(37)

Re-evaluation of the NRC Methylmercury Committee Estimate of "Over 60,000 Newborns ... at Risk" Annually from Fish Consumption

November 6, 2000

Prepared for:

National Food Processors Association
1350 I Street N.W., Suite 300
Washington, DC 20005

Prepared by:

F. Jay Murray, Ph.D., D.A.B.T.
Murray & Associates
5529 Perugia Circle
San Jose, CA 95138

Re-evaluation of the NRC Methylmercury Committee Estimate of "Over 60,000 Newborns ... at Risk" Annually from Fish Consumption

Executive Summary

The purpose of this report is to critically evaluate the estimate of "over 60,000 children...at risk" in the NRC Methylmercury Committee Report (the Committee Report). Overall, the Committee Report is a thorough and well-written scientific review of the toxicological effects of methylmercury (MeHg). The Committee Report contains an estimate that "over 60,000 children are born each year at risk for adverse neurodevelopmental effects due to in utero exposure to MeHg" (the Committee Estimate). Unfortunately, the Committee's specific estimate of over 60,000 newborns "at risk" is ambiguous, consisting of only two sentences that do not contain sufficient explanation. This estimate appears to grossly overstate the potential risk to newborns of maternal fish consumption. Even relying on the Committee's dubious assumptions regarding maternal fish consumption, to suggest that 60,000 newborns per year are at risk is scientifically indefensible. For the reasons discussed below, I believe that the actual number is closer to zero.

First, the Committee does not define its basis for determining when a newborn might be "at risk." If the Committee Estimate is based on the EPA Reference Dose (RfD) of 0.1 μg/kg/day, the Committee employed an inappropriate uncertainty factor in its estimate of the number of newborns "at risk" of neurodevelopmental effects, since the RfD includes a specific uncertainty factor for effects other than neurodevelopmental effects. In particular, it is not scientifically appropriate to estimate the risk of neurodevelopmental effects based on an uncertainty factor that may include uncertainty factors for other health effects. Using a more appropriate uncertainty factor (eliminating the uncertainty factor for other effects) and what I believe to be the same assumptions and methodology as the Committee, the 60,000 newborns at risk for adverse neurodevelopmental effects from *in utero* exposure to MeHg is a gross overestimate even at the highest levels of maternal fish consumption.

Second, the Committee Estimate is based on the results of a study in the Faroe Islands where exposure to MeHg is far higher than in the U.S. The use of the Faroe Islands study to estimate risk in the U.S. is highly controversial because the pattern and magnitude of MeHg exposure in the U.S. is very different from that encountered in the Faroe Islands. The major source of MeHg exposure in the Faroe Islands is the consumption of whale meat and blubber, which is not consumed in the U.S. The levels of MeHg in whale meat and blubber are far in excess of levels found in commercial fish in the U.S. In addition, extremely high levels of PCBs and other pollutants in fish and whale meat and blubber further confound the Faroe Islands study. Recent EPA research indicates synergistic neurodevelopmental effects between PCBs and MeHg. In addition, the Joint FAO/WHO

Expert Committee on Food Additives (JECFA; WHO Food Additive Series:44; Safety evaluation of certain food additives and contaminants, 2000) expressed concern about the confounding role of PCBs, stating such effects could lead to false-positive associations between exposure to MeHg and child development. JECFA recommended that the Faroe Islands study be reassessed.

Third, the Committee Estimate disregards the results of an important epidemiological study in the Seychelles that demonstrated no adverse neurodevelopmental effects at levels of MeHg exposure considerably greater than those encountered in the U.S. The reasons for the contradictory findings between the Faroe Islands and Seychelles studies are still being investigated. However, the higher peak levels of MeHg achieved through whale meat consumption and the extraordinarily high levels of PCB contamination of fish and whale meat and blubber in the Faroe Islands may account for much of the difference. The pattern of fish consumption in the Seychelles is closer to that in the U.S. than is the combined fish and whale meat and blubber consumption in the Faroe Islands. Accordingly, other scientific organizations and regulatory agencies have relied upon the Seychelles study for purposes of setting acceptable levels of exposure to MeHg. If the Committee Estimate had been based on the Seychelles study, rather than the Faroe Islands study, the estimated risk to newborns would have been insignificant and a change to FDA's consumption advisory for fish would be unnecessary.

Finally, the consumption pattern of fish in the U.S. does not present a significant risk of neurodevelopmental effects requiring a change in the FDA's current consumption advisory for fish. A recent study by ENVIRON International Corp. (ENVIRON, 2000) showed that the average daily consumption of fish by U.S. women age 15-44 is 46 grams at the 95th percentile of fish consumption; in contrast, the Committee Report assumed a figure of 100 grams per day. Using ENVIRON's exposure data, the exposure of women age 15-44 to MeHg at the 95th percentile of fish consumption does not exceed even the RfD of 6 μg per day. However, as noted previously, the RfD is not an appropriate basis for estimating the number of newborns at risk of neurodevelopmental effects. Better estimates of the actual number of children at risk may be achieved by using alternative approaches. The alternative approaches ("Adjusted Reference Dose," BMDL) presented in this report provide a more scientifically accurate basis for estimating the number of children at risk for neurodevelopmental effects. Regardless of whether the exposure assumptions of the Committee or ENVIRON are used, these estimates indicate that the figure of over 60,000 newborns at risk of neurodevelopmental effects from maternal fish consumption is wrong. Based on these estimates, I believe the actual number is closer to zero.

Introduction

Mercury (Hg) is a heavy metal that may occur in the form of elemental mercury, inorganic mercury, or methylmercury (MeHg). In aquatic environments, Hg may be converted to MeHg by acquatic biota, and MeHg bioaccumlates in fish. Humans are exposed to MeHg primarily through the consumption of fish, particularly large predatory species of fish (e.g., shark, swordfish) and in some cultures, marine mammals (e.g., whale).

While it is well accepted that MeHg can be neurotoxic at some levels of exposure, there are significant disagreements within the scientific and regulatory communities regarding an appropriate level of concern for MeHg exposure. In 1995, U.S. EPA established a Reference Dose (RfD) for MeHg of 0.1 µg/kg/day, based on a study of acute poisoning from contaminated grain in Iraq. More recently, U.S. EPA has proposed to revise the basis for its RfD for MeHg. Specifically, U.S. EPA has proposed keeping its current RfD of 0.1 µg/kg/day, based on an evaluation of a recent study in the Faroe Islands. Because there have been disagreements among scientists over the appropriate level of concern, the U.S. Congress directed U.S. EPA to fund a review of its proposed RfD by the Committee on the Toxicological Effects of Methylmercury of the National Research Council (the Committee).

The Committee conducted a detailed scientific review of the U.S. EPA's proposed RfD, and published its results in a report entitled "Toxicological Effects of Methylmercury" (the Committee Report).[1] The Committee Report concluded:

> "On the basis of its evaluation, the committee's consensus is that the value of EPA's current RfD for MeHg, 0.1 µg/kg per day, is a scientifically justifiable level for the protection of public health. However, the committee recommends that the Iraqi study no longer be used as the scientific basis of the RfD. The RfD should be based on the developmental neurotoxic effects of MeHg, but the Faroe Islands study should be used as the critical study for the derivation of the RfD."

The Committee Report contains a statement estimating that "over 60,000 children are born each year at risk for adverse neurodevelopmental effects due to in utero exposure to MeHg" (the Committee Estimate). However, the Committee Estimate is highly controversial, and the justification for this estimate is not described in the Committee Report. The Committee Estimate does not appear in the Executive Summary of the Committee Report, but it is included among the "Committee Findings and Recommendations" in the final chapter.

[1] National Research Council (2000) Toxicological Effects of Methylmercury. National Academy Press, Washington, DC.

The goal of this report is to understand the meaning of and basis for the Committee Estimate of "over 60,000 children ... at risk." Alternative estimates of the number of children at risk will also be explored. The current report is not designed to be a comprehensive risk assessment of MeHg in fish. It is intended to be a critical evaluation of the validity of the Committee Estimate of 60,000 children at risk.

The Committee Estimate

The Committee Report (page 327) states: "The population at highest risk is the offspring of women of child-bearing age who consume large amounts of fish and seafood. The committee estimates that over 60,000 children are born each year at risk for adverse neurodevelopmental effects due to in utero exposure to MeHg." The basis for this estimate is unclear. Although this estimate was presented as one of the "findings" of the committee, the Committee Report does not identify the basis and assumptions of this estimate.

The only explanation of this estimate in the entire Committee Report is limited to two sentences on page 325:

> "To further characterize the risks of MeHg, the committee developed an estimate of the number of children born annually to women most likely to be highly exposed through high fish consumption (highest 5% estimated to consume 100 g per day). Available consumption data and current population and fertility rates indicate that over 60,000 newborns annually might be at risk for adverse neurodevelopmental effects from in utero exposure to MeHg."

This statement differs significantly from the "finding" on page 327 of the Committee Report. On page 327, the Committee estimates that 60,000 children "***are ... at risk***" for neurodevelopmental effects, whereas the estimate on page 325 says 60,000 newborns "***might be at risk***" for neurodevelopmental effects. In either case, this estimate is grossly inaccurate and misleading, as will be shown below.

U.S. EPA believes that the Committee Estimate is based on an estimate that 60,232 newborns are born to mothers in the top 5% of fish consumption (Table 1). But, this simply means that the fish-consuming mothers of 60,232 newborns eat more fish than the other 95% of fish-consuming mothers. It says nothing about risk *per se*.

There are several problems with the Committee Estimate. First, the basis for determining when newborns "might be at risk" from MeHg exposure is not explained. Second, no source is given for the estimate that the highest 5% consume 100 g per day of fish.[2]

---

[2] The basis for the Committee's figure of 100 g per day is unclear. Environ International Corp. (2000) estimated that the 95th percentile of fish consumption is only 46 g per day, less than half of the Committee estimate.

Third, the basis for determining the total number of newborns born to mothers consuming fish is not clear. Each of these is discussed more fully below.

Table 1. Estimate of the number of newborns born annually to U.S. women aged 15-44 years at the 95th percentile of fish consumption[3]

No. of U.S. women aged 15-44 years	60,208,000
Percent reporting fish consumption	30.5%
No. of U.S. women aged 15-44 years consuming fish	18,363,440
No. of U.S. women aged 15-44 years in the highest 5% of fish consumption (100 g per day)	918,172
Annual birth rate for women aged 15-44	65.6 per 1000
No. of newborns born annually to U.S. women aged 15-44 years in the highest 5% of fish consumption (100 g per day)	60,232

The basis for "at risk"

The Committee Estimate does not define the basis for determining when a newborn might be "at risk." It may be presumed that the Committee Estimate is based in part on the U.S. EPA Reference Dose (RfD). For example, if the Committee Report assumed that the top 5% of fish consumers among women aged 15-44 eat 100 g of fish per day and assumed that the average fish contains 0.1-0.2 ppm of MeHg, it may be calculated that the top 5% of fish consumers would exceed the RfD, as illustrated in Table 2.

If, in fact, the Committee Estimate is based on the RfD, the estimate is inaccurate and misleading. It is important to recognize that the RfD is ***not*** the dose level above which neurodevelopmental effects are anticipated. The RfD is defined by U.S. EPA as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." An exposure above the RfD does not mean that an adverse event will occur.

[3] EPA suggestion for Committee Estimate of 60,000.

Table 2. "Best Guess" of Committee's Estimate of the number of newborns "at risk" if defined as maternal exposure to MeHg exceeding the Reference Dose

No. of newborns born annually to U.S. women aged 15-44 years in the highest 5% of fish consumption (100 g per day)	60,232
Estimate of amount of fish consumed at 95th percentile	100 g per day[4]
Estimate of average MeHg concentration in fish in U.S.	0.1-0.2 μg/g (ppm)
Estimated daily dose of MeHg at the 95th percentile of fish consumption	10-20 μg per day[5]
EPA Reference Dose for MeHg (0.1 μg/kg/day x 60 kg)	6 μg per day
No. of newborns whose mothers exceed the Reference Dose at the 95th percentile of fish consumption	60,232

The RfD is a conservative estimate of the dose level estimated to have no effect in the selected study and includes uncertainty factors. In the case of the RfD for MeHg, the Committee proposed two uncertainty factors. The first uncertainty factor was designed to provide a margin of safety based on variation in MeHg kinetics among sensitive individuals. The second uncertainty factor was designed to provide an additional degree of protection in the event that toxic effects other than neurodevelopmental toxicity (e.g., immune or cardiovascular effects) could occur at lower levels of exposure.

The Committee Report estimated that 60,000 newborns "are ... at risk" or "might be at risk" of neurodevelopmental toxicity, presumably based on exposures in excess of the RfD. However, as noted, the RfD contained an additional uncertainty factor for adverse effects other than neurodevelopmental toxicity. It is inappropriate to apply an uncertainty factor for toxic effects other than neurodevelopmental toxicity to estimate the risk of neurodevelopmental toxicity. In reality, 60,000 newborns are not potentially "at risk" of neurodevelopmental toxicity. Rather, using more scientifically appropriate methodologies, as described below, there are essentially no newborns at risk for neurodevelopmental effects.

[4] The basis for the Committee's figure of 100 g per day is unclear. Environ International Corp. (2000) estimated that the 95th percentile of fish consumption is only 46 g per day, less than half of the Committee estimate.

[5] This estimate of 10-20 μg per day is based on the Committee Estimate that the 95th percentile of fish consumption for women age 15-44 is 100 g per day and an assumption that the average concentration of MeHg in fish is in the range of 0.1-0.2 ppm. In comparison, Environ International Corp. and EPA estimate that exposure to MeHg at the 95th percentile of fish consumption for women age 15-44 is 5.7 and 7.8 μg per day, respectively (7.8 μg is derived from EPA's Report to Congress, 1997).

Better Estimates

Estimate based on the "Adjusted Reference Dose"

A more accurate estimate of the number of newborns that "might be at risk" for neurodevelopmental toxicity may be calculated by eliminating the additional uncertainty factor for toxic effects other than neurodevelopmental toxicity, as shown in Table 3. By eliminating the inappropriate uncertainty factor (for effects other than neurodevelopmental) and using the presumed methodology in the Committee Report, it is estimated that no children would be at risk of neurodevelopmental toxicity even at the Committee's estimated 95th percentile of maternal fish consumption.

Table 3. Estimate of the number of newborns "at risk" if defined as maternal exposure to MeHg exceeding the "Adjusted Reference Dose"

No. of newborns born annually to U.S. women age 15-44 years in the highest 5% of fish consumption (100 g per day)	60,232
Estimate of amount of fish consumed at highest 5%	100 g per day[6]
Estimate of average MeHg concentration in fish in U.S.	0.1-0.2 μg/g (ppm)
Estimated daily dose of MeHg at the 95th percentile of fish consumption	10-20 μg per day
"Adjusted Reference Dose" for neurodevelopmental toxicity[7]	20 μg per day
No. of newborns whose mothers exceed the "Adjusted Reference Dose" at the 95th percentile of fish consumption	0

While a small number of mothers would be expected to consume more than the Committee's estimated 95th percentile of fish consumption, it is also important to remember that this estimate still contains a 3-fold uncertainty factor to account for variation in kinetics among sensitive individuals.

Estimate based on the BMDL

A better estimate of the number of newborns which may actually be at risk of neurodevelopmental harm may be calculated by comparing maternal exposure against the Committee's benchmark dose (BMD) model, using the lower confidence limit and the

[6] The basis for the Committee's figure of 100 g per day is unclear. Environ International Corp. (2000) estimated that the 95th percentile of fish consumption is only 46 g per day, less than half of the Committee estimate.

[7] Adjusted by removing the Committee's uncertainty factor for effects other than neurodevelopmental toxicity (i.e., approximated by multiplying EPA's RfD times 3 and rounding to one digit)

best estimate of the benchmark dose. The lower limit of the benchmark dose (BMDL) is a conservative estimate of the true BMD. The BMDL approach yields a value which is lower than the benchmark dose (BMD). The use of the BMDL as a point of departure offers a "worst case" estimate of the BMD for the actual number of newborns at risk. This estimate assumes that the U.S. and Faroe Islands populations are equally sensitive to the neurodevelopmental effects of MeHg. Using the BMDL and otherwise using the same methodology presumed to have been used by the Committee, it may be estimated that a mother at the Committee's estimated 95th percentile of fish consumption is 2.2-7.3[8] times below the BMDL for neurodevelopmental toxicity (Table 4). Therefore, the number of newborns at actual risk (defined as exceeding the BMDL) due to maternal exposure to MeHg from consumption of fish at the 95th percentile is zero.

Table 4. Revised Estimate of the number of newborns "at risk" if defined as maternal exposure to MeHg exceeding the BMDL

No. of newborns born annually to U.S. women age 15-44 years in the highest 5% of fish consumption (100 g per day)	60,232
Estimate of amount of fish consumed at highest 5%	100 g per day[9]
Estimate of average MeHg concentration in fish in U.S.	0.1-0.2 μg/g (ppm)
Estimated daily dose of MeHg at the 95th percentile of fish consumption	10-20 μg per day
Daily dose at BMDL (95th lower limit of the benchmark dose) for neurodevelopmental toxicity	44-73 μg per day
No. of newborns whose mothers exceed the BMDL at the 95th percentile of fish consumption	0

The Committee Estimate Is Based Solely on the Faroe Islands Study, a Study with Serious Limitations

The Committee Estimate relies on the results of a single study, the Faroe Islands study. At the heart of the Committee Estimate is the assumption that the Faroe Islands study accurately predicts the neurodevelopmental risk of exposure to MeHg from consumption of fish. The Faroe Islands study appears to be well conducted, but even the best epidemiological studies have their limitations.

[8] 44-73 μg per day (daily dose at BMDL for neurodevelopmental effects) divided by 10-20 μg per day (estimated daily does of MeHg at 95th percentile of fish consumption)

[9] The basis for the Committee's figure of 100 g per day is unclear. Environ International Corp. (2000) estimated that the 95th percentile of fish consumption is only 46 g per day, less than half of the Committee estimate.

In fact, for the purposes of developing a RfD for MeHg, the Faroe Islands study has numerous and serious limitations. First, unlike the U.S., the major source of MeHg exposure in the Faroe Islands is the consumption of whale meat and blubber. The average concentration of MeHg in whale meat is about 2 ppm, and can range up to 3 ppm (clearly in excess of the 1 ppm FDA Defect Action Level [DAL]). People in the Faroe Islands also consume fish, but because the MeHg concentration in whales is so high relative to fish, the consumption of whale meat and blubber dominates exposure to MeHg in the Faroe Islands. In addition, exposure to MeHg in the Faroe Islands is about an order of magnitude higher than it is in the U.S.

Second, not only is the magnitude of exposure ten times higher in the Faroe Islands compared to the U.S., but the pattern of exposure is completely different between the U.S. and the Faroe Islands in terms of peak levels of exposure. In the U.S., fish consumers eat fish on a more or less continuous basis, and the average concentration of MeHg in fish consumed in the U.S. is 0.1-0.2 ppm, well below the FDA DAL. In comparison, whale meat and blubber is consumed intermittently in the Faroe Islands. However, when whale meat and blubber is consumed in the Faroe Islands, it is consumed in large quantities over a short period of time (episodic binge consumption patterns). This high acute consumption, combined with MeHg levels ranging up to 3 ppm, results in much higher peak blood levels of MeHg in the Faroe Islands than is typically encountered in the U.S. It is not clear whether the neurodevelopmental toxicity of MeHg is associated with peak blood levels or the area-under-the-curve. With many developmental toxicants, the peak blood concentration determines developmental toxicity. Therefore, if the peak levels are an important determinant of MeHg neurodevelopmental toxicity, the Faroe Islands study is a poor predictor of the risk of fish consumption in the U.S.

Third, in the Faroe Islands, exposure to MeHg may be a surrogate for whale meat and blubber consumption. Any association between MeHg and neurodevelopmental effects in the Faroe Islands may be due to MeHg, to other chemicals in whale meat and blubber, to whale meat and blubber itself, or to any combination of these factors.

The presence of PCBs, DDT, and other chemicals in whale and fish in the Faroe Islands represents a major confounding factor. The people in the Faroe Islands study were exposed to massive levels of PCBs, as well as other pollutants. Although the authors of the study indicated that they controlled for the presence of these other chemicals, it is difficult to accurately control for such high levels of confounding chemicals. Ordinarily, prenatal exposure to PCBs is determined by measuring the concentration of PCBs in the cord blood or maternal blood or milk. But, in the Faroe Islands study, PCB levels were measured in umbilical cord tissue, an unconventional practice. Further, PCB levels were measured in only half the participants of the study.

It is also unclear whether the study authors controlled for these factors at the correct time. The investigators measured PCBs and other chemicals in cord blood at the time of parturition. However, neurological development does not just occur only around the time of parturition. Neurological development occurs throughout most of the nine months of

gestation and continues postnatally. At the levels reported in cord blood in the Faroe Islands study, chemicals like PCBs and DDT would be significant confounding factors. In addition, PCBs and DDT would be expected to be significant contaminants in the maternal milk during breast feeding. The authors of the Faroe Islands did not control for the possible confounding presented by exposure to other chemicals via breast milk. This raises the possibility that neurodevelopmental effects attributed to MeHg by the authors may actually be due to other chemicals (not MeHg) in the whale and fish consumed in the Faroe Islands.

And finally, the extent of PCB contamination in the Faroe Islands study appeared to be much greater than recognized by the Committee Report. For example, Weihe et al. (*Sci Total Environ* 1996; 186: 141-148) reported that the average daily intake of PCBs from whale blubber could exceed of 200 μg per day in the Faroe Islands. Stuerwald et al. (*J. Pediatrics* 2000; 136(5): 599-605) indicated that milk consumption in the Faroe Islands may contribute an additional 840 μg per day of PCBs. In comparison, the RfD for Aroclor 1254 (commercial mixture of PCBs) is 0.02 μg/kg per day, or approximately 1.2 μg per day. Therefore, daily average exposure to PCBs in the Faroe Islands study was 600-fold greater than the RfD for Aroclor 1254.[10]

In its recent review of the Faroe Islands study, the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2000) stated:

> "Because PCBs and persistent organic pollutants are associated with both exposure to methylmercury and child development in this study, and because any confounding effects of PCBs will lead to a false-positive association between exposure to methylmercury and child development, the confounding role of PCBs and persistent organic pollutants should be reassessed in order to determine the role of methylmercury in the adverse effects reported in this study."

The Seychelles Study Indicates No Risk

The Committee Report described another well-conducted epidemiology study of MeHg, i.e., the Seychelles study. In contrast to the Faroe Islands study, the study of neurodevelopmental effects from MeHg exposure from fish consumption in the Seychelles demonstrated no adverse effects. The Committee Report acknowledged the inconsistency in the findings between the Faroe Islands and Seychelles studies. However, the Committee Report recommended the use of the Faroe Islands study for purposes of quantitative risk assessment on the basis of policy, not science. The Committee Report stated: "On the basis of its consideration of the body of evidence, the committee concluded that a well-designed study with positive effects provides the most appropriate public-health basis for the RfD." In other words, the Committee Report chose the Faroe

[10] For this comparison I picked the RfD for Aroclor 1254. This is because Fangstrom et. al. (2000) state that the most prevalent congeners are 138, 153, and 180. None of these congeners are present in Aroclor 1016. Arcoclor 1254 has all three of these most prevalent congeners (*TERA*, unpublished observations).

Islands study over the Seychelles study as the pivotal study not because it was a better study, but because the results were positive. As a policy decision, the Committee Report chose the study that would lead to a lower RfD.

The Committee Report offered a number of hypotheses to explain the difference in results between the Faroe Islands and Seychelles studies. Yet, the Committee Report noted that none of the between-studies differences "appears to be determinative." In other words, the Committee Report did not identify a solid explanation for the contradictory results. For example, the Committee Report noted that there was evidence of positive findings in the pilot study in Seychelles, suggesting that the findings in the pilot study were more consistent with those in the Faroe Islands study than were the findings of the main Seychelles study. However, a recent update of the Seychelles pilot study population revealed no evidence of a neurodevelopmental effect, even with more sensitive testing. The results of this updated pilot study were not available at the time that the Committee conducted its evaluation.

There are many reasons to think that the Seychelles study is more appropriate than the Faroe Islands study for estimating the risks of MeHg in the U.S. In contrast to the Faroe Islands study, exposure to MeHg in the Seychelles results from the more continuous consumption of fish, not from peaks due to episodic consumption of whale meat. Also, the Seychelles study does not have confounding problems with other chemical contaminants, such as PCBs, that plague the Faroe Islands study.

Despite the fact that exposure to MeHg is much higher in the Seychelles study than it is in the U.S., neurodevelopmental effects were not found in the Seychelles study. Before basing a RfD on the Faroe Islands study, it is desirable to understand why these studies yielded contradictory findings. Before extrapolating the results of the Faroe Islands study to fish consumption in the U.S., it is important to understand why the results in the Faroe Islands study do not even extrapolate to the Seychelles.

Further, the results of an update of the Seychelles main study cohort are expected within a few months. Obviously, the Committee Report did not have the benefit of these additional results, but any new action that is contemplated should consider the results of the Seychelles update.

If the Committee Estimate had been based on the results of the Seychelles study instead of the Faroe Islands study, the Committee Estimate would have been very different. If the Committee Estimate had been based on the Seychelles study, the number of children at risk would have been zero at the 95th percentile of maternal fish consumption.

Acceptable Levels of Exposure to MeHg Established by Other Organizations Yield Much Lower Estimates of Risk

Various regulatory agencies and scientific organizations have recommended a range of acceptable levels of MeHg exposure, as summarized in Table 5. There are significant differences in the assumptions and approaches used by these various organizations. The proposed U.S. EPA RfD, which apparently served as the basis for the Committee Estimate, is 2-5 times lower than acceptable daily intake levels recommended by other regulatory and scientific organizations. Also, the proposed U.S. EPA RfD is the only level which is based solely on the results of the Faroe Islands study. Other organizations, including ATSDR, have recommended the use of the Seychelles study.

Table 5. Comparison of acceptable levels of exposure to MeHg established by various scientific and regulatory organizations

Organization	Critical Study	Basis (ppm hair)	Basis (μg/kg/day)	Uncertainty or Safety Factor	Acceptable Level (μg/kg/day)
ICF-Kaiser	Seychelles (Davidson et al., 1998)	21 (BMD)	0.9-3.0	3 (UF)	0.3-1.0
JECFA	Friberg et al., 1971	nd	4.3	10 (SF)	0.5
FDA	Friberg et al., 1971	nd	4.3	10 (SF)	0.5
ATSDR	Seychelles (Davidson et al., 1998)	15 (NOAEL)	1.3	4.5 (UF)	0.3
Health Canada	Seychelles, Faroe Islands and New Zealand	10 (BMD)	1.0	5 (UF)	0.2
EPA (1995)	Iraq (Marsh et al., 1987)	11 (BMD)	1.1	10 (UF)	0.1
EPA (proposed 2000)	Faroe Islands (Grandjean et al., 1997)	12 (BMD)	1.1	10 (UF)	0.1

The Committee Estimate of 60,000 children at risk was predicated on the Faroe Islands study being the most appropriate study for risk assessment purposes. Other organizations, including many regulatory agencies, have not agreed that the Faroe Islands study is the most appropriate study, and as a result, other organizations have

recommended acceptable daily intakes higher than the proposed RfD. If acceptable daily intake levels recommended by other organizations (other than U.S. EPA) had been used to calculate the number of children at risk, an estimate approaching zero would have emerged.

Consumption of Fish Poses No Significant Risk of Neurodevelopmental Effects in the U.S.

Table 6 compares the distribution range of MeHg exposure from fish consumption among women age 15-44 in the U.S. against levels of exposure considered acceptable by various organizations. The 95th percentile of fish consumption (46 g/day) is estimated to provide an average daily dose of 5.7 μg MeHg per day[11], a value that does not exceed the EPA RfD of 6 μg per day. The estimated average daily dose of MeHg at the mean (average) fish consumption for women age 15-44 in the U.S. is 1.5 μg per day, or 4 times less than the EPA RfD.

Table 6. Comparison of fish consumption and various acceptable levels of exposure to MeHg

Level of Exposure	Exposure to MeHg[a] (μg per day)
BMDL	44-73
JECFA (FAO/WHO)	30
FDA	30
"Adjusted Reference Dose"[b]	20
ATSDR	18
Health Canada	12
EPA RfD	6
Fish consumption among women aged 15-44[c]	
-- 95th percentile	5.7
-- 90th percentile	3.4
-- 75th percentile	1.5
-- 50th percentile	0.5
-- 25th percentile	0.1

[a] Daily exposure to MeHg for a 60 kg women.
[b] Adjusted by removing the uncertainty factor for effects other than neurodevelopmental effects.
[c] Environ International Corp. (2000)

[11] Environ International Corporation. Estimated Usual Intake of Fish and Mercury from Fish by U.S. Women Age 15-44. Unpublished report prepared for the U.S. Tuna Foundation, November, 2000.

As noted previously, the RfD is not an appropriate basis for estimating the number of newborns at risk of neurodevelopmental effects. The "Adjusted Reference Dose" and BMDL for neurodevelopmental effects offer more reasonable bases for such an estimate. As shown on Table 6, the 95th percentile of fish consumption is well below either of these target levels.

FDA's current consumption advisory for fish Is a change warranted?

NO

Presentation Outline

I. Re-evaluation of the NRC MeHg Committee Estimate--F. J. Murray
II. Fish Consumption and MeHg Exposure--J. T. Heimbach
III. Risk/Risk Tradeoffs in Risk Management--G. M. Gray
IV. Comparison of Risk and Benefits from Fish Consumption--J. R. Coughlin
V. Industry Impact--Companies
VI. Conclusions--R. S. Applebaum

Re-evaluation of the NRC Methylmercury Committee Estimate

F. Jay Murray, Ph.D.
Murray & Associates

Introduction

- Asked by NFPA:
  - To assess the scientific validity of the estimate of 60,000 newborns "at risk" of neurodevelopmental defects
  - To examine the underlying assumptions
  - To provide a better estimate

Overview

- Basis and assumptions of estimate are unclear
- No definition of "at risk"
- Gross overestimate of the number of newborns "at risk"
- Not scientifically defensible

Topics of Discussion

- Why is the estimate wrong?
- Better estimates
- Choice of critical study
- Potential risks and benefits of fish consumption

Why Is the Committee Estimate Wrong?

- Uncertainty factors
- Fish consumption (100 g per day)
- Based solely on the Faroe Islands study
- Disregards Seychelles study

"Best Guess" of Committee Estimate

No. of U.S. women age 15-44 consuming fish	18,363,440
Top 5% fish consumption	918,172
No. of newborns born to top 5% annually	60,232
Fish consumed by top 5%	100 g per day
MeHg in fish	0.1-0.2 ppm
Estimated dose of MeHg	10-20 μg per day

Uncertainty Factor

- Estimate presumed to be based on Reference Dose (RfD) of 6 μg per day
- 2 uncertainty factors
- Inappropriate uncertainty factor
- "Adjusted Reference Dose"
- BMDL

Number of Newborns at Risk (Committee Exposure Estimates)

Basis	Dose of MeHg (μg per day)*	No. at risk at 95th percentile
RfD	6	60,232
Adjusted RfD	20	0
BMDL	44-73	0

Fish Consumption and MeHg Exposure at 95th Percentile

Organization	Fish (g per day)	MeHg (μg per day)
Committee (2000)	100	10-20 ?
EPA (1997)	--	7.8
Environ (2000)	46	5.7

Number of Newborns at Risk (Environ Exposure Estimates)

Basis	Dose of MeHg (µg per day)	No. at risk at 95th percentile
RfD	6	0
Adjusted RfD	20	0
BMDL	44-73	0

Limitations of Faroe Islands Study for Estimating Risk in U.S.

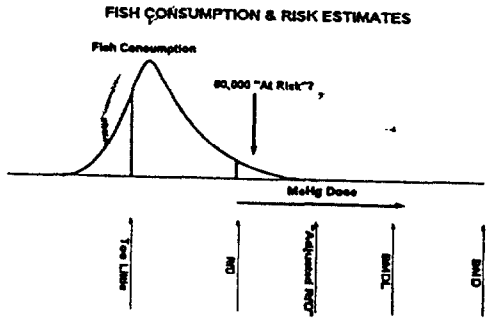
- Controversial choice
- Exposure to MeHg is far higher
- Whale meat and blubber is major source of exposure (2+ ppm)
- Pattern of exposure (episodic binge)
- PCBs and other chemicals are significant confounders

PCBs as a Confounder in the Faroe Islands Study

- PCB levels in whale meat and blubber are very high
- Exposure exceeds RfD by 600-fold
- Synergism between PCBs and MeHg
- JECFA (2000) recommended reassessing the confounding role of PCBs in this study

No Effect in Seychelles Study

- No adverse neurodevelopmental effects
- Fish consumption and MeHg exposure greater than in U.S.
- No confounding problem with PCBs
- Committee disregarded Seychelles study on the basis of policy, not science
  - Other agencies disagree



Conclusions

- Newborns are not at risk for neurodevelopmental effects from fish consumption at 95th percentile
- The Committee Estimate is scientifically unjustified
- It is important to weigh the benefits and risks of fish consumption

Fish Consumption and MeHg Exposure

J. T. Heimbach, Ph.D.
ENVIRON International Corp.

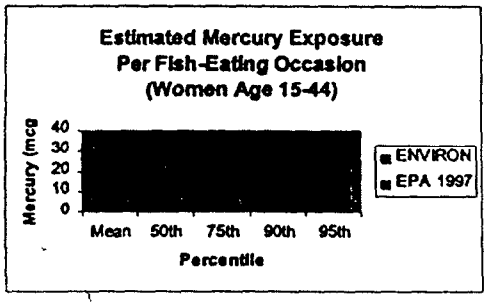
EPA Suggestion of Basis for Committee Estimate

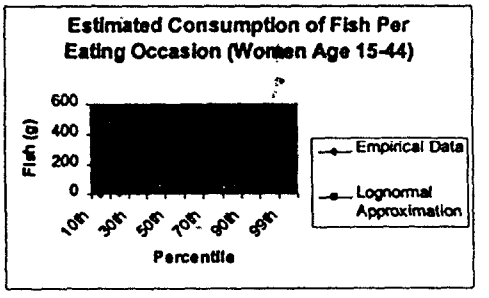
EPA Information

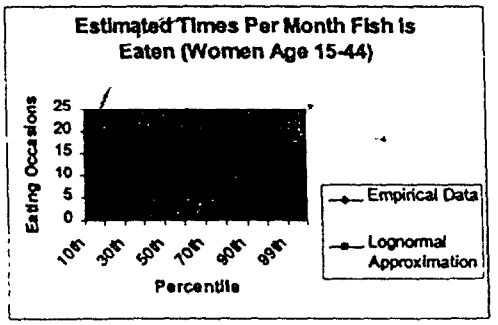
- 30.5% of women age 15 to 44 report fish consumption
- 95th percentile of consumption is 100g fish/day
- Data source: 1989/90 CSFII

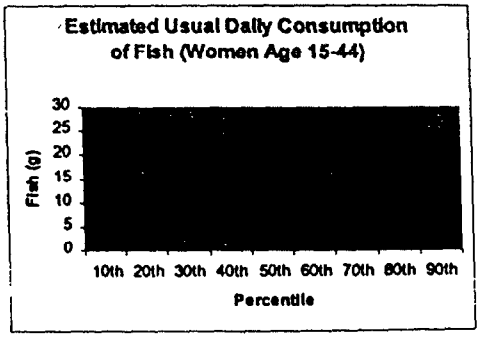
ENVIRON Comments

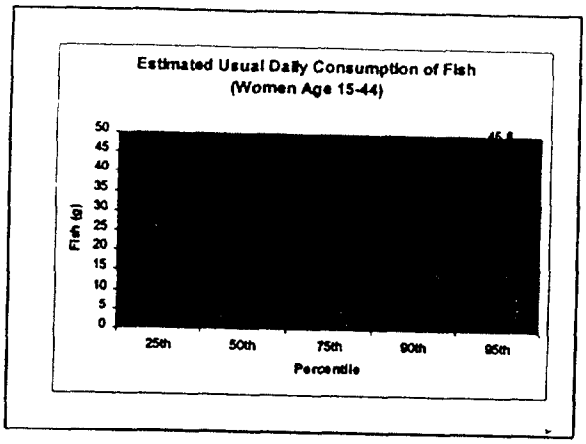
- Other data indicate that approximately 86% of women age 15 to 44 eat fish
- EPA appears to have used "3-day average" intake
- Method leads to severe overestimates of intake of infrequently consumed food
- Why use 89/90 CSFII?

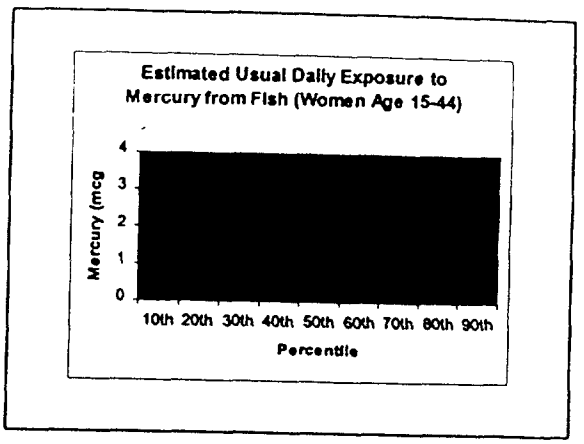


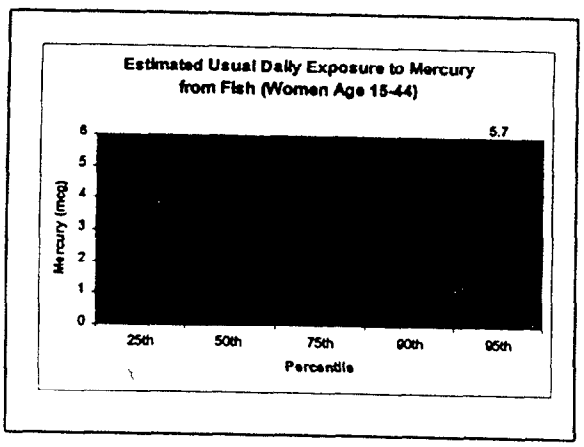












American Heart Association - Dietary Guidelines -

Two (2) servings of fish per week:

- About 1/2 fresh fish (RACC = 85g)
- About 1/2 canned/smoked fish (RACC = 55g)
- Average portion = 70g
  - Actual average for women age 15 to 44 = 71g

American Heart Association - Dietary Guidelines -

Two (2) servings of fish per week:
= 140g fish/week
= 20g fish/day

- 85th percentile of current consumption
- Twice current mean (11.3g) consumption
- Five times current median (4.1g) consumption
- AND... 14% of women age 15 to 44 do not eat fish at all

Risk/Risk Tradeoffs in Risk Management

George M. Gray, Ph.D
Harvard Center for Risk Analysis
Harvard School of Public Health

What are Risk/Risk Tradeoffs?

- Occur when risk reducing action may have risky consequences
- Target risk is often only focus of analytic and management efforts
- "Side effects" may offset, or outweigh, the benefits of a risk management policy

Confronting Risk/Risk Tradeoffs

- More commonly recognized and addressed in personal decisions
  - Osteoporosis *vs.* cancer risk for hormone treatment
  - Psychological effects of restricting elderly driver
- Rarely considered in broader social decisions
  - Increased benzene exposure with phase-out of lead in gasoline
  - Fish consumption advisories

Risk/Risk Tradeoffs with Methylmercury and Fish

- Target risk
  - Neurodevelopmental effects
  - Maybe others? (Cardio, immuno)
- Countervailing risks
  - Decreased fish consumption
    - Chronic heart disease risk
    - Neurodevelopmental effects
    - Immune system effects
  - Substitute foods
    - Increased fat intake
    - Contaminant in other foods

Risk Tradeoff Analysis

- Qualitative
  - Highlight areas of concern
  - Communication - looking after "common sense" questions
- Quantitative
  - Necessary for sense of magnitude of tradeoffs
  - Only way to know if risk management action helping or doing more harm than good

Summary

- Risk tradeoffs are pervasive
- Tradeoffs often transform risks or change population at risk
- Ignoring tradeoffs may reduce efficiency of risk management actions or even make things worse
- Need careful evaluation and risk comparison
- First--DO NO HARM

Comparison of Risks and Benefits from Fish Consumption

James R. Coughlin, Ph.D.
Coughlin & Associates

Omega-3 Fatty Acids in Fish

- Protective effect in cardiovascular disease risk:
  - Lower plasma triglycerides
  - Inhibit plaque formation
  - Decrease platelet aggregation
  - Alter arrhythmogenesis
- Eicosapentaenoic acid (EPA) and docosahexenoic acid (DHA) found in fatty fish
- Fish consumption also provides high quality protein and other nutrients (niacin, B12, vitamins A and D, Se)
- *Amer. J. Clin. Nutr. Suppl.* (Jan. 2000) - "Highly Unsaturated Fatty Acids in Nutrition and Disease Prevention," 38 articles from Barcelona Conference, 1996.

Beneficial Health Effects of Fish Consumption

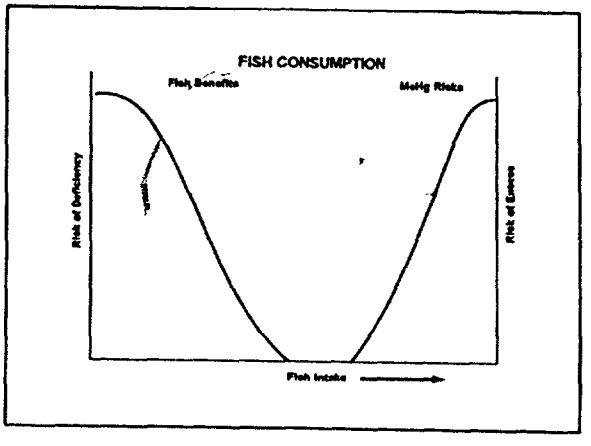
- Decreased risk of CHD and MI
- Enhanced immune and nervous system development
- Reduced risk of stroke and arthritis
- More long-term studies and randomized controlled clinical trials are needed to further confirm these observations
- If individuals do reduce their consumption of fish and replace it with other non-fish foods, these dietary changes may actually result in greater overall health risks.

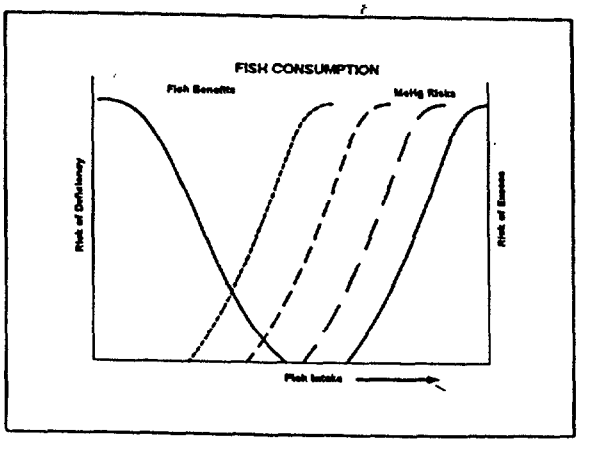
Risks and Benefits of Fish Consumption

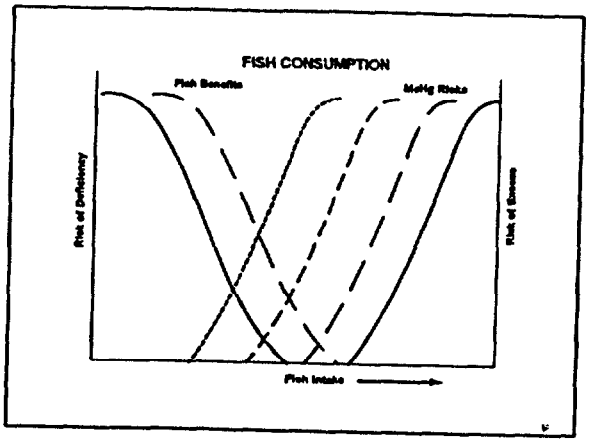
- Ponce et al., *Risk Analysis* (2000)
  - FDA's Clark Carrington and Michael Bolger as co-authors
  - Use of Quality Adjusted Life Years (QALYs) to compare risks of two different disease endpoints:
    - Increase in neurodevelopmental risk of delayed talking versus decrease in myocardial infarction
- Alternative Approach:
  - Directly compare risks and benefits for same adverse effects or diseases
  - This approach was not considered by the NRC Committee

Toxic Effects of MeHg versus Health Benefits of Fish Consumption

Effect	RfD	Health Benefit
Neurodevelopment	• Toxicity Endpoint for BMDL • UF = 2-3	Membrane function and brain/retina development
Cardiovascular Disease	Contributes to database UF	Reduced risk
Immune System	Contributes to database UF	Immunoinflammatory function improved
	TOTAL UF = 10	







In closing...

A change in FDA's current advisory for fish consumption is not scientifically justified:

- 60,000 children are not at risk for neurodevelopmental defects
  - Uncertainty factors, as apparently used in deriving the estimate, are inappropriate
  - Faroe Islands Study, alone, is inappropriate
    - Consumption patterns of population studied
    - Confounding role of PCBs

In closing...

A change in FDA's current advisory for fish consumption is not scientifically justified (cont'd):

- Seychelles Study is not considered in the analysis
- The harm of reducing/eliminating fish consumption in women of child bearing age and the public in total is real (not theoretical)
  - adverse neurodevelopmental effects
  - loss of cardiovascular health benefits
  - adverse impact to immune system

In closing...

A change in FDA's current advisory for fish consumption is not scientifically justified (cont'd):

- Conflicting dietary guidance
  - Confused public--who do they believe?
- Adverse impact to an Industry and the livelihood of many--nationally and internationally
- View of the International Community
  - Precautionary Principle?
  - There they go again...

In closing...

"...the Committee recommended that methylmercury be re-evaluated in 2002, when the 96-month evaluation of the Seychelles cohort and other relevant data that may become available can be considered." (Methylmercury, JECFA 2000)

In closing...

Data to date do not support a change in FDA's current consumption advisory for fish.

Before any change is considered:

- Risk comparison (risk/risk tradeoffs) must be done
- Seychelles Study, in total, must be considered