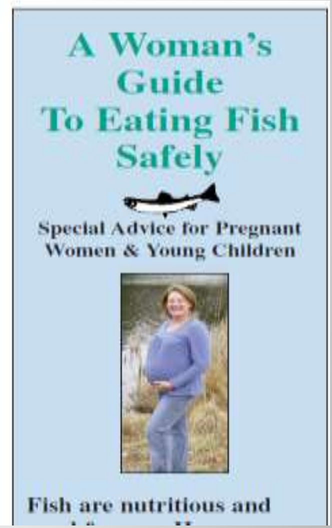
Balancing the Risks and Benefits of Fish Consumption on Neurodevelopmental Endpoints

Gary Ginsberg
Toxicologist
Conn Dept Public Health



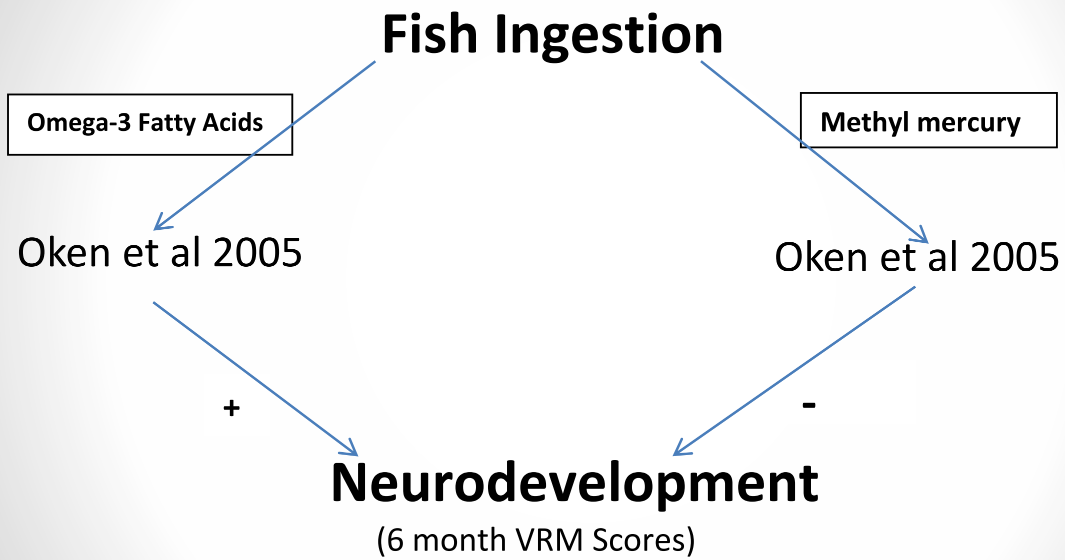
Collaborative on Health and the Environment
May 7, 2015

History of Fish Advisories

- Mercury or PCB RfD as driver
- Health or cultural benefits of fish consumption not weighed
- Concern was scaring people from fish in general
- Risk-benefit, species specific advice:
  - Take stock of the beneficial attributes
  - Compare to (or quantitatively account for) toxicant effects
  - Guide consumers to healthiest fish to eat

2009 Risk Benefit Model

- Based upon visual recognition memory (VRM) at 6 months in Boston area children



- Risk benefit results at that time:
  - 9 of 16 species net ND risk
  - Does this make sense given (+) effect of fish on ND?
    - Daniels et al. 2004; Hibbeln et al. 2007; Oken 2005, 2008

Updated Approach

- Review lit for Hg and O-3 FA slopes on ND
- Evaluate recent risk/benefit models of fish consumption
- Calibrate VRM model for net effect of fish on ND
  - **Construct baseline marketshare diet**
  - Does the 2009 model predict a net benefit from baseline diet
  - Adjust model to benefit seen in epi
- Calibrated model compared to IQ-based models
- Calibrated model used to predict risk/benefit of market species
- Calibrated model used in new Consumption Advisory Framework
- Evaluation of (DHA+EPA)/Hg ratio to screen fish species

Hg ND Risk Epi

- 14 studies, various ages, biomarkers, endpoints
- Some adjusted for beneficial effect of fish consumption, others did not
- 10 of the 14 found significant effect of Hg
  - Faroes, NZ, Boston, New Bedford, Brazil, Hong Kong, NYC, Poland

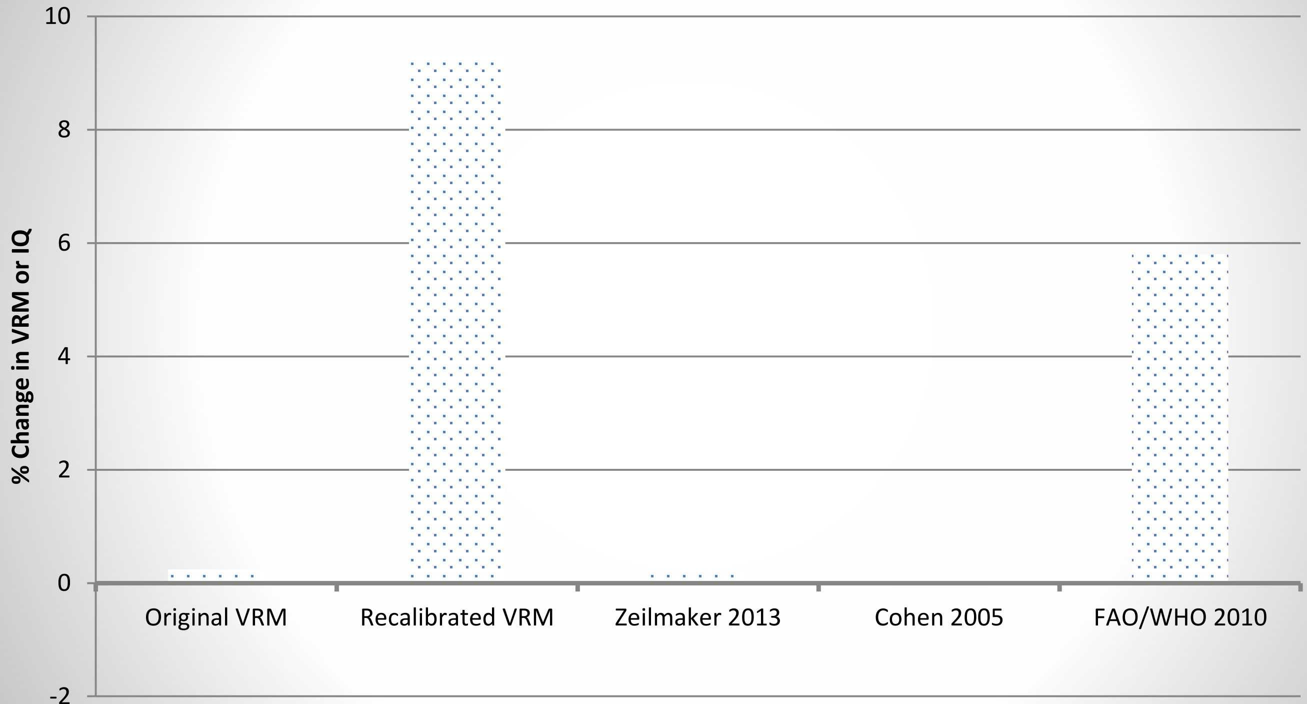
Omega-3 Effect on ND

- 6 studies of maternal fish ingestion on ND
- Some corrected for maternal Hg, others not
- 5 of 6 show beneficial effect
  - UK, Boston, NYC
- Benefit incorporated into FDA 2014, FAO/WHO 2010 models
- Earlier analysis of O-3 postnatal supplementation showed lower ND benefit (Cohen et al. 2005)

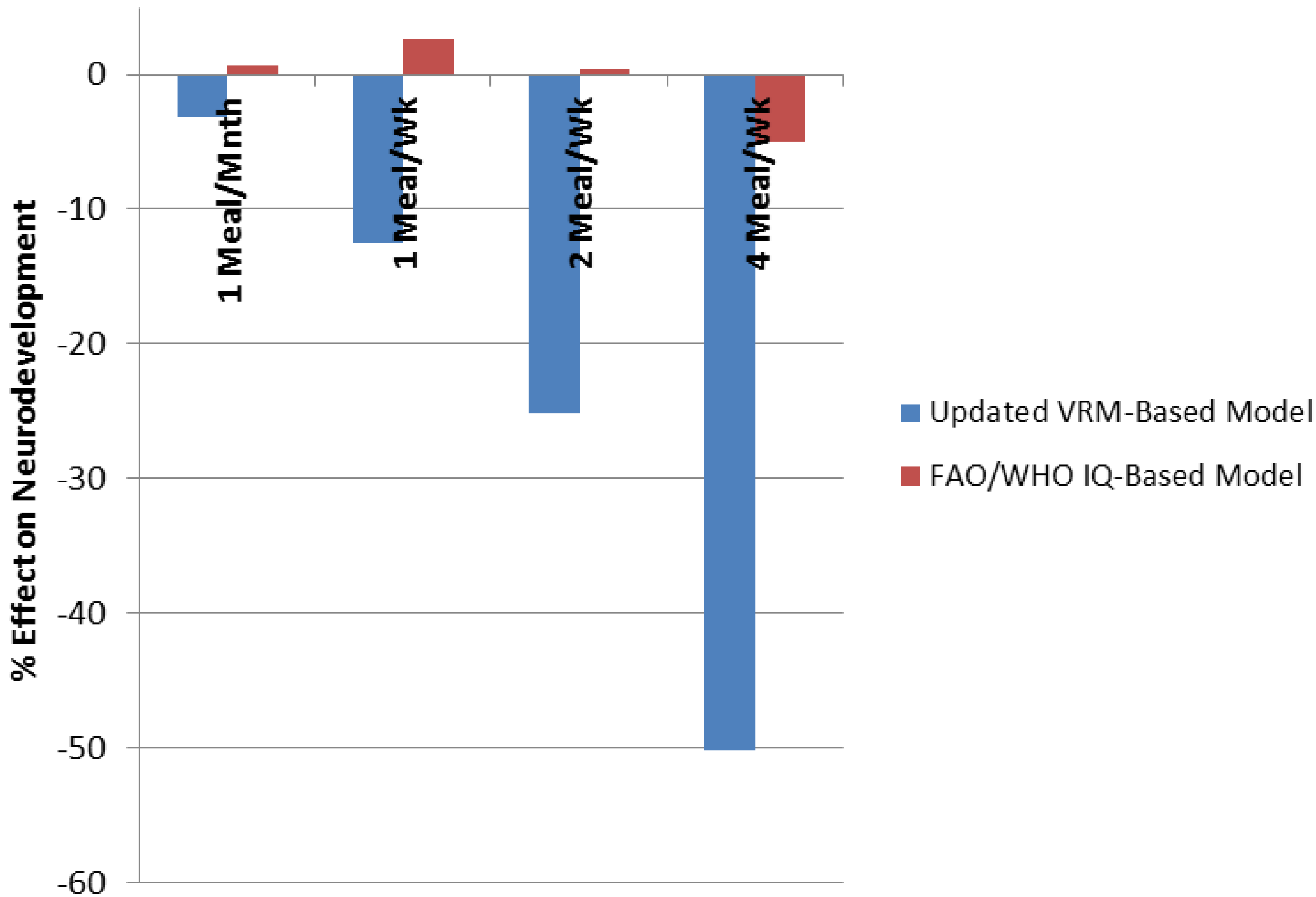
Calibration of VRM Model Against MarketShare Diet

- Previous risk/benefit model: +0.072 VRM pts per fish meal/wk
- Oken et al. 2005: +2.8 pts
- Iteratively lowered Hg slope and raised O-3 slope to match +2.8 pts per meal of marketshare fish
  - 47% decrease in Hg slope
  - 52% increase in O-3 slope

Comparison Across Risk/Benefit Models: Two Composite Fish Meals/Week



Comparison of Calibrated VRM Model vs FAO/WHO IQ Model for Swordfish Effects on ND



FDA 2014 Table V-7. Fish Consumption Effects on IQ

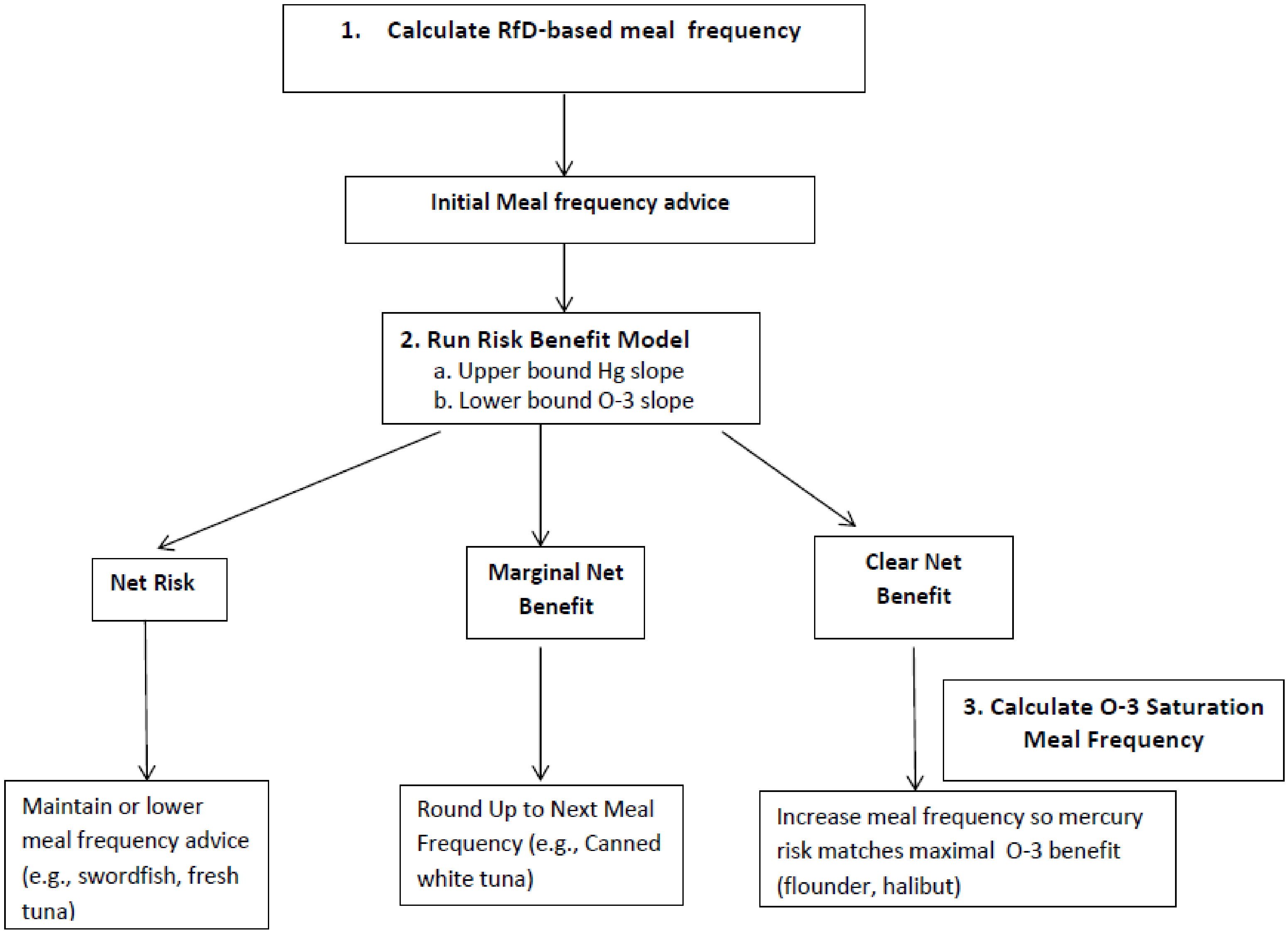
SPECIES OR MARKET TYPE	MEAN MeHg LEVEL*	OZ. PER WEEK TO REACH MAXIMUM BENEFIT	SIZE OF MAXIMUM BENEFIT EXPRESSED AS A NUMBER OF IQ POINTS	OZ. PER WEEK TO BECOME ADVERSE
Tilefish, Gulf	1.45 ppm	8 (0, 13)	1.4 (0.0, 2.6)	16 (0, 30)
Swordfish	1.00 ppm	8 (7, 13)	2.0 (0.7, 3.0)	24 (12, 43)
Shark	0.98 ppm	8 (7, 13)	2.0 (0.7, 3.0)	24 (12, 44)
Mackerel, King	0.73 ppm	8 (7, 13)	2.4 (1.4, 3.2)	32 (16, 59)
Orange Roughy	0.57 ppm	8 (8, 13)	2.6 (1.7, 3.4)	41 (21, 76)
Grouper	0.46 ppm	8 (8, 13)	2.7 (1.9, 3.6)	54 (26, 94)
Tuna, Fresh	0.39 ppm	9 (8, 13)	2.8 (2.1, 3.7)	60(31, 111)
Mackerel, Spanish	0.37 ppm	9 (8, 13)	2.8 (2.2, 3.7)	64 (33, 117)
Sable Fish	0.37 ppm	9 (8, 13)	2.8 (2.2, 3.7)	64 (33, 117)
Bluefish	0.35 ppm	9 (8, 13)	2.8 (2.2, 3.7)	64 (33, 117)
Tuna, Albacore Canned	0.35 ppm	9 (8, 13)	2.8 (2.2, 3.7)	67 (35, 123)

Risk/Benefit Analysis of Commercial Fish Species Based Upon the Calibrated VRM Model (results shown for 1 meal/week)

Fish Species	O-3 Content mg/170 g meal	Hg Content (ug/g)	O-3/Hg Ratio (mg/ug)	Net VRM Score	Net VRM Upperbound Hg Slope[1]	Net VRM Lowerbound O-3 Slope[2]
Marketshare Meal	918	0.085	63.5	2.8	1.7	1.4
Cod	268	0.11	14.3	-0.37	-1.0	-0.8
Flounder	852	0.05	100.2	3.0	2.7	1.7
Halibut	1398	0.26	31.6	2.43	0.9	0.3
Herring Atlantic	3424	0.04	503.5	14.3[b]	14	9.0
Lobster	816	0.24	20.0	0.2	-1.3	-1.0
Pollack	922	0.06	90.4	3.2	2.8	1.8
Salmon Atlantic (Farmed)	3650	0.014	1534	15.7[b]	15.6	10.2
Sea Bass	1294	0.27	28.2	1.9	0.2	-0.1
Shark	1170	0.99	7.0	-8.1	-15	-11
Shrimp	535	0.01	314.7	2.2	2.1	1.4
Swordfish	1392	0.97	8.4	-7.5	-13	-9.6
Tilapia	240	0.01	141.2	0.90	0.84	0.54
Tuna: Canned Light	425	0.1	25	0.45	-0.15	-0.2
Tuna: Canned White	1462	0.36	23.9	1.31	-0.85	-0.88
Tuna: Fresh[a]	474	0.325	8.6	-2.5	-4.4	-3.2

[1]Upperbound Hg slope is the calibrated mercury slope + SE = -5 VRM points/ppm hair Hg.
[2]Lowerbound O-3 slope is the calibrated O-3 slope minus SE = 1.99 VRM points/100 mg O-3/d.

Fish Consumption Advisory Framework



Derivation of Risk Specific Advice for Several Illustrative Species

Fish Species	Step 1. Meal Frequency at Rfd[a]	Step 2. Net VRM Score	OK to Exceed RfD?	Step 3. Max Meal Frequency[b]	Suggested Advice
Flounder	4.9/wk	3.0, Clear Benefit	Yes	7/wk	Unlimited
Halibut	0.95/wk	2.4, Clear Benefit	Yes	2.3/wk	2/wk
Tuna, canned light	2.5/wk	0.5, Marginal Benefit	No	2.5/wk	2-3 wk
Tuna, canned white	0.69/wk	1.3, Marginal Benefit	No	0.69/wk	1/wk
Tuna, fresh	0.76/wk	-2.5,Marginal Risk	No	0.76/wk	1-2/month
Seabass	0.92/wk	1.9, Marginal Benefit	Yes/No	2.2/wk	1-2/week
Swordfish	0.25/week	-7.5, Clear Risk	No	0.25/wk	Do not eat

[a]Step 1 meal frequency based upon default approach for setting risk-based consumption limits (USEPA, 2000)which utilizes the following equation: #meals/day = (RfD*body wt - kg)/(Meal size*Hg conc) where mercury concentrations are listed in Table 4, RfD = 0.1 ug/kg/d, body wt = 62 kg, meal size = 6oz or 170g. This gets multiplied by 7 to get meals/week.

[b]Calculated as the meal frequency at which mercury VRM decrease exceeds saturation of O-3 benefit (8.4 VRM points) for species which have a net benefit. For species with a net risk, maximum meal frequency defaults to RfD-based frequency.

Screening Use of O-3/Hg Ratio

- <20 – unlikely to provide net benefit
- 20-30 – marginal benefit – round consumption up
- >30 – clear benefit – increase consumption to next category or to O-3 benefit saturation

Summary

- Calibration of VRM-based model provides net benefit from average fish meal (5%)
  - Greater benefit compared to our earlier model
- Three step Framework can determine whether benefit sufficient to alter RfD-based approach
  - And set consumption limits on saturation of benefit
- O-3FA/Hg ratio can help screen individual species
- Numerous uncertainties – more research needed

Calibration of VRM Model

- Develop estimate of baseline fish diet – Composite MarketShare Model
  - US National Marine Fisheries Service survey
  - Relative % of fish sold in US market, 51 species
- Hg in fish from FDA TDS database (FDA 2009)
- O-3 in fish from USDA database (USDA, 2010; FAO/WHO, 2010)
- Resulted in Hg and O-3 content of composite marketshare fish meal

Basic Features of Composite Marketshare Fish Diet

	Fish Content	Dietary Exposure (2 meals/week)	Recommended Value
EPA+DHA	918 mg/6 oz	262 mg/d	100 mg/d [1]
meHg	0.085 ug/g	0.069 ug/kg/d	0.1 ug/kg/d[2]
Ratio mg O-3/ug Hg	64 mg/ug	---	17 mg/ug [1]

[1]Recommended for optimal neurodevelopment as cited in Tsuchiya et al. (2008). The O-3 FA/Hg ratio recommended by Tsuchiya et al. (2008) is based upon DHA content of fish.

[2]USEPA methyl mercury RfD.

- **Mercury exposure from 1 meal/wk yields 0.34 ppm adult hair Hg**
  - this matches NHANES 50th percentile hair Hg
  - this approximates Oken et al. 2005 mean hair Hg

Uncertainties

- Model Slopes
  - Updated slopes based upon model calibration
    - Based upon runs of composite marketshare meal
    - Only 1 datapoint but ….
    - Updated O-3 FA slope consistent with FAO/WHO and FDA
    - Updated Hg slope smaller than original and supported by other considerations
  - Mercury risk slope – wide disparity
    - Studies which correct for fish benefit have higher slope
      - Oken et al. 2005, Lederman et al. 2008; Orenstein et al. 2014
    - Higher slope consistent with benefit from baseline fish and risk from high Hg fish
  - O-3 FA used to represent all that is beneficial in fish
    - Protein, iodine, selenium, etc. may also contribute
    - O-3FA and selenium status correspond to fish intake (Berr et al. 2009)

Uncertainties (cont)

- Additional contaminants can impact advice
  - Especially where Hg neurodevel suggests frequent consumption
- Variability in fish content in Hg and O-3s
  - Fish can come from many places, be called same thing
  - Marketbasket survey for commercial fish reasonable to capture average case and overall variability
    - Are there regional fish that are much different
    - Locally caught fish may be highly variable in O-3, Hg or both