Asia-Pacific Economic Cooperation

Risk-Benefit Assessment of Food: Fish Consumption During Pregnancy

Philip Spiller
CFSAN
U.S. Food and Drug Administration

Janell R. Kause
FSIS
U.S. Dept. of Agriculture

1

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

But on the other hand…

- *Beneficial effect* apparently does not increase indefinitely in proportion to consumption.
  - 3 studies produced evidence of a "plateau"
- *MeHg* can adversely affect the outcome. (3 of 4 studies that examined that question.)
  - Can cause effect to be a smaller benefit; or…
  - Can replace benefit with adverse effect.

Need Risk-Benefit Analysis

- 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.

Risk-Benefit Analysis Approach

- 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 – Data for Dose-Response Relationships

- 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.

Risk-Benefit Analysis – Data for Dose-Response Relationships (continued)

- 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

Risk-Benefit Analysis – Measuring Endpoints

- 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

Risk-Benefit Analysis – Measuring Endpoints (continued)

- 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

Risk-Benefit Analysis – Control Confounding

- 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?

Risk-Benefit Analysis – Control Confounding (continued)

- 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

Risk-Benefit Analysis – Control Confounding (continued)

- Solution for evaluating effect of fish: used data from studies of the benefits of fish
- Correct for potentially small effect of undetected MeHg

Risk-Benefit Analysis – Combining Countervailing "Effects"

- 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

Risk-Benefit Analysis – Common Denominator

- 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?

Risk-Benefit Analysis – Common Denominator (continued)

- 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"

Risk-Benefit Analysis – Combining Dose-Response Relationships

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

Risk-Benefit Analysis – Combining Dose-Response Relationships (continued)

- Solution: Add dose-response relationships together based on the assumption that the adverse and beneficial effects on fetal neurodevelopment are independent of one another.
  - Note: no evidence that the two effects interact
- So,
  - Where the sum of the two dose-response relationships is positive, the net effect is beneficial
  - Where the sum is negative, the net effect is adverse

Risk-Benefit Analysis – Assuming All Fish the Same Except for MeHg

- 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 benefit s 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.