Thimerosal in Vaccines: Some Recent Research

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Behavioral Teratogens/Developmental Neurotoxicants (Functional Effects)

Idealized dose-response curves for the major manifestations of teratogenesis.
## Behavioral Teratogens/Developmental Neurotoxicants (Functional Effects)

### List of Human Behavioral Teratogens/Developmental Neurotoxicants

<table>
<thead>
<tr>
<th>Environmental Chemicals</th>
<th>Maternal Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>Mercury</td>
<td>Depression</td>
</tr>
<tr>
<td>PCBs</td>
<td></td>
</tr>
<tr>
<td>Manganese</td>
<td></td>
</tr>
<tr>
<td>Pesticides</td>
<td></td>
</tr>
</tbody>
</table>

### Drugs of Abuse

- Ethanol
- Cocaine
Methylmercury - Fetal Minamata Disease

http://www.geocities.com/minoltaphotographyw/williameugenessimith.html
Comparison of the distribution of lesions among the adult, non-fetal infantile and fetal infantile Minamata disease.
Methylmercury - Functional Effects
Faroe Island Study

Cognitive Deficit in 7-Year-Old Children with Prenatal Exposure to Methylmercury

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**Institute of Clinical Research, Odense University Hospital, Odense, DK-5000 Denmark

Cord Blood Mercury Levels Associated with Poor Performance on Neuropsychological Tests.

FIG. 1. Prenatal mercury exposure levels (in quartile groups) of Faroese children with scores in the lowest quartile after adjustment for confounders. For each of five major cognitive functions, one neuropsychological test with a high psychometric validity was selected. Motor: NES2 Finger Tapping with preferred hand ($p$-value for trend, 0.23). Attention: Reaction time on the NES2 Continued Performance Test ($p = 0.003$). Visuospatial: Bender Visual Motor Gestalt Test error score ($p = 0.16$). Language: Boston Naming Test score after cues ($p = 0.02$). Memory: California Verbal Learning Test (Children) long-delay recall ($p = 0.004$).
EPA Safety Standard for Methylmercury Intake (RfD) is based on Human Studies of Exposure through Fish Consumption During Pregnancy

In 2000, NAS panel supported EPA’s action to lower Safety Standard (RfD) to 0.1ug/kg/day
The Controversy: Thimerosal in Vaccines

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>1999 Maximum Mercury Dose (µg)</th>
<th>2001 Maximum Mercury Dose (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 doses of DTaP</td>
<td>75.0</td>
<td>0</td>
</tr>
<tr>
<td>3 doses of Hep B</td>
<td>37.5</td>
<td>0</td>
</tr>
<tr>
<td>3 doses of HIB</td>
<td>75.0</td>
<td>0</td>
</tr>
<tr>
<td>3 doses of IPV</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>[1 dose of influenza]</td>
<td>[12.5]</td>
<td>[12.5]</td>
</tr>
<tr>
<td><em>(selected populations)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>187.5 [200]</td>
<td>[12.5]</td>
</tr>
</tbody>
</table>
The Controversy: Thimerosal in Vaccines

Mercury exposure from vaccines during first 6 months of life exceeds EPA safety standard for methylmercury.
The Controversy: Thimerosal in Vaccines

Rising levels of cumulative mercury exposure from childhood vaccines, compared with rising incidence of autism in California.

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>California autism prevalence (cases per 10,000)</td>
<td>5</td>
<td>7</td>
<td>9</td>
<td>11</td>
<td>13</td>
<td>15</td>
<td>17</td>
<td>19</td>
<td>21</td>
<td>23</td>
<td>25</td>
<td>27</td>
</tr>
</tbody>
</table>

Source: Presentation by Mark Blaxill, Safe Minds, to meeting of Immunization Safety Review Committee, Institute of Medicine, Cambridge, Massachusetts, July 16, 2000.
The Controversy: Thimerosal in Vaccines

1999 Statement from American Academy of Pediatrics and US Public Health Service

Conclusion: Thimerosal containing vaccines should be removed as soon as possible to reduce exposure to mercury.
Basic Question
“What do we know about what happens to the mercury in Thimerosal (or ethylmercury) when it is injected in infants (human or animal).”

Answer: Very Little
Delayed-type hypersensitivity reported in humans
Acute poisonings reported in humans (coma, death)
Acute toxicity studies reported in adult animals (several species)
Only one study could be found that actually measured mercury levels in infants following a vaccine
Levels of Mercury in Blood of Preterm and Term Newborns after administration of Hepatitis B Vaccine

Figure. Difference in mean mercury levels (in micrograms per liter) between preterm and term infants. †P < .01; ‡P < .001; *P = .2.

From: Journal of Pediatrics, Vol 136, Number 5, May 2000
Estimates of Mercury Doses from Vaccines

**FIGURE 2** Mercury (µg/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 and 6 months, 50 at 4 months.

## Thimerosal Monkey Study
(Comparison of Thimerosal and Methylmercury Toxicokinetics)

<table>
<thead>
<tr>
<th></th>
<th>Birth</th>
<th>2</th>
<th>4</th>
<th>7</th>
<th>9</th>
<th>11</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>21</th>
<th>23</th>
<th>25</th>
<th>28</th>
<th>31</th>
<th>35</th>
<th>38</th>
<th>42</th>
<th>45</th>
<th>49</th>
<th>Age (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mercury Dose(^1)</strong></td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td></td>
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<tr>
<td>(Oral MeHg)</td>
<td>(µg/kg)</td>
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</tr>
<tr>
<td><strong>Mercury Dose(^2)</strong></td>
<td></td>
<td>OPV-0</td>
<td></td>
<td></td>
<td></td>
<td>OPV-0</td>
<td></td>
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</tr>
<tr>
<td>(I.M. Thimerosal in Vaccine)</td>
<td>HB-4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HB-4</td>
<td></td>
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<td>DTP-8</td>
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<td>DTP-10</td>
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<td>Hib-8</td>
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<td>Hib-10</td>
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</tr>
<tr>
<td><strong>Blood Draws(^3)</strong></td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td>14</td>
<td>17</td>
<td>21</td>
<td>24</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td><strong>Sacrifice Day(^4)</strong></td>
<td></td>
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<td></td>
<td>2</td>
</tr>
</tbody>
</table>

\(^1\) Dose of MeHg in µg/kg  
\(^2\) Dose of ethylmercury in µg/kg  
\(^3\) Days after most recent dose  
\(^4\) Days after last (4\(^{th}\)) dose

From: Burbacher, et al. Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methylmercury or Vaccines Containing Thimerosal
Mean Blood Total Hg Concentration During and After Four Weekly Oral Doses (20 μg/kg) of Methylmercury

Methylmercury
Total Mercury in Blood
Half-Life = 21.5 days

From: Burbacher, et al. Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methylmercury or Vaccines Containing Thimerosal
Mean Blood Total Hg Concentration During and After Four Weekly I.M. Injections of Vaccine Containing Thimerosal at 20 μg/Kg Hg

Thimerosal Total Mercury in Blood Half-Life = 6.9 days

From: Burbacher, et al. Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methylmercury or Vaccines Containing Thimerosal
Mean (SE) Total Mercury Concentrations in Brain of Oral Methylmercury and I.M. Thimerosal Groups

<table>
<thead>
<tr>
<th>Days Post 4th Injection</th>
<th>Oral Methylmercury</th>
<th>IM Thimerosal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>100 ± 5</td>
<td>120 ± 6</td>
</tr>
<tr>
<td>Day 4</td>
<td>100 ± 5</td>
<td>110 ± 7</td>
</tr>
<tr>
<td>Day 7</td>
<td>80 ± 4</td>
<td>100 ± 6</td>
</tr>
<tr>
<td>Day 28</td>
<td>40 ± 2</td>
<td>40 ± 2</td>
</tr>
</tbody>
</table>

Sacrifice or Washout Period (Brain)
MeHg Half-Life = 59.5(24.1) days
Thimerosal Half-Life = 24.2(7.4) days

From: Burbacher, et al. Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methylmercury or Vaccines Containing Thimerosal
Mean (SE) Inorganic Mercury Concentrations in Brain of Oral Methylmercury and I.M. Thimerosal Groups

Sacrifice or Washout Period (Brain) Half-Life could not be estimated (previous estimates over 1 year)

From: Burbacher, et al. Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methylmercury or Vaccines Containing Thimerosal
Review of Study Results and Recommendations

- **Methylmercury is not a good reference for Thimerosal Risk**
  - Absorption rate and initial distribution are similar
  - Blood clearance rates are different (thimerosal cleared more quickly)
  - Brain levels of total mercury are different (levels are lower for thimerosal)
  - Brain clearance of total mercury are different (thimerosal cleared more quickly)
  - Ratio of total mercury in brain to blood is different (thimerosal is higher)
  - Brain levels of inorganic mercury are different, with no clearance (levels are higher for thimerosal)

- **Future studies of Thimerosal should focus on the neurotoxic effects of organic and inorganic mercury following exposure.**
  - Inorganic mercury has been associated with activation of microglia in the brain of adult non human primates (neuroinflammation)
  - Inorganic mercury has a very long half-life in the brain (years)
  - A recent report suggests that neuroinflammation is present in brains of autistic children
  - Information on the developmental neurotoxicity of thimerosal is critical if we are to respond to public concerns regarding the safety of childhood immunizations.
Recent epidemiologic research into PCBs' effects on human TH function has been inconsistent, and some studies have found no effect at exposure levels higher than those in this study. But the current finding of a relationship at such low levels indicates that more investigations are needed in pregnant women, including monitoring of even subtle environmental exposures that can disturb maternal and/or fetal thyroid status. For this purpose, the biomarkers should include not only TSH—which currently is the only element of the thyroid system routinely monitored in pregnant women—but all forms of TH.

Valerie J. Brown

Thimerosal and Animal Brains
New Data for Assessing Human Ethylmercury Risk

Since the 1930s, vaccines have contained thimerosal, a mercury-based preservative that breaks down to ethylmercury and thiosalicylate in the body. By some calculations, children given the usual schedule of vaccines containing thimerosal receive ethylmercury in doses exceeding the U.S. Environmental Protection Agency's guidelines for methylmercury, a known neurotoxicant. Because of the lack of pharmacokinetic and toxicity data for ethylmercury, methylmercury has been used as a reference for ethylmercury toxicity based on the assumption that the two compounds share similar toxicokinetic profiles. However, a new animal study shows that methylmercury is an inadequate reference for ethylmercury due to significant differences in tissue distribution, clearance rates, and ratios of organic to inorganic mercury in the brain [EHP 113:1015–1021]. Inorganic mercury concentrations were measured in brain samples. Organic mercury concentrations were calculated from those values.

The initial absorption rate and tissue distribution of mercury was similar in both exposed groups. However, total mercury progressively accumulated in the blood of methylmercury-exposed monkeys and remained detectable 28 days after the last dose. Among thimerosal-exposed monkeys, total mercury in blood declined rapidly between doses, and the researchers estimated clearance to be 5.4-fold higher than in the methylmercury group. In the thimerosal group, the half-life of total mercury in blood was 6.9 days, compared to 19.1 days for the methylmercury group.

Brain concentrations of total mercury were approximately 3–4 times lower in the thimerosal group than in the methylmercury group, and total mercury cleared more rapidly in the thimerosal group (with a half-life of 24.2 days versus 59.5 days). However, the proportion of inorganic mercury in the brain was much higher in the thimerosal group (21–86%

A sticky situation. New data show that using methylmercury as a reference for calculating risk from ethylmercury in vaccines may be fraught with problems.
Projected Levels of Mercury in Blood of Infants after administration of Vaccines

Fig. 1. Projected levels of ethyl mercury in blood after administration of a birth dose of HBV and other infant vaccines. The shape of the peaks drawn above are modeled from the paper by Pichichero et al. [43], but the paper was not able to ascertain the entire curve. Thus, there remains speculation about the peak values that may well be rounded peaks and lower maximum values than are shown above. The maximum value could well be below the 5.8 level EPA cut-off. A healthy 3 kg infant can be expected to increase his body mass to around 5.5 kg (80%) by 3 months. Thus, the blood concentration of ethyl mercury will be proportionately less (not shown graphically). This is being tested empirically in up-coming studies. In any case, the immediate post-immunization level is not directly relevant as the blood compartment does not equilibrate with the brain compartment for several days after vaccination, at a time when the blood level has reached a steady state at a yet-to-be determined (but lower) value.

Projections based on data from 40 full-term infants aged 6 months and younger.
From: The Lancet, Vol 360, November 2002
Reduced Levels of Mercury in First Baby Haircuts of Autistic Children

Amy S. Holmes, Mark F. Blaxill, and Boyd E. Haley

1 Baton Rouge, Louisiana, USA
2 SafeMinds, Cambridge, Massachusetts, USA
3 Chemistry Department, University of Kentucky, Lexington, Kentucky, USA

FIGURE 1
A plot of the birth hair mercury levels of nonautistic versus autistic children. Solid circles represent individual female subjects and open circles represent individual male subjects.

TABLE 2
Exposure differences in autistic group as compared to controls

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Autistic group (N = 94)</th>
<th>Control group (N = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercury levels in first baby haircut (ppm, mean ± SD)</td>
<td>0.47 (±0.28)</td>
<td>3.63 (±3.56)</td>
</tr>
<tr>
<td>Rho D immunoglobulin shots during pregnancy (number per mother, mean ± SD)</td>
<td>0.53 (±0.67)</td>
<td>0.09 (±0.29)</td>
</tr>
<tr>
<td>Amalgam fillings during pregnancy (number per mother, mean ± SD)</td>
<td>8.35 (±3.43)</td>
<td>6.60 (±3.55)</td>
</tr>
</tbody>
</table>

*Statistically different from control group (p < .0000004).
*Statistically different from control group (p < .0000004).
*Statistically different from control group (p < .01).

Disorder in Mercury Excretion in Children with Autism?

Reduced Levels of Mercury in First Baby Haircuts of Autistic Children

Amy S. Holmes,1 Mark F. Blaxill,2 and Boyd E. Haley3

1Baton Rouge, Louisiana, USA
2SafeMinds, Cambridge, Massachusetts, USA
3Chemistry Department, University of Kentucky, Lexington, Kentucky, USA

![Graph showing mercury levels in autistic children]

**FIGURE 2**
A plot of the birth hair mercury levels in autistic children based on the clinical severity of the disease. Solid circles represent individual female subjects and open circles represent individual male subjects.

A Case-Control Study of Mercury Burden in Children with Autistic Spectrum Disorders

Jeff Bradstreet, M.D.
David A. Geier, B.A.
Jerald J. Kartzinel, M.D.
James B. Adams, Ph.D.
Mark R. Geier, M.D., Ph.D.

REVISED: A summary of the urinary mercury concentrations of the provocation cases and controls (control group 1)

<table>
<thead>
<tr>
<th>Mercury Concentration (μg/gram Creative)</th>
<th>Autistic Spectrum Children (N = 117)</th>
<th>Neurotypical Control Children (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 60</td>
<td>4.80 ± 10.4 **</td>
<td>1.29 ± 1.59</td>
</tr>
<tr>
<td>[Range: 0 - 68]</td>
<td></td>
<td>[Range: 0 - 6.2]</td>
</tr>
</tbody>
</table>

All p-values determined using the t-test statistic
** Relative Increase = 3.72 (P < 0.002)
Biochemical Basis of Thimerosal Neurotoxicity?

Thimerosal Neurotoxicity is Associated with Glutathione Depletion: Protection with Glutathione Precursors

S.J. James, W. Slikker Jr, S. Melnyk, E. New, M. Pogrissa, S. Jornigan

Department of Pediatrics, University of Alabama for Medical Sciences and Alabama Children’s Hospital Research Institute, USA.

NeuroToxicology, Vol 26, 1-8, 2005

Abstract

Thimerosal is an anesthetic containing 49.9% ethyl mercury that has been used for years as a preservative in many pharmaceutical and vaccine formulations. Environmental studies have been shown to be highly toxic, especially to the developing brain. Because mercury has a high affinity for their (sulfhydryl -SH) groups, the thiol-containing antioxidant, glutathione (GSH), provides the major intracellular defense against mercury-induced neurotoxicity. Cultured neuroblastoma cells were found to have lower levels of GSH and increased sensitivity to thimerosal toxicity compared to glial progenitor cells that have higher levels of intracellular GSH. Thimerosal-induced cytotoxicity was associated with depletion of intracellular GSH in both cell types. Pretreatment with 100 μM glutathione ethyl ester (GSH-EE) or N-acetylcysteine (NAC), but not methionine, reduced the significant increase in intracellular GSH in both cell types. Further pretreatment of the cells with glutathione ethyl ester or NAC partially restored GSH content to 15 μM Thimerosal. Although pretreatment has been recently removed from most children’s vaccines, it is still present in flu vaccines given to pregnant women, the elderly, and to children in developing countries. The potential protective effect of GSH or NAC against mercury toxicity warrants further research on possible adverse effects to individuals still receiving Thimerosal-containing vaccines.

Keywords: Thimerosal; Neurotoxicity; Glutathione; N-acetylcysteine

Introduction

Thimerosal (sodium ethylmercurithiosalicylate) was developed by Eli Lilly in the 1930s as an effective bacteriostatic and fungistatic preservative and has been widely used in multivalent viral vaccines and in ophthalmic, otic, nasal, and topical products. Until the removal of Thimerosal from most pediatric vaccines in 2001, the largest human exposure in the US (μg/kg body weight) was in children under 18 months of age undergoing routine childhood immunization schedules. Prior to 2001, a child may have received a cumulative dose of over 200 μg/kg in the first 18 months of life (Ball et al., 2003). Although the neurotoxicity of mercury in mercury has been relatively well studied, limited information is available on the relative neurodevelopmental toxicity of methylmercury, the mercury derivative of Thimerosal. Based on the known toxicity of methylmercury, the cumulative ethylmercury exposure to US pediatric populations in Thimerosal-containing vaccinations was re-examined in 1999 and found to exceed EPA recommended guidelines.

Immediate Communication

Activation of methionine synthase by insulin-like growth factor-1 and dopamine: a target for neurodevelopmental toxins and thimerosal


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Neurotoxicology, Vol 26, 1-8, 2005

Methylation events play a critical role in the ability of growth factors to promote normal development of the central nervous system. Health effects of perinatal neurotoxic factors, such as methylmercury and heavy metals, also depend on growth factor signaling, implying the possibility that they might exert adverse effects on methylation. We found that insulin-like growth factor-1 (IGF-1) and dopamine- and growth factor-activated methionine synthase (MS) activity, and inositol monophosphate kinase in phospho-inositol pathway, altered by thimerosal, in RINm5F cells, a P72/95 and MAPK-activated neuronal cell line. The stimulation of this pathway increased DNA methylation, while its inhibition increased methylation-sensitive gene expression. IGF-1 rapidly inhibited DNA methylation, whereas it did not inhibit the effects of dopamine and thimerosal. Inositol monophosphate kinase activity, as well as thimerosal-dependent inhibition of DNA methylation, was restored by co-treatment with dopamine and the MS inhibitors, 5'-amino-4'-isobutyric acid (AIBA) and 5'-amino-4'-isobutyric acid (AIBA). The ethanol, lead, mercury and thimerosal suggest that it may be an important target of neurodevelopmental toxins.

Keywords: insulin; growth factor; methionine synthase; P72; dopamine; DNA methylation; phosphatidylinositol 3-kinase; thimerosal; DNA methylation; lead; mercury

From: Neurotoxicology, Vol 26, 1-8, 2005

From: Molecular Psychiatry, 2004
Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism\(^1,2\)

S Jill James, Paul Cutler, Stepan Melnyk, Stefanie Jernigan, Laurette Janak, David W Gaylor, and James A Neubrander

**FIGURE 1.** The methionine cycle involves the remethylation of homocysteine to methionine by either the folate–vitamin B-12–dependent methionine synthase (MS) reaction or the folate–vitamin B-12–dependent betaine homocysteine methyltransferase (BHMT) reaction. Methionine is then activated by methionine adenosyltransferase (MAT) to S-adenosylmethionine (SAM), the major methyl donor for cellular methyltransferase (MTase) reactions. After methyl group transfer, SAM is converted to S-adenosylhomocysteine (SAH), which is further metabolized in a reversible reaction to homocysteine and adenosine. Adenosine may be phosphorylated to adenosine nucleotides by adenosine kinase (AK) or catabolized to inosine by adenosine deaminase (ADA). Homocysteine may be permanently removed from the methionine cycle by irreversible conversion to cystathionine by vitamin B-6–dependent cystathionine β-synthase (CBS). Cystathionine is converted to cysteine, which is the rate-limiting amino acid for the synthesis of the tripeptide glutathione (Glu-Cys-Gly). THF, tetrahydrofolate; 5-CH\(_2\)THF, 5-methyltetrahydrofolate; SAHH, SAH hydrolase.

**TABLE 1**

Comparison of methionine cycle and transsulfuration metabolites between autistic children and control children\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>Control children ((n = 33))</th>
<th>Autistic children ((n = 20))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine (μmol/L)</td>
<td>31.5 ± 5.7 (23-48)</td>
<td>19.3 ± 9.7 (15-25)(^2)</td>
</tr>
<tr>
<td>SAM (nmol/L)</td>
<td>96.9 ± 12 (77-127)</td>
<td>75.8 ± 16.2 (68-100)(^3)</td>
</tr>
<tr>
<td>SAH (nmol/L)</td>
<td>19.4 ± 3.4 (16-27)</td>
<td>28.9 ± 7.2 (14-41)(^2)</td>
</tr>
<tr>
<td>SAM:SAH</td>
<td>5.2 ± 1.3 (4-8)</td>
<td>2.9 ± 0.8 (2-4)(^2)</td>
</tr>
<tr>
<td>Adenosine (μmol/L)</td>
<td>0.27 ± 0.1 (0.1-0.4)</td>
<td>0.39 ± 0.2 (0.17-0.83)(^4)</td>
</tr>
<tr>
<td>Homocysteine (μmol/L)</td>
<td>6.4 ± 1.3 (4.3-9.0)</td>
<td>5.8 ± 1.0 (4.0-5.8)(^5)</td>
</tr>
<tr>
<td>Cystathionine (μmol/L)</td>
<td>0.17 ± 0.05 (0.1-0.27)</td>
<td>0.14 ± 0.06 (0.04-0.2)(^2)</td>
</tr>
<tr>
<td>Cysteine (μmol/L)</td>
<td>202 ± 17 (172-252)</td>
<td>163 ± 15 (133-189)(^5)</td>
</tr>
<tr>
<td>tGSH (μmol/L)</td>
<td>7.6 ± 1.4 (3.8-9.2)</td>
<td>4.1 ± 0.5 (3.3-5.2)(^2)</td>
</tr>
<tr>
<td>Oxidized glutathione</td>
<td>0.32 ± 0.1 (0.11-0.43)</td>
<td>0.55 ± 0.2 (0.29-0.97)(^2)</td>
</tr>
<tr>
<td>tGSH:GSSG (nmol/L)</td>
<td>25.5 ± 8.9 (13-49)</td>
<td>8.6 ± 3.5 (4-11)(^2)</td>
</tr>
</tbody>
</table>

\(^1\) All values are \(\bar{x} \pm SD\); range in parentheses. SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; tGSH, total glutathione; GSSG, oxidized glutathione.

\(^2\) Significantly different from control children: \(^2\) \(P < 0.001\), \(^3\) \(P < 0.01\), \(^4\) \(P < 0.05\), \(^5\) \(P < 0.002\).
The Controversy: Thimerosal in Vaccines

2002 IOM Report on Thimerosal and Neurodevelopmental Disorders

Conclusions
Hypothesis of a link is biologically plausible.

Current evidence is inadequate to accept or reject a causal relationship.

Additional studies are needed at all levels, epidemiology, clinical, basic science.
The Controversy: Thimerosal in Vaccines

2004 IOM Report on Thimerosal and Autism

Conclusions
Evidence favors rejection of a causal relationship.

Continue surveillance for autism as exposure to thimerosal declines.

Increase efforts to quantify the level of prenatal and postnatal exposure to thimerosal and other forms of mercury in infants, children, and pregnant women.

Available funding for autism research be channeled to the most promising areas.
Early Downward Trends in Neurodevelopmental Disorders Following Removal of Thimerosal-Containing Vaccines

David A. Geier, B.A.
Mark R. Geier, M.D., Ph.D.

ABSTRACT

Contemporaneously with the epidemic rise in neurodevelopmental disorders (NDs), first observed in the United States during the 1990s, the childhood immunization schedule was expanded by the U.S. Centers for Disease Control and Prevention (CDC) to include several additional thimerosal-containing vaccines (TCVs). On July 7, 1999, a joint recommendation was made by the American Academy of Pediatrics (AAP) and the U.S. Public Health Service (PHS) to remove thimerosal from vaccines. A two-phase study was undertaken to evaluate trends in diagnosis of new NDs entered into the Vaccine Adverse Event Reporting System (VAERS) and the California Department of Developmental Services (CDDS) databases on a reporting quarter basis, from 1994 through 2005. Significant increasing trends in newly diagnosed NDs were observed in both databases 1994 through mid-2002. Significant decreasing trends in newly diagnosed NDs were observed in both databases from mid-2002 through 2005. The results indicate that the trends in newly diagnosed NDs correspond directly with the expansion and subsequent contraction of the cumulative mercury dose to which children were exposed from TCVs through the U.S. immunization schedule.

Thimerosal is an ethylmercury-containing compound (49.6% mercury by weight) that was historically added to many vaccines at the preservative level (0.005% to 0.01%). The U.S. Centers for Disease Control and Prevention (CDC), from the late 1980s through the 1990s, expanded the number of doses of TCVs to be administered to U.S. infants. To five doses of diphtheria-tetanus-whole-cell-pertussis (DTP) vaccine were added three doses of hepatitis B (Hep b) vaccine and four of Haemophilus influenzae type b (Hib) vaccine. Additionally, the CDC began recommending three doses of influenza vaccine for certain infant populations. An infant who received all of these vaccines on schedule could have received as much as 200 micrograms (μg) of mercury during the first 6 months of life.14

In response to theoretical concerns about the cumulative doses of mercury from TCVs, the AAP and the U.S. Public Health Service (PHS) issued a joint statement on July 7, 1999, calling for the removal of thimerosal from all vaccines.14 It has been estimated that the last thimerosal-containing Hep b, diphtheria-tetanus-acellular-pertussis (DTaP) and Hib vaccines were manufactured in 2000-2001 and expired at the end of 2002 (or early 2003).14 Table 1 summarizes significant historical dates in the use of pediatric TCVs in the United States.

Considering all significant environmental exposures to mercury, such as through breast milk, TCVs represent almost 50% of the total mercury dose some infants received.15 The 182 figure 6

Early Downward Trends in Neurodevelopmental Disorders Following Removal of Thimerosal-Containing Vaccines

Figure 1. Trends in New Autism Adverse Events Reported to VAERS. The trend from Jan 1, 1994, through Dec 31, 2002, is significantly increasing, with $P < 0.0001$. The trend from Jan 1, 2002, through June 30, 2005, is significantly decreasing, with $P < 0.02$. The difference in the slope of the regression lines for the number of new autism adverse events in the earlier compared with the later periods is significant, with $P < 0.0005$.

Figure 2. Trends in New Cases of Speech Disorders Reported to VAERS. The trend from Jan 1, 1994, through Dec 31, 2002, is significantly increasing, with $P < 0.0001$. The trend from Jan 1, 2002, through June 30, 2005, is significantly decreasing, with $P < 0.03$. The difference in the slope of the regression lines for the number of new speech disorder adverse events in the earlier compared with the later periods is significant, with $P < 0.005$.

Figure 3. Trends in New Cases of Autism Entered into the CDDS. The trend from Jan 24, 1994, through Jan 6, 2003, is significantly increasing, with $P < 0.0001$. The trend from Jan 6, 2002, through Oct 4, 2005, is significantly decreasing, with $P < 0.05$. The difference in the slope of the regression lines for the number of new autism cases in the earlier compared with the later periods is significant, with $P < 0.0001$.

Note: The NIEHS is working with CDC to convene an expert panel in May 2006 to review the use of the CDC-supported Vaccine Safety Data Link (VSDL) to address questions about changes in autism rates and their potential association with thimerosal exposure through childhood vaccination.