Risk-Benefit Initiative in the U.S.

Initiative is designed to better understand the health consequences of the developing nervous system of the fetus from a pregnant woman’s consumption of fish.

The Risk of Concern Has Been Methylmercury

- **MeHg** is a neurotoxin
  - The unborn child is generally more sensitive to it than the adult
- MeHg is essentially in all commercial fish
- Is eating commercial fish during pregnancy causing harm to unborn children in the U.S.?
  - Always? Sometimes? Never? And if so, how much harm?

Risk Management Concern

- Poisoning events in Japan and Iraq in last century demonstrated that at extreme levels of exposure, methylmercury can be highly neurotoxic
  - Methylmercury - pass from pregnant woman to fetus
  - Fetus could be more sensitive than mother
  - Children exposed during pregnancy were severely harmed, while mothers were only mildly affected

U.S. Fish Consumption Advice in 1994

**Message:** To pregnant women, women who might become pregnant, nursing mothers, and young children on what & how much fish to eat to limit their exposures to MeHg.

- Avoid 4 commercial species with the most MeHg.
- Do not eat more than 12 ounces/week (340 g) of other commercial species.
- Do not eat over 6 oz/wk (170 g) of albacore tuna.
- Most recent advice was issued in 2004.

What We Did Not Know When We Issued That Advice in 2004

- The “risk” (i.e. likelihood and severity of harm) from MeHg in commercial fish.

  **In particular:** The likelihood and severity of harm to unborn child when fish consumption during pregnancy is:
  - higher than 12 oz/wk (340 g);
  - equal to 12 oz/wk (340 g); or
  - less than 12 oz/wk (340 g).
More We Did Not Know: From Research Published After the Advice

- Eating fish during pregnancy would become associated with improved neurodevelopment in offspring.
  (6 of 6 studies)

More From Research Published After the Advice

- 12 oz. fish/week Became a Research Target
  - Eating more than 12 oz (340 g) fish/wk during pregnancy would become associated with improvements rather than with deficits.
    (4 of 4 studies than examined that question)
  - Also, eating more than 12 oz (340 g) fish/wk would be associated with greater benefits than eating less than 12 oz (at least under some circumstances).

More From Research Published After the Advice

- Countervailing beneficial and adverse effects on exactly the same health endpoint of fetal neurodevelopment.
- “Net effect” of eating fish.
  1. Adverse: MeHg
  2. Beneficial: presumably from one or more nutrients in fish, with omega-3’s being potential candidates.

Need Risk-Benefit Analysis

- Approach based on generally accepted QRA techniques, but with multiple dose-response functions
  - An adverse dose-response function for MeHg
  - A beneficial dose-response function for “fish”
  - And a dose-response function for the net effects that is a combination of the first two functions
- “Net effects” could be adverse, neutral or beneficial, depending on the amounts and types of fish consumed

Risk-Benefit Analysis Approach

- First: Where would the data for the adverse and beneficial dose-response functions come from?
  - Observational-type research published in peer reviewed journals
  - Studies measure either:
    - prenatal exposure to methylmercury; or
    - maternal fish consumption of fish; or
    - both.
Problem: Only summary data in journal articles; need raw data to develop dose-response relationship

Solution:
- U.S. FDA obtained raw data directly from researchers (e.g., at least 6 data points)
- Used dose-response relationships developed by others when neither raw data nor adequate summaries of data not available

Second: Would it be possible to measure the net effect of fish consumption on neurodevelopment as a whole, or only on aspects of neurodevelopment?
- Neurodevelopment involves many "domains"
- Verbal, motor, and social endpoints
- Many different tests of neurodevelopment administered at various stages of childhood development

Problem: Not possible to model results from every possible test at every possible age in a single assessment (note: even if results for all possible tests were in the scientific literature)

Solution: model results on a few tests that could be regarded as representative of the "net effects" of fish consumption on neurodevelopment as a whole
- Modeled the net effects of early age verbal development & net effects on IQ

Third: Would it be possible to ensure that the data for the methylmercury dose-response function was not confounded by the beneficial effect from fish?
- Also - the beneficial effect from fish would not be confounded by methylmercury

Solution for evaluating effect of methylmercury: use data from situations where the possibility of confounding was limited
- A study of extreme poisoning event in Iraq, where exposure was 100x average U.S. exposure
  - Bread made from seeds tainted w/ MeHg
- Studies in the Seychelles Islands, the Faroe Islands, and New Zealand, where exposure were around 10x average U.S. exposure
  - Effects at high consumption levels (beyond "plateau" of the benefits of consuming fish) attributed only to MeHg

Solution for evaluating effect of fish: used data from studies of the benefits of fish
- Correct for potentially small effect of undetected MeHg
Fourth: How to match adverse effects data from one or more studies with beneficial effects data from one or more studies in order to combine them into a dose-response function for “net effects”?

**Solution:** Combine effects from the same “domain” of neurodevelopment
- Language skills among children of the same age
- Data on IQ for both adverse MeHg & beneficial fish effect

Fifth: How to develop a common denominator in order to combine and compare non-identical effects?
- Dose-response function from: adverse MeHg effect on age of first talking and beneficial “fish” nutrients effect on scores on tests of early age verbal development
- How to compare the net effects on early age verbal development against net effects for IQ to determine how consistent they are with each other?

Sixth: How to combine an adverse dose-response relationship with a beneficial dose-response relationship (given a common denominator) for the “net effects”?

Solution: Use of z-scores
- Converted results from both age of first talking and the early age verbal test scores in Z-score
- Convert Z-scores into IQ points multiplied by 15 (“IQ Size Equivalents”)
- If sum is positive, then net effect is “beneficial”
- If negative, then net effect is “adverse”

Seventh: What is causing the beneficial effect? How to model it if the cause is unknown?

Solution: Treat all fish as identical “packages” of nutrients
- Assume all fish only differ from one another in terms of the amounts of MeHg
- Note: assumption unlikely correct
- Consider conducting a “sensitivity analysis”
**Risk-Benefit Analysis Decisions**

- U.S. FDA faced several major decisions; probably inherent in this kind of assessment
- Recent FAO/WHO is also an assessment of the “net effects” and it faced the same kinds of issues
  - Not identical to those made by FDA, but the results appear to be consistent

**Risk-Benefit Analysis Findings**

- Final results not published yet
- Draft 2009 assessment estimated
  - 1/10th of one percent of U.S. children experience net effects that are adverse due to their mother’s consumption of fish during pregnancy
    - Due to a diet that include high MeHg contaminated fish
  - All other children whose mothers ate fish during pregnancy experience a net benefit
    - Most net benefits are equivalent to a fraction of a single IQ point
    - Highest benefits are equivalent to 3.5 IQ points
    - Due to eating a lot of fish low in MeHg

**Revisit Advise to Pregnant Women: Fish Consumption**

- **Focus of U.S. advice in 2004:**
  - How pregnant woman can minimize risk to the developing nervous system from methylmercury without avoiding fish.

- **How we could re-focus that advice now:**
  - How pregnant woman can maximize benefit to the developing nervous system from fish while minimizing risk from methylmercury.