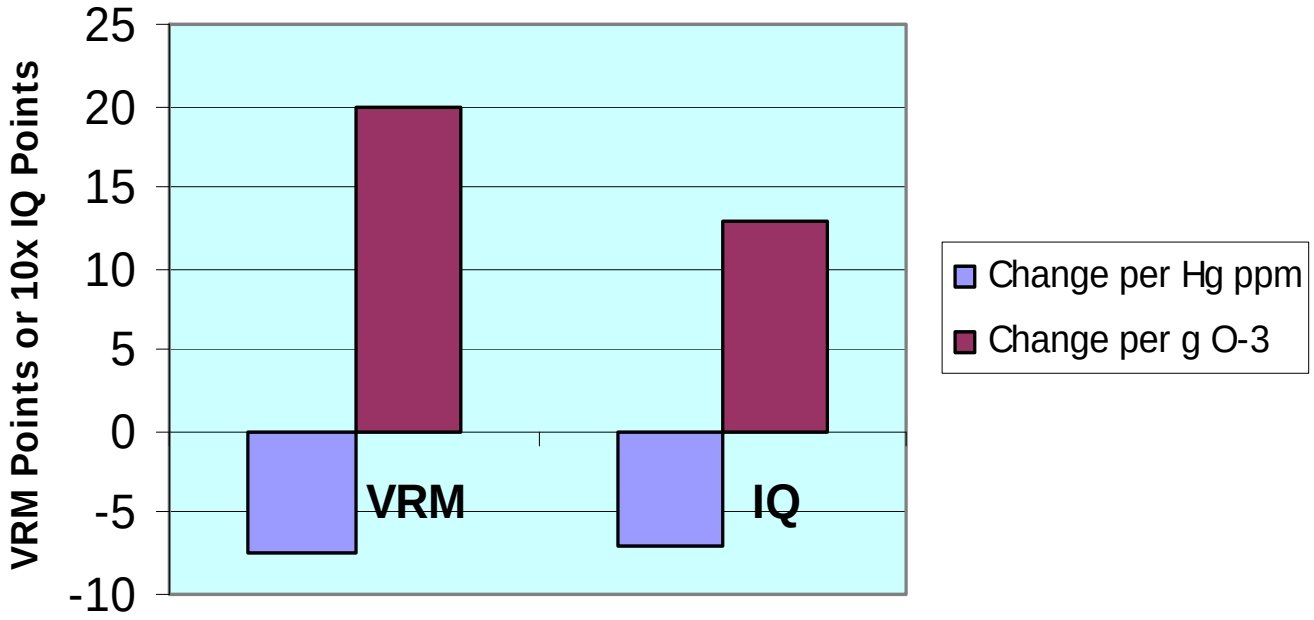
Quantitative Analyses

- Ponce, et al., 2000
  - MI prevention benefits of fish vs
  - meHg neurodevelopmental effects
    - delayed speech - Iraq - maternal hair
  - weighted by QALYs
  - evaluated net effect of fish consumption
    - Risk - benefit of MI vs CNS development
    - Across range of fish concs (0-2 ppm)
    - Endpoints differ, key receptors differ, not species specific

More Quantitative Analysis

- Cohen et al, 2005
  - Regression slopes for
    - meHg on IQ
    - DHA on IQ
    - fish consumption on stroke and CHD
  - Evaluated ↓ed consumption from advisories and over-reaction
  - Standardized fish consumption patterns and federal databases for meHg and omega-3
    - no individual fish analyzed
  - Converted health endpoints to QALYs

Comparison of Effect Sizes for meHg and Omega-3s on IQ (Cohen, et al., 2005) or VRM (Oken, et al., 2005)



Conclusions – Cohen et al.

- Fish consumption advisories can yield developmental benefits if followed
- Can lead to increased risks if advisory → worry → fish avoidance

- ***Are fish advisories that focus on good species less likely to cause avoidance?***

EHP, E Article:
http://www.ehponline.org/docs/2008/11368/abstract.html

Quantitative Approach for Incorporating Methyl MercuryRisks and Omega-3 Fatty Acid Benefits in Developing Species-Specific Fish Consumption Advice

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Table 1
Dose Response Relationships for Key MeHg and Omega-3 FA Endpoints

Endpoint	Agent	Dose-Response	Comments	Reference
Adult CHD Mortality	Omega 3 FA	14.6% decreased relative risk per 100mg/d	Combined data across 20 studies for EPA+DHA intake vs CHD mortality; possible saturation of benefit above 250 mg/d	Mozaffarian and Rimm 2006
Adult MI Risk	MeHg	23% increased relative risk per ppm hair Hg	Slope adjusted for DHA content of lipid as index of fish oil intake; Risk not apparent < 0.51 ppm hair Hg; Toenail Hg measured but converted to ppm in hair	Guallar et al. 2002 Ohno et al. 2007 for toenail to hair Hg conversion; Zhang and Yu 1998 for odds ratio conversion to relative risk
Infant VRM Score	Omega 3 FA	2.0 point increase per 100 mg/d	VRM measured at 6 months in 135 mother-infant pairs; fish oil intake estimated from dietary survey	Oken et al. 2005
Infant VRM Score	MeHg	7.5 point decrease per ppm hair Hg	VRM measured at 6 months in 135 mother-infant pairs; Direct measurement of maternal hair Hg	Oken et al. 2005

Abbreviations: CHD: coronary heart disease; MI: myocardial infarction; VRM: visual

Risk-Benefit Analysis of Oken et al., 2005

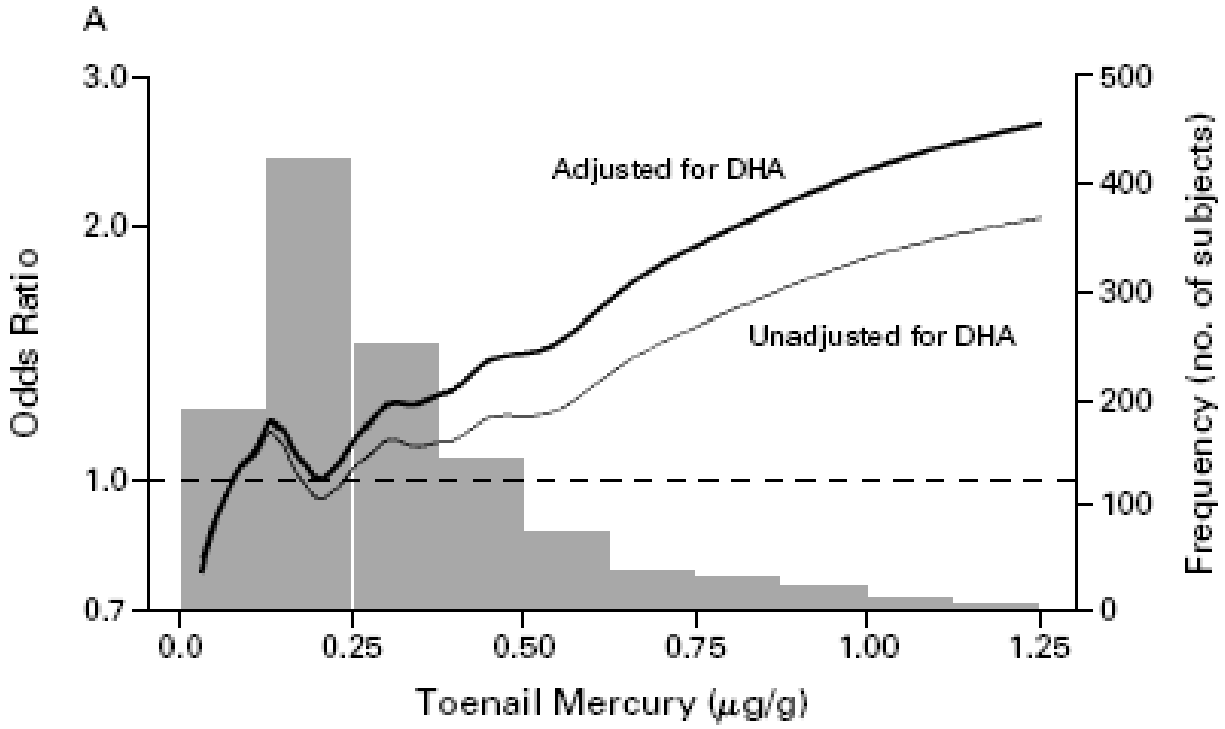
Table 2. Associations of maternal second-trimester fish consumption and maternal hair mercury at delivery with infant cognition at 6 months (VRM score): results from six linear regression models among 135 mother–infant pairs in Project Viva.

Model	Change in VRM score [% novelty preference (95% CI)]	
	Effect per weekly fish serving	Effect per ppm maternal hair mercury
Fish only	2.5 (–0.01 to 5.0)	—
Fish and participant characteristics[a]	2.8 (0.2 to 5.4)	—
Mercury only	—	–4.6 (–10.3 to 1.1)
Mercury and participant characteristics[a]	—	–4.0 (–10.0 to 2.0)
Fish and mercury	3.9 (1.2 to 6.5)	–8.1 (–14.1 to –2.0)
Fish, mercury, and participant characteristics[a]	4.0 (1.3 to 6.7)	–7.5 (–13.7 to –1.2)

[a]Participant characteristics adjusted for include maternal age (continuous), race/ethnicity (white vs. nonwhite), education (college graduate vs. not), marital status (married or cohabiting vs. not), and infant sex, gestational age at birth (continuous), birth weight for gestational age (continuous), breast-feeding duration (continuous), and age at cognitive testing (continuous).

Guallar, et al. 2002

Risk of MI in 684 men in Eastern Finland

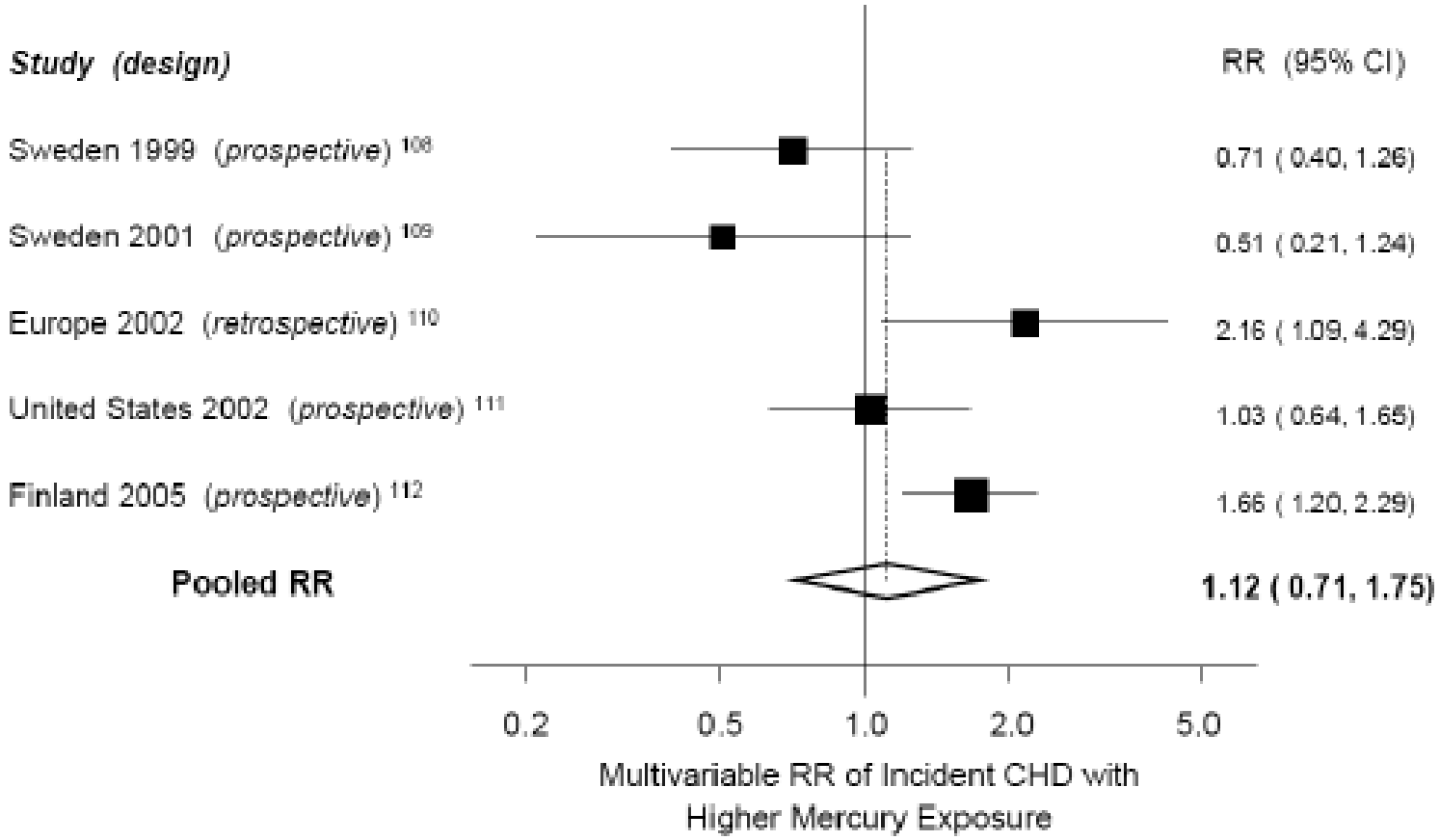


Mercury and CVD

- **Salonen 1995**
  - 1833 Finnish men
  - 2x ↑ed MI > 2 ppm
- **Salonen 2000**
  - 1014 Finnish men
  - ↑ed athero > 2.83 ppm
- **Guallar 2002**
  - 684 European men
  - Linear D-R for MI
- **Virtanen 2005**
  - 66 Finnish cases
  - OR 1.66 for high Hg
- **Ahlqwist 1999**
  - 1462 Swedish women
  - Amalgam exposure
    - Serum Hg not assoc with MI or stroke
- **Hallgren 2001**
  - 78 Swedish men/wom
  - Poss assoc in low O-3 and high RBC Hg grp
- **Yoshizawa 2002**
  - 33,737 US men
  - Mostly dentists

Mozaffarian (2009) Int J Environ Res Pub Health 6: 1894-1916

Figure 3. Meta-analysis of studies of mercury exposure and risk of coronary heart disease (CHD). Relative risk (■) and 95% CIs (–) are shown comparing the highest to the lowest quantile of mercury exposure after adjustment for other risk factors. Adapted from Mozaffarian and Rimm [1].



Components of Quantitative Risk/Benefit Analysis

- Dose response relationships
- Fish Hg & O-3 data from FDA, USDA, etc
- One compartment PK model to convert fish meal (3oz) to hair Hg concentration

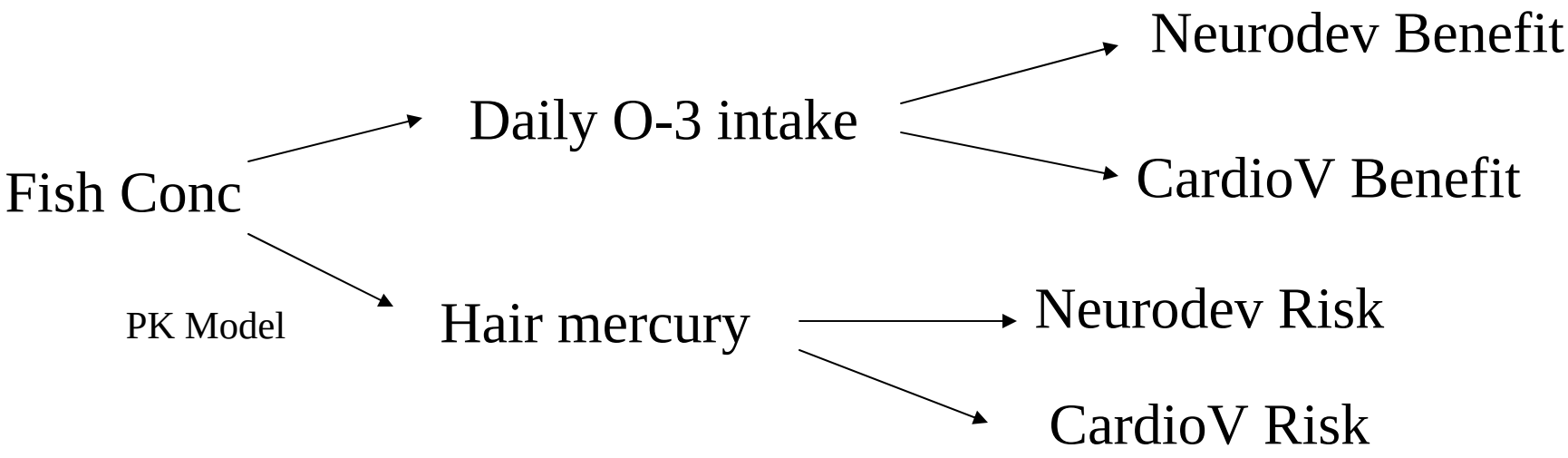


Table 2. Omega 3 FA and MeHg Levels in Commonly Eaten Fish

Fish Species	Omega-3[a] (mg/ 6oz)	MeHg[b] (ug/g)
Cod, Atlantic	269	0.11
Flounder/Sole	852	0.05
Halibut	1398	0.26
Herring, Atlantic	3424	0.04
Lobster	1129	0.24
Pollack	922	0.06
Salmon, Atlantic, farmed	3658	0.014
Sea Bass	1295	0.27
Shark	1170	0.99
Shrimp	536	0.01
Swordfish	1392	0.97
Tilapia	240	0.01
Trout	1744	0.03
Tuna, canned, light	425	0.12
Tuna, canned, white	1462	0.35
Tuna, fresh, yellowfin	474	0.325

[a]Omega-3 FA represents the sum of EPA and DHA. Data from USDA, 2005 although shark data from Mozaffarian and Rimm, 2006.

[b]MeHg data from USFDA 2006; data for salmon reported as fresh/frozen and not distinguished according to source.

Risk/Benefit Equations for Coronary Heart Disease and Neurodevelopment

Net Risk/Benefit for Adult CHD =

((Omega-3 FA mg/meal) (#meal/wk)(1 wk/7d)*(14.6% ↓edrisk/100mg Omega-3 FA)) –

(([(Hair Hg change/fish meal) (# meals/wk)] - (0.51 ppm hair Hg)) * (23% ↑ed risk/1 ppm Hair Hg))

Net Risk/Benefit for Infant VRM =

((Omega-3 FA mg/meal) (#meal/wk)(1 wk/7d)*(2 VRM pts/100mg Omega-3 FA)) –

((Hair Hg change per fish meal) (# meals/wk) (7.5 VRM pts/1 ppm Hair Hg))

Figure 1
Net Effect of meHg and Fish Oils on Neurodevelopment at 6 months of Age: 1 Fish Meal/Week

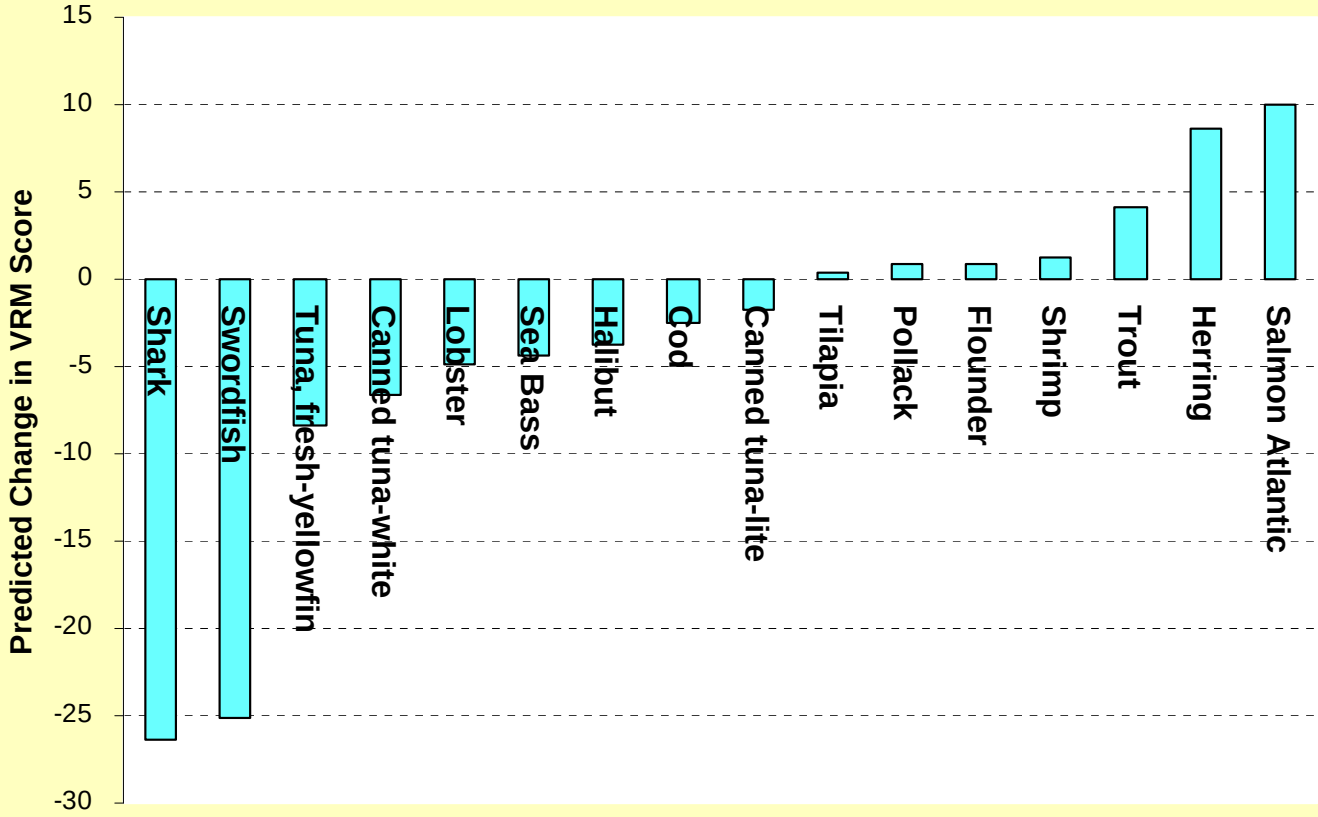


Figure 2
Net Effect of meHg and Fish Oils on Cardiovascular Risk: One Fish Meal per Week

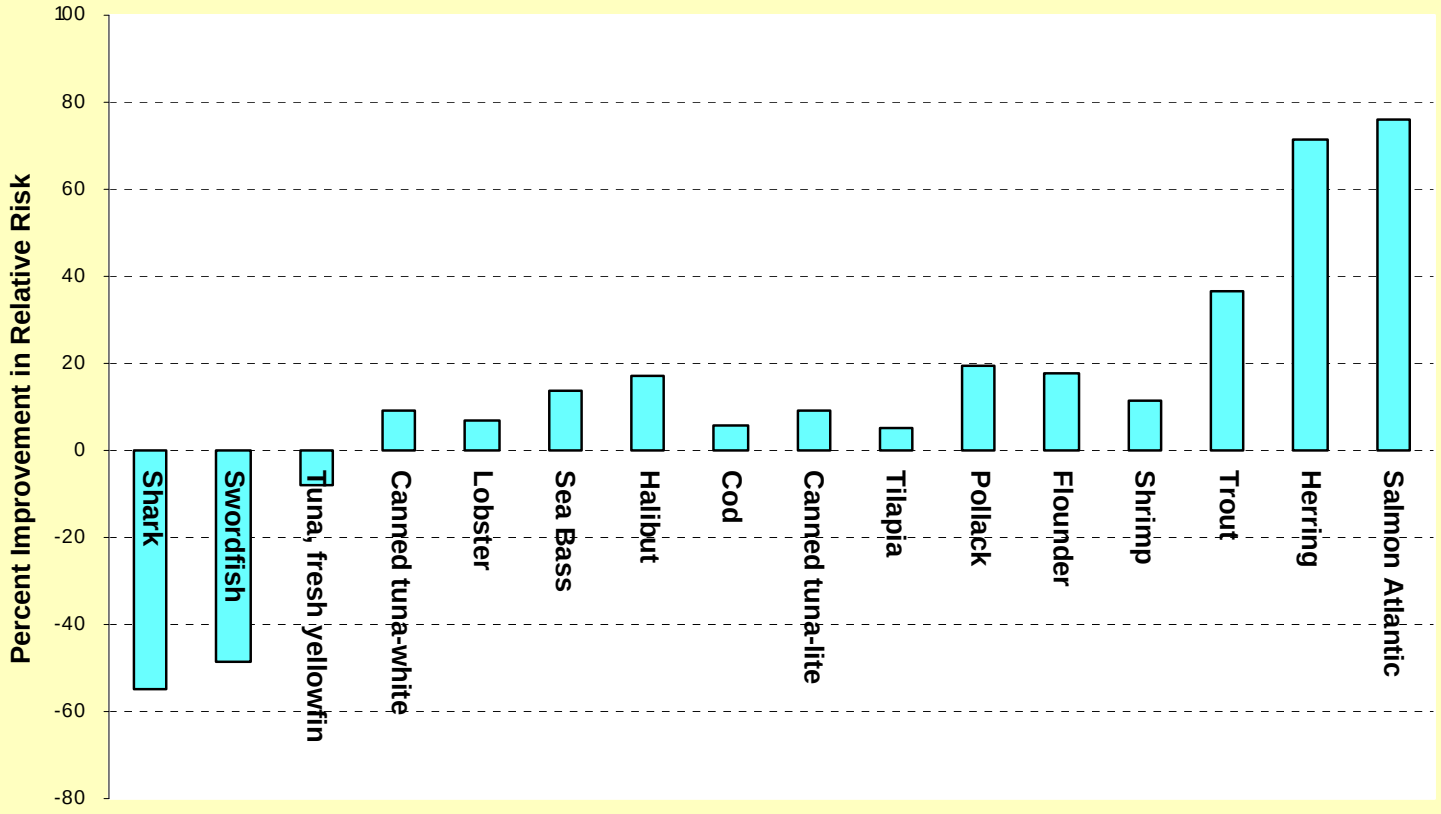


Figure 3
Net Effect of meHg and Fish Oils on Cardiovascular Risk: Two 6 oz Fish Meals per Week

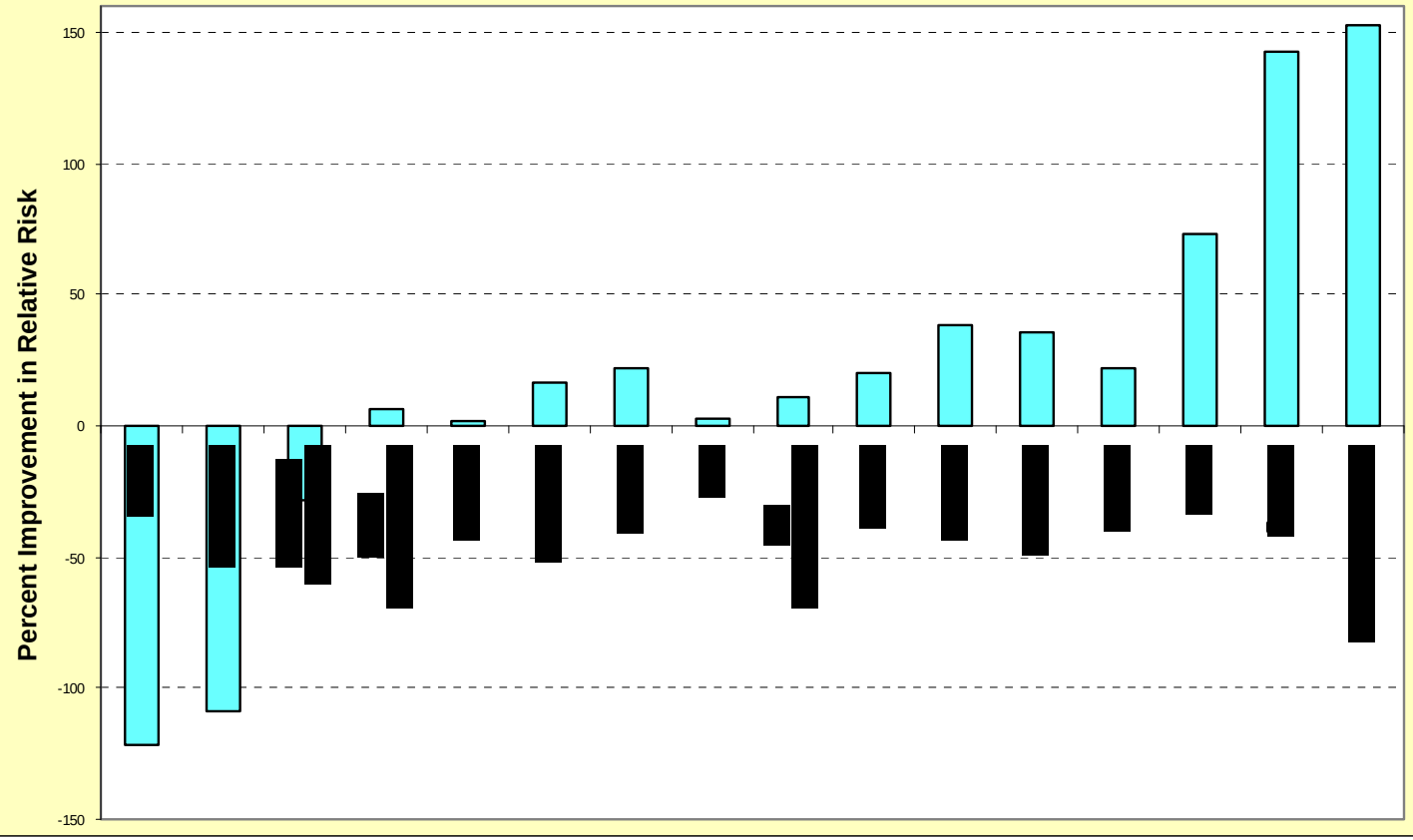


Table 3
Tentative Fish Consumption Categories for the 16 Species
Analyzed in the Current Risk/Benefit Assessment
(Based upon 6 oz meal size)

Consumption Category	Receptors	Fish Species
Unlimited (pending evaluation of other contaminants)[a]	Neurodevelopment Risk Group[b]	Tilapia, Pollack, Flounder, Shrimp, Trout, Herring, Salmon
Twice per week		Canned light tuna, Cod
Once per week		Canned white tuna, Tuna steak, Halibut, Sea bass, Lobster
Do not eat		Swordfish, Shark
Unlimited (pending other contaminants)	Cardiovascular Risk Group[c]	Tilapia, Pollack, Flounder, Shrimp, Trout, Herring, Salmon, Canned light tuna, Cod
Twice per week		Canned white tuna, Halibut, Sea bass, Lobster
Once per week		Tuna steak
Do not eat		Swordfish, Shark

[a]Unlimited taken to mean daily consumption.
[b]Pregnant women, women of child-bearing age, nursing mothers, young children
[c]General adult population.

If Some Fish Risky Why Do Various Studies Show Fish Benefit

- Population eats a variety of fish
  - Some provide major benefit – salmon, shrimp
  - Net benefit in general pop – more salmon than swordfish
    - FDA approach – evaluate overall fish consumption patterns
  - In subgroups – e.g., frequent sushi – meHg excess and symptoms
  - In Finland – where fish low in omega-3 – CV morbidity

Oken et al. Amer J Epidemiol 167: 1171-1181, 2008

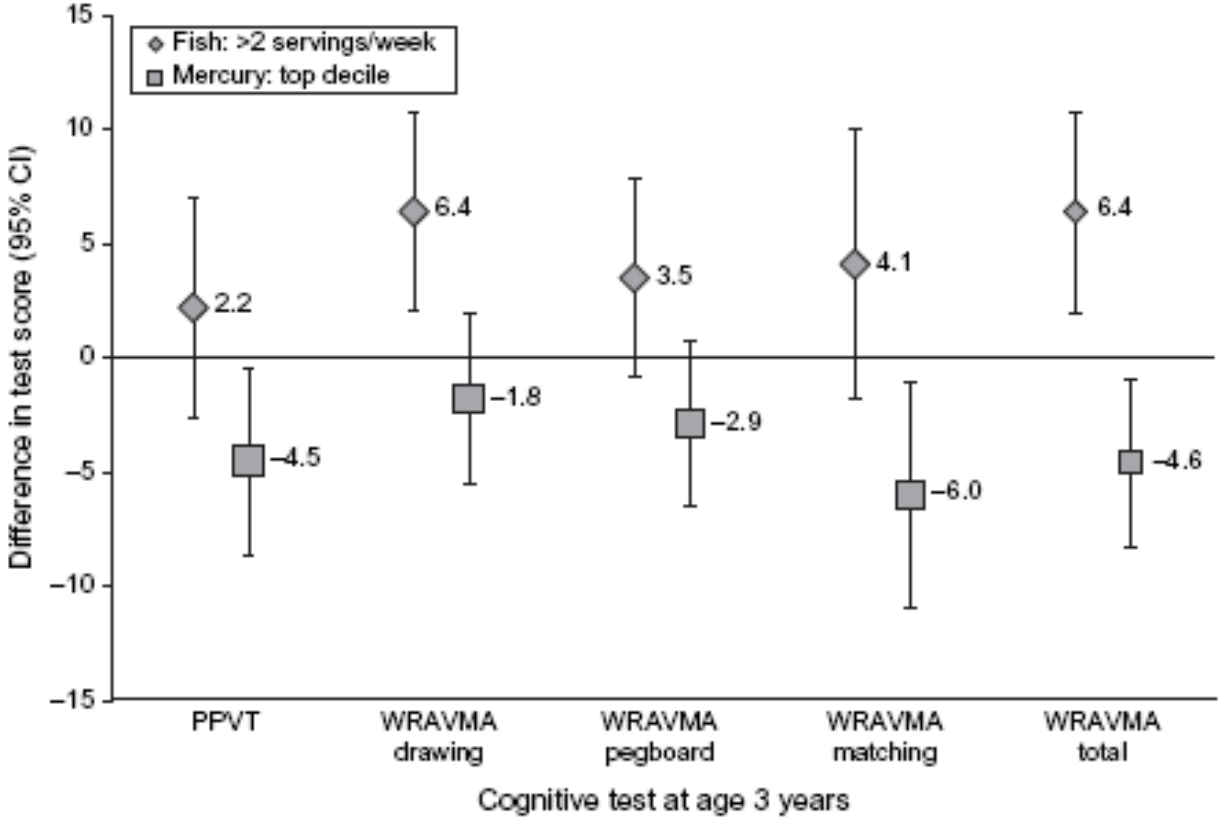


FIGURE 1. Associations of maternal second-trimester fish intake (>2 weekly servings vs. never) and erythrocyte mercury levels (top decile vs. below) with child cognitive test results at age 3 years, Project Viva, Massachusetts, 1999–2002. Effect estimates were adjusted for each other as well as for parent and child characteristics. CI, confidence interval; PPVT, Peabody Picture Vocabulary Test; WRAVMA, Wide Range Assessment of Visual Motor Abilities.

Oken et al. Amer J Epidemiol 167: 1171-1181, 2008

TABLE 5. WRAVMA* total score for children aged 3 years according to maternal prenatal fish intake and mercury levels, Project Viva, Massachusetts, 1999–2002

Fish intake	Mercury ≤90th percentile			Mercury top decile		
	No.	Estimate†	95% CI*	No.	Estimate†	95% CI
>2 weekly servings	31	5.9	1.0, 10.9	9	4.1	−3.4, 11.7
≤2 weekly servings	229	1.8	−1.8, 5.3	25	−4.2	−9.6, 1.2
Never	47	0	Referent			

* WRAVMA, Wide Range Assessment of Visual Motor Abilities; CI, confidence interval.

† Adjusted for child sex, age at testing, fetal growth, gestation length, breastfeeding duration, birth order, and primary language; maternal Peabody Picture Vocabulary Test score, age, prepregnancy body mass index, race/ethnicity, education, marital status, and alcohol consumption and smoking during pregnancy; and paternal education.

Limitations in Current Data

- Multiple contaminants and nutrients
  - Hg, PCBs, dioxin, pesticides, PBDEs
  - O-3s, iodine, selenium, iron, protein
- Multiple endpoints – cancer separate issue?
- Dose response – should equal wt be given to mercury CV risk as omega-3 CV benefit?
- Data inputs – need more omega-3 and Hg fish data

Summary

- Quantitative Risk-Benefit FCA approach demonstrated
- Species-specific advice should be focus
- Net benefit for certain fish – unlimited consumption if no PCB/POPs issues
- Net risk for certain fish – no or very low consumption even if not in “hi risk” group
- Risk/benefit tilted more towards risk for neurodevelopmental vs CV outcomes