Recent Evidence on Adverse Effects of Comparatively Low-Dose Methylmercury Exposure

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Multiple Effects

- Developmental Neurotoxicity
  - Prenatal
  - During childhood
- Adverse Cardiovascular Effects (heart attack, stroke)
- Benefits of Fish Consumption
  - Prenatal neurodevelopment
  - Cardiovascular (lifelong)

Cardiovascular Risk

"A growing body of evidence suggests [that] MeHg exposure can also lead to increased risks of adverse cardiovascular impacts in exposed populations…. we consider the current epidemiological literature sufficiently robust to support the development of a dose-response function."

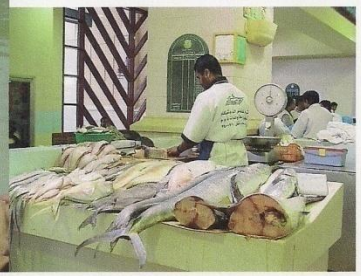
H.A. Roman, et al., EHP 2011 (doi: 10.1289/ehp.1003012)

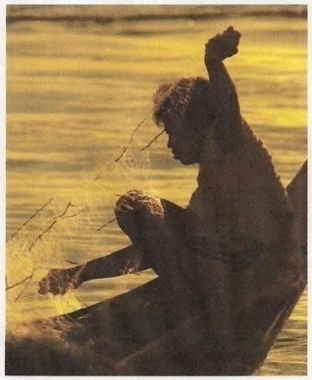
Recent Evidence on Developmental Neurotoxicity

- Three phases of research
  - Studies of Early Disasters (Minamata, Iraq)
  - Populations with High-Fish Diets (NZ, Faroes, Seychelles, Native American Tribes)
  - Average Consumers with Typical Fish Intake
- Suggestions from Recent Studies
  - Even "normal" exposure has adverse effects
  - Harm occurs at or below Reference Doses
  - Fish consumption is beneficial for some of the same outcomes that methylmercury damages

An Overview of Epidemiological Evidence on the Effects of Methylmercury on Brain Development, and A Rationale for a Lower Definition of Tolerable Exposure

December 2012





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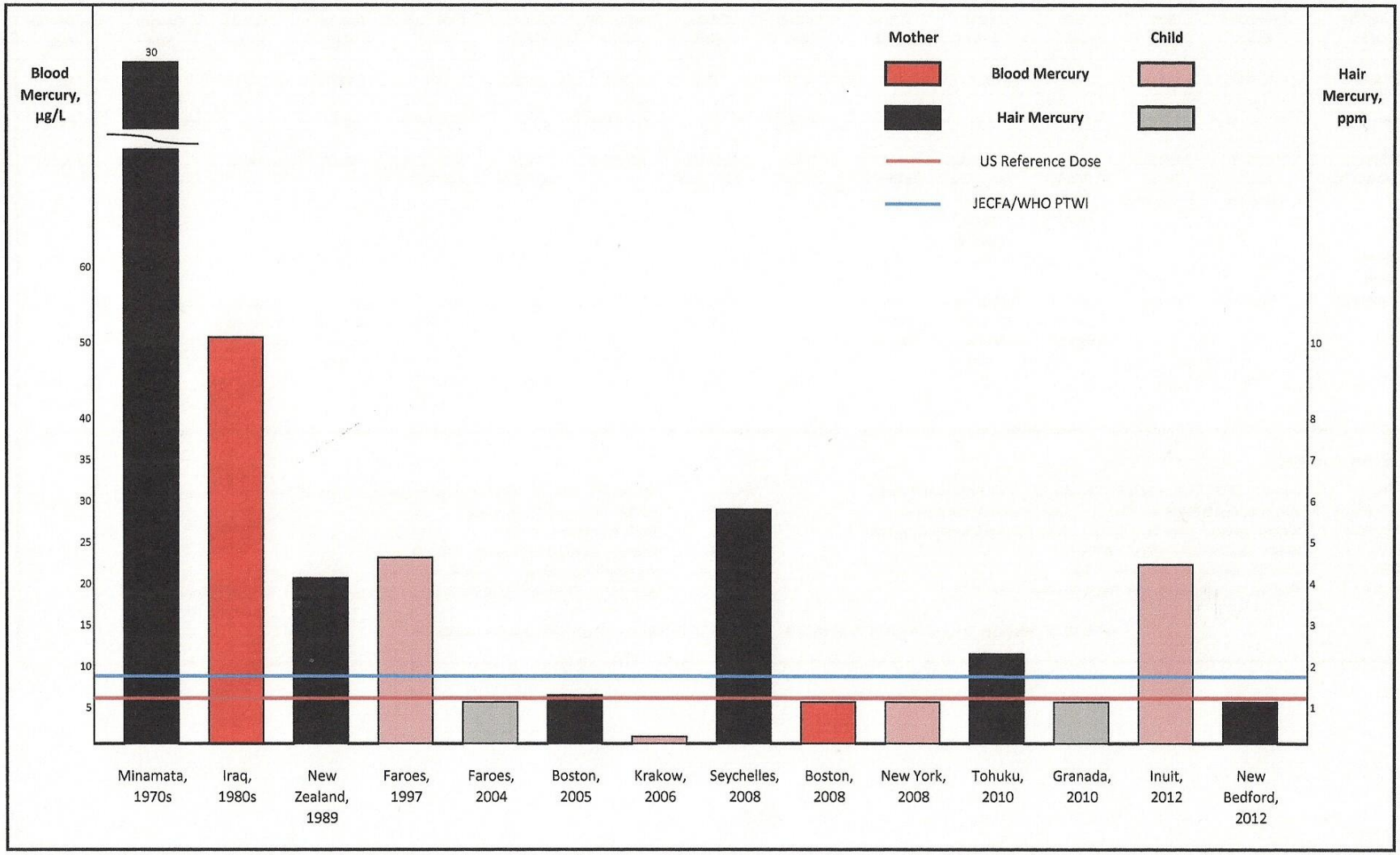
Nine Key Recent Studies

- Faroes, 2004 (Murata et al.)
- Boston, 2005 (Oken et al.)
- Krakow 2006 (Jedrychowski et al.)
- Boston 2008 (Oken et al.)
- New York 2008 (Lederman et al.)
- Tohuku 2010 (Suzuki et al.)
- Granada 2010 (Freire et al.)
- Inuit Territory 2012 (Boucher et al.)
- New Bedford 2012 (Sagiv et al.)

Figure 1. Methylmercury Levels in Blood and Hair Associated with Adverse Neurodevelopmental Effects, 1960-2012



Murata et al. (2004)

- Examined 882 14-year-old adolescents in the Faroe Islands
- Measured a delay in brainstem auditory evoked potential latency
- Effect correlated with children's post-natal MeHg exposure, but not with their prenatal exposure
- Exposure was relatively low, average hair Hg level was 1 ppm

Oken et al. 2005

- Project Viva, a long-term prospective study of exposures during pregnancy and developmental outcomes
- 135 6-month-old infants, maternal fish consumption raised visual recognition memory (VRM) score by 4.0 points
- MeHg exposure above 90th percentile lowered VRM score by 7.5 points
- "High" mercury was hair Hg $\geq$ 1.2 ppm

Jedrychowski et al. 2006

- 233 1-year olds in Krakow evaluated with Bayley Scales of Infant Development
- Those with highest mercury exposure scored 16.6 points lower on Psychomotor Development Index and 10 points lower on the Mental Development Index
- "High mercury" in this population was 1.05 μg/L in umbilical cord blood
- Follow-up at 2 &3 yrs: no lasting effects

Oken et al. 2008

- 341 3-year-olds in Project Viva cohort
- High fish consumption raised scores on Peabody Picture Vocabulary Test (PPVT) by 2.2 points and on Wide Ranging Assessment of Visual Motor Abilities (WRAVMA) by 6.4 points
- High MeHg exposure lowered PPVT by 4.5 points and WRAVMA by 4.6 points
- Mother's blood Hg levels $\geq$ 5.2 μg/L

Lederman et al. 2008

- 151 children in a multi-ethnic NYC cohort
- Tested at ages 1, 2, 3 and 4 years with age-appropriate instruments
- Maternal fish consumption raised Bayley PDI score 8.7 points and IQ by 5.6 points
- High MeHg exposure lowered Bayley PDI score 4.2 points and IQ by 3.8 points
- Each doubling Hg level → - 2.5 IQ points
- Average maternal blood Hg = 2.29 μg/L

Suzuki et al. 2010

- Evaluated 498 mothers and infants aged 3 days, in the Tohuku prospective study
- Maternal fish consumption improved scores on the Motor Cluster of the Neonatal Behavioral Assessment Scale
- Elevated mercury exposure lowered scores on the same performance index
- The median maternal hair Hg level in this population was 1.96 ppm

Freire et al. 2010

- 72 4-year-old children in Granada, Spain
- McCarthy Scales of Children's Abilities
- Above-average hair mercury lowered the general score by 6.6 points, the memory score by 8.4 points, and verbal score by 7.5 points
- Mercury exposure was from children's own fish consumption
- Average hair Hg level = 0.96 ppm

Boucher et al. 2012

- Inuit population with diet similar to that of the Faroes study (fish, marine mammals)
- 279 school-age children evaluated for Attention Deficit Hyperactivity Disorder
- Children with elevated prenatal Hg exposure had a relative risk of 4 for ADHD diagnosis
- This was a high-exposure group: Average umbilical cord Hg level was 21.6 μg/L

Sagiv et al. 2012

- Recruited New Bedford, MA mothers around their time of giving birth, took hair samples for Hg analysis
- Evaluated 421 children at age 8 for ADHD
- Higher Hg exposure associated with RR of 1.4 for inattention component and 1.7 for impulsivity component of ADHD
- "High exposure" was hair Hg > 1.0 ppm; mean hair Hg level was 0.45 ppm

Tentative Conclusions

- The evidence is neither overwhelming nor conclusive
- The MeHg/ADHD link is provocative
- The studies span six different countries and cultures, examine subjects ranging in age from 3 days to 14 years, and look at a wide variety of outcome measures
- A meta-analysis is thus not feasible

- NEVERTHELESS:

Conclusions, Continued

- The overall pattern of results from these nine studies is coherent and consistent
- All show clear adverse effects of MeHg exposure associated with both prenatal and childhood exposure
- Effects are neither small nor rare—e.g., 2 to 17 points, in 10% or more of subjects
- Studies also show beneficial effects of maternal fish intake during pregnancy

A Few Necessary Caveats:

- The association between ADHD and Hg exposure obviously requires further research
- Some of the studies had rather small sample sizes or other methodological weaknesses (e.g., Krakow study did not control for confounding by maternal fish intake)
- More studies are definitely needed
- BUT:

Conclusions, Continued

- Seven of the nine studies looked at populations with "ordinary" fish intake and methylmercury exposure
- The exceptions: The Inuit study on ADHD (exposure similar to Faroes) and the Japanese study (exposure about twice as high as in other populations)
- Most of the effects seen here occur at dose levels previously considered "safe"

Conclusions, Continued

- The Boston, New York and New Bedford populations all are very close to average for US exposure (per NHANES data)
- I.e., "high" mercury exposure is $\geq$ 1 ppm in hair or $\geq$ 5 μg/L in blood
- Exposure in the Polish cohort was even lower; that of the Spanish children, a bit higher than in the US (but mean hair level still < 1 ppm)

Conclusions, Continued

- In all, 6 of these 9 studies found adverse effects at exposures around or below the current US Reference Dose (adopted in 1999, based on 1997 Faroes data)
- This suggests that the current RfD does not adequately protect public health
- Clearly, advice to consumers needs to strongly emphasize consumption of low-mercury fish and shellfish

Risk/Benefit Trade-offs

Apply to cardio and neurotox effects

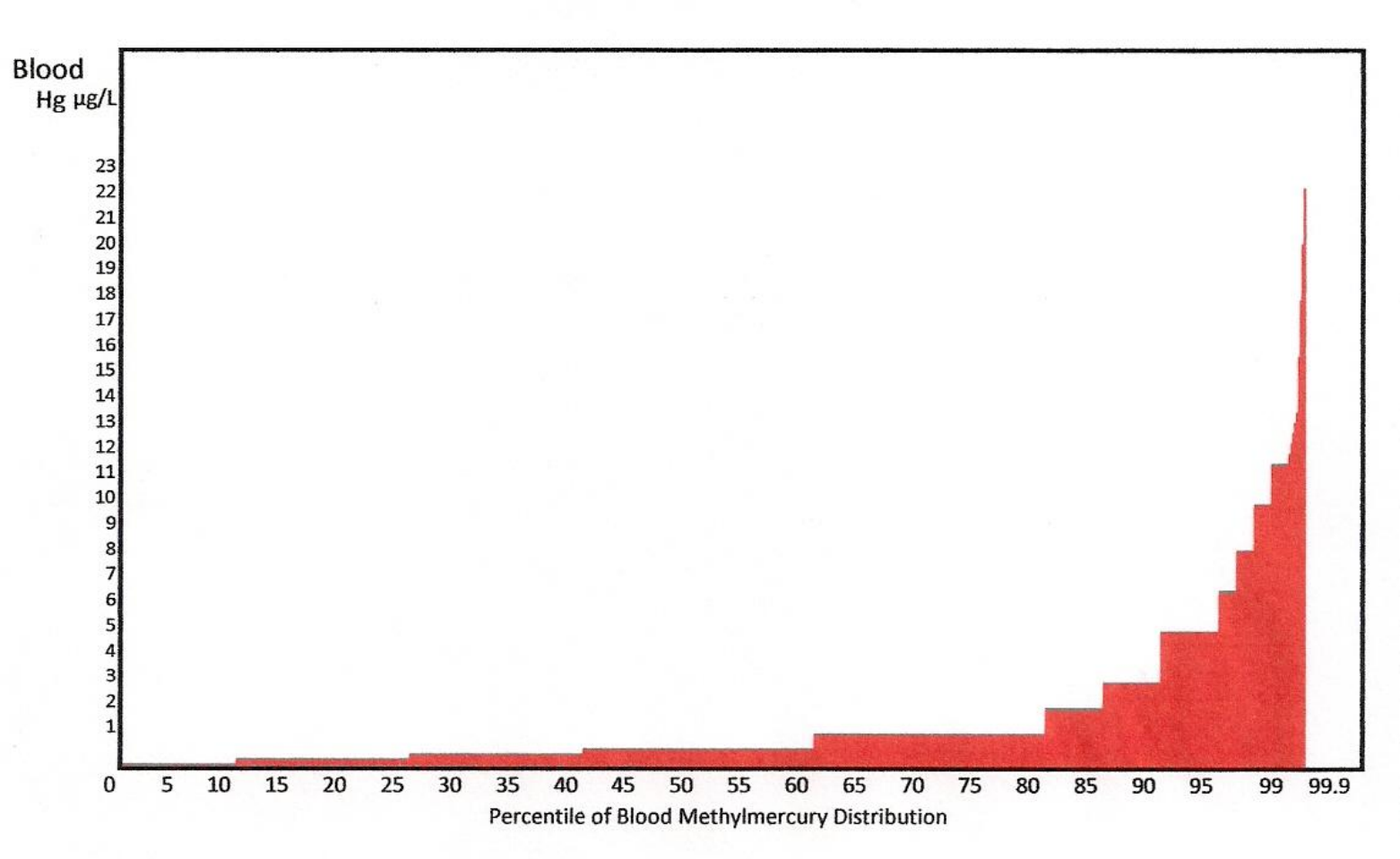
Three issues in each case::

- Distribution: Who benefits? Who is harmed? How large is each group?
- Magnitude: How large is each effect?
- Comparisons: Do the benefits outweigh the risks?
  - For individuals
  - For society as a whole

Distribution of Benefits

- Everyone who eats some fish (cardio) and every child whose mother eats some fish during pregnancy (neurodevelopment) appears to benefit
- High omega-3 fish may offer more benefits
- Those who eat more fish benefit more, up to a point, but benefits seem to plateau at 2-3 fish servings/week
- About 15-20% of Americans eat little or no fish and average is ~ 1 serving/week; i.e., lots of opportunity to increase benefits

Distribution of Blood Hg in US Women Ages 16-49 (NHANES)



Distribution of Risks

- Adverse effects (cardio, neurotox) occur primarily in those with the highest MeHg exposure – but how high is that?
- Some DNT studies (by statistical design) have focused on the top 10% of exposure
- Other studies have found dose-related adverse neurodevelopmental effects across the entire range of exposure
- No studies have determined a threshold

A Critical Difference

- Benefits and risks are distributed quite differently
- Benefits are diffusely distributed among all people who eat fish
- Risks fall mostly on people who eat the largest amounts of higher-mercury fish
- These are different groups of people
- I.e., across the population as a whole, the benefits do not "erase" the risks

Magnitude: Benefits and Risks

- Cardiovascular Benefit: Potential for tens of thousands of lives saved per year
- Cardiovascular Risk: Not well quantified yet (needs to be)
- Neurodevelopmental Benefit: Equivalent to several additional IQ points
- Neurodevelopmental Damage: Equivalent to a loss of several IQ points
- I.e., similar size, but different distribution

Do Benefits Outweigh Risks?

- For many if not most individuals, YES – benefits appear to be greater
- But minority with higher MeHg exposure suffer net adverse effects
- Is benefit > risk the correct guideline for individuals? Many prefer to get benefits while minimizing risk
- Even if majority benefits, ethically, risk to minority must be managed & reduced

And Last But Not Least

- A recent analysis by the EPA of NHANES blood mercury data from 1999 through 2010 found that women's blood Hg has declined substantially, while fish intake has not changed much
- I.e., the 2004 advisory is working, and it needs to be updated and strengthened to keep up with advances in science