Commentary on Potential Risk From Thimerosal for Infants

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Key Points

• What is the maximum safe dose of thimerosal that can be administered on one day?

• Is ethylmercury from thimerosal additive to methylmercury?

• Not: Vaccinating vs not vaccinating. It is making vaccines as safe as possible.
FDA Risk Assessment

- Initial reaction to FDA assessment:
  - surprise, disbelief
- Calculations correct
- Why missed?
  - Label: thimerosal concentration (.01%)
  - Guidelines for exposure to Hg in ug
Thimerosal is Neurotoxic in Large Doses

- HBIG and IVIG
- IM Chloramphenicol
- Painting omphaloceles
- Irrigation of ears

- What is safe for the developing brain?
FDA Risk Assessment
Maximum Cumulative Exposure

- Routine schedule:
  - Birth, 2, 4, 6 months
  - 187.5 ug maximum
  - Exceeded EPA RfD for most children
  - Exceeded ATSDR for < 5th percentile

Ball L. Pediatrics 2001;107(5):1147-54
FDA Risk Assessment

Maximum Cumulative Exposure

- Accelerated immunization schedule:
  - Birth, 6, 10, 14 weeks
  - Pertussis outbreaks, travel to developing countries
  - Exceeded ATSDR guidelines for many children

What Time Period Should be Used for Cumulating Exposures?

• Birth to 6 months? 187.5 ug
• Birth to 3 months-accelerated schedule? 175 ug?
• Birth to 2 months? 75 ug
• One day? 62.5 ug
## Weight in Kg for Girls by Percentile and Age

<table>
<thead>
<tr>
<th>Age</th>
<th>-3 SD</th>
<th>5th</th>
<th>50th</th>
<th>95th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>1.8</td>
<td>2.4</td>
<td>3.2</td>
<td>3.8</td>
</tr>
<tr>
<td>2 mo</td>
<td>2.7</td>
<td>3.6</td>
<td>4.7</td>
<td>5.8</td>
</tr>
<tr>
<td>4 mo</td>
<td>3.7</td>
<td>4.7</td>
<td>6</td>
<td>7.4</td>
</tr>
<tr>
<td>6 mo</td>
<td>4.6</td>
<td>5.8</td>
<td>7.2</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Epi info: CDC
Mercury (ug/Kg) Administered by Age and Weight If Thimerosal-containing Vaccines Are Given for Hepatitis B, Hib, and DTaP

Amount of Hg received (in micrograms) = 12.5 at birth, 62.5 at 2 & 6 months, 50 at 4 months
Mercury (ug/Kg) Administered by Age and Weight If Thimerosal-containing Vaccines Are Given for Hepatitis B, Hib, and DTaP

Weight of Child
-3 SD
5th Percentile
50th Percentile
95th Percentile

Amount of Hg received (in micrograms) = 12.5 at birth, 62.5 at 2 & 6 months, 50 at 4 months
Mercury (ug/Kg) Administered by Age and Weight If Thimerosal-containing Vaccines Are Given for Hepatitis B, Hib, and DTaP

Amount of Hg received (in micrograms) = 12.5 at birth, 62.5 at 2 & 6 months, 50 at 4 months
Amount of Mercury Administered If Only One Thimerosal-containing Vaccine Is Given (Hib or DTaP)

Weight of Child
-3 SD
5th Percentile
50th Percentile
95th Percentile

Mercury: ug/kg

Age (in months)
Birth 2 4 6

Weight of Child
mo* mo@ wk d

*ATSDR @EPA
# Summary of MeHg Reference Values

<table>
<thead>
<tr>
<th>AGENCY</th>
<th>Values (ug/kg/day)</th>
<th>TERMINOLOGY</th>
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<tbody>
<tr>
<td>EPA</td>
<td>0.1</td>
<td>RfD</td>
</tr>
<tr>
<td>FDA</td>
<td>0.4</td>
<td>ADI</td>
</tr>
<tr>
<td>ATSDR</td>
<td>0.3</td>
<td>MRL</td>
</tr>
<tr>
<td>WHO</td>
<td>3.3 ug/kg/wk</td>
<td>PTWI</td>
</tr>
</tbody>
</table>
Toxicological Effects of Methylmercury

Committee on the Toxicological Effects of Methylmercury
Board on Environmental Studies and Toxicology
Commission on Life Sciences
National Research Council
Washington DC
National Academy Press
2000
National Research Council Review of Methylmercury

• RfD should be 0.1 ug/Kg/d

• Over 60,000 children born per year at risk for neurodevelopmental effects

• Other forms of mercury should be taken into consideration
Fish Consumption Rates of Various Populations

PROTECT YOUR KIDS
RELEASE YOUR CATCH
Due to MERCURY CONTAMINATION of Inland Waters;
DO NOT EAT WARM WATER FISH SPECIES:
If You Are Pregnant, Nursing, May Soon Become Pregnant or Are Less Than 8 Years Old
Additionally, Consumption of Cold Water Species Should Be Limited to 1 Meal Per Month. Other Individuals Limit Consumption of Warm Water Species to 2-3 Meals Per Month.

While providing certain health benefits, eating fish caught from these waters may also expose you to chemicals which can cause cancer, birth defects, and learning disabilities. Animals like the bald eagle, loon, and otter are also at risk. Scientists have documented deformities, reproductive problems, and tumors in fish, amphibians, mammals, birds, and other wildlife in polluted water bodies.

This posting is a public service of the Maine Toxins Action Coalition [MTAC]
For a full copy of the State consumption advisories and more information on toxins in the environment call MTAC at 1-800-287-2345 or Maine Bureau of Health at 287-6455
Maine fish consumption advisories are not restricted to mercury contamination.
Non-posted waters should NOT be assumed to be free of contaminants.
Estimates of Methylmercury Levels in Women of Childbearing Age in the United States

- EPA dietary consumption
  - 7% >.1 ug/Kg/d, 1% >.37ug/Kg/d
- NRC modeling
  - 60,000 children born per year to mothers with elevated levels
- CDC NHANES* blood mercury
  - Mean 1.2 ppb (90th % 6.2 ppb)
  - 10% have levels within 1/10th of potentially hazardous levels

* MMWR 2001;50(08);140.
FDA Fish Advisory
March 2001

• Pregnant women and women of childbearing age should avoid:
  • Shark, mackerel, swordfish, tilefish

• Swordfish ~1 ppm methylmercury
  • 28.5 ug Hg per ounce

www.fda.gov/bbs/topics/ANSWERS/2001/advisory.html
July 1999

- AAP/PHS joint statement
  - Could exceed guidelines for MeHg
  - Delay hep B vaccine for infants born to HBsAg negative women
  - Reduce or eliminate thimerosal
- AAP interim report
  - Amounts of Hg in each vaccine
  - Limit exposure to Hg from other sources
Suggested Guidelines (1999) for Limiting Infant Exposure to Thimerosal in Vaccines

- Preference for vaccines without thimerosal preservative
- No more than one vaccine with thimerosal preservative per regularly scheduled visit

Halsey NA. JAMA 1999; 282(18):1763
DTaP, Hep B, and Hib Vaccines Without Thimerosal Preservative
July 1999

DTaP
- Infanrix

Hepatitis B
- COMVAX

Hib
- ActHIB
- Omni Hib
- HibTITER
  Single dose
- PedvaxHIB
  Liquid
- COMVAX
DTaP, Hep B, and Hib Vaccines Without Thimerosal Preservative
July 2001

DTaP
- Infanrix
- Tripedia

Hepatitis B
- COMVAX
- Recombivax HB “preservative free”
- Engerix B “preservative free”

Hib
- ActHIB
- Omni Hib
- HibTITER Single dose
- PedvaxHIB Liquid
- COMVAX

Pediatrics 2001;108(1):197
VSD Studies

• Delayed speech, language, LD
  • Multifactorial etiologies
  • Large studies needed
• Harvard Pilgrim study:
  • Power?
• Data inconclusive, but suggestive of an effect from thimerosal
Why Additional Studies Are Needed

- The public deserves an answer:
  - If toxicity, VICP?
- Exposures continuing in other countries
  - Obligation to find answers
  - Assistance will be needed for removal if toxic effects demonstrated
Additional Studies Needed

- CDC/NIH cohort follow-up study
  - Strongest design
  - Power uncertain for some outcomes
  - Power likely to be greater for more subtle effects
- Other populations with high baseline methylmercury exposures
  - Case-control studies?
Animal Studies Needed

- Is ethylmercury equivalent to methylmercury?
- Is ethylmercury additive to methylmercury?
- Are bolus doses more toxic than small daily doses?
Lessons from Thimerosal

- FDA, manufacturers, and advisory bodies can mobilize and act rapidly when indicated to improve safety.
- Actions taken have minimized potential risks to children from mercury
- Public needs to be confident that vaccines are made as safe as possible
Encourage IOM to Stop Using: “The Evidence is Inadequate to Accept or Reject a Causal Relation”

- Not informative
- Overused - always some doubt
- Misinterpreted as there is scientific evidence supporting hypotheses
  - Hepatitis B and MS
  - MMR and autism
- Just summarize the evidence