

Thimerosal Safety

**The International Child Development Resource Center
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Response to The National Academy of Science, Institute of Medicine Request for Original Research On Thimerosal Safety

**Copy Provided to:
U.S. House of Representatives, Committee on Government Reform
The Honorable Dan Burton, Chairman**

Presented to the IOM-NAS, June 15, 2001

Prepared by James Jeffrey Bradstreet, M.D., F.A.A.F.P, Director, ICDRC

Introduction: Several factors greatly complicate the Institute's study of the thimerosal issue. Among these, there is a significant lack of defining studies in both humans and animals. Dr. Sudhir Gupta of the University of California - Irvine presented data in Atlanta on May 12, 2001, that children with autism have lower levels of glutathione and are significantly more sensitive to thimerosal than the normal controls. Dr. Haley at the University of Tennessee has extensive research on the relative toxicity of thimerosal to other forms of mercury indicating it is significantly more neurotoxic than methylmercury. In his statement on thimerosal safety to the US House of Representatives, July 18, 2000 (Congressional Record and FDA), William Egan, Ph.D., Acting Office Director, Office of Vaccine Research and Review (OVR), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration (FDA or Agency), assumed similar toxicity profiles between methyl and ethylmercury. That does not appear to be a safe assumption. All of these new findings will hopefully create a sense of caution when making recommendations. These new observations are also inline with the historical observations from Pink's Disease, where only a few children exposed to mercury containing teething powder, ever developed symptoms of toxicity - implying marked individual susceptibility.

Again, mercury is an undisputed serious human health hazard. It also appears from the literature, which will be discussed in reference to the new data presented, that these individual susceptibilities to mercury makes determination of a "safe" exposure level nearly impossible. A growing body of evidence points us to concerns about low-level mercury exposure in early life and future implications for autoimmunity and neurodevelopmental disorders.

As the committee is aware, both the prevalence and incidence of autism may have increased dramatically in the last 20 years. The recent discussions in JAMA (March 2001) suggests, but the British Medical Journal (February 2001) article of Kaye, et al,

documents for us as much as a seven fold incidence increase for autism in just the past decade. Using the government's own data, we see a U.S. prevalence of approximately 6/1000 students (1/166 students and approximately 1/80 boys given a 5 to one preference for the boys with this disorder.) Source: USDE as provided to Congress and supplied by the House Reform Committee.

This recent increase in autism directs us to look for environmental factors, since neither genetics nor increased recognition of the disorder, can be reasonably explain these data. Of the long list of potential environmental factors with a spectrum of toxicity which could explain the neurological findings in autism, mercury is high on the list. Having said that, it appears the effect of thimerosal on the total body burden of mercury is not the most critical concern. I do, however, suspect the combined effects of the route of administration, preexisting high methylmercury titers, and the individual susceptibility to mercury could explain at least some of the observed neurological stigmata observed in children in the autism spectrum. These include: sensory-motor (praxis) issues, fine motor control problems, hypotonia, cognitive disorders, specific learning deficits and auditory processing problems. But it is also unlikely we will be able to accurately know the effect of thimerosal in neurodevelopmental disorders without a prospective, double-blind study on a large-scale population basis. For a starting point, we chose to investigate the prevalence of mercury burden in autism.

To do this we selected two different methodologies: 1) assessment of heavy metals in packed erythrocytes - an indicator of recent exposure, and, 2) DMSA chelatable mercury in urine - an indicator of total body burden. Further, since mercury is known to induce anti-myelin basic protein autoantibodies, we are evaluating the relationship between mercury and anti-MBP. We are also working with several researchers in Indonesia (where autism may also be reaching epidemic proportions) to see if they have a distinct pattern of autism.

This first study does not attempt to answer the question of causality between mercury and autism. As mentioned, that will require a much more complicated prospective approach. While the numbers of controls in this early study is less than desired, the trends -if sustained as we gather more controls - are very concerning for mercury - but not for lead or cadmium.

In addition to control children, we draw on the recent work of Frumkin, et al, to provide us normative adult pre and chelatable DMSA urinary mercury levels. Comparing children to adults is reasonable since everyone seems to agree children are more sensitive to mercury and should ideally not have levels comparable to adults. We avoided hair analyses because several studies in the past have cast doubt on the validity of this test for mercury exposures. Frumkin dealt with both healthy adults, and adults well removed from occupational exposure. A further distinction with our work and his is our exclusion of children with dental amalgams. We also chose a commonly used three-day challenge rather than a two-dose challenge. The rationale in the longer challenge was to clear trivial body burdens from the children prior to collection of samples. In this early, work we do not attempt to control for potential prenatal exposure from maternal fish consumption or

thimerosal from anti-Rh immunoglobulin preparations and maternal vaccination schedules.

The work is being prepared for submission as a follow-up of the Frumkin work and should be presented to the Environmental Health Perspectives publication within a few months. What we present here is an early analysis of 221 children with autism, following DMSA provocation, with 19 neurologically normal children (9 of which were exempted from vaccination for religious reasons).

1) Mercury Burden Among Children with Autism Spectrum Disorders. J.J. Bradstreet and J.J. Kartzinel The International Autism Research Center, Palm Bay Florida 32907

Abstract: These preliminary observations of laboratory findings assessed diagnostic chelation challenge with dimercaptosuccinic acid (DMSA) as a measure of mercury body burden among children with autism. Concern regarding the relationship of mercury, particularly in the form of ethylmercury from thimerosal catabolism, to at least some of the common autism symptoms has increased the awareness of mercury's potential neurotoxicity in developing children. All autistic children involved were established patients of the IARC prior to the study. Children with either autism (DSM-IV 299.00) or Pervasive Developmental Disorder, NOS, (DSM-IV 299.80) (n=221) were selected as the "ASD Group". Further, neurologically normal children "NNC Group", N=19, and the ASD Group were given a three-day provocation with DMSA (10 mg/kg three times daily or nine total doses.) After the ninth dose, first-voided morning urine was collected (when possible), or an overnight urine collection bag was worn. The response to DMSA was measured as mcg/g of creatinine using induction coupled plasma mass spectrometry and creatinines were measured using the Jaffe method. Of the children with autism tested, 193/221 (87.33%) "ASD Hg Group", demonstrated measurable (greater than .0001 mcg/g creatinine) urinary mercury persisting to the end of the three-day provocation, compared with a similar percentage 15/19 (79.5%) in the controls. These 15 controls were designated the "NNC Hg Group". The average urinary post-DMSA mercury titer in the 193 ASD Hg Group children was 8.63 mcg/24 hours versus 1.48 mcg/24 hours in the NNC Hg Group, as estimated by converting from the urinary volume and creatinine concentrations. This represents more than 500% greater chelatable mercury in the ASD Hg Group compared to NNC Hg Group.

A recent study in adults by Frumkin et al, demonstrated a post-DMSA mercury level of 7.8 micrograms per 24 hours. Therefore children with autism have 110% of mercury in their post-DMSA urine compared to adults. However, a more realistic comparison of burden can be found by adjusting for body mass index. Using a body mass index of 27 for average American adult males and 14.5 for autistic six-year old males, we can adjust the mercury excreted during the challenge for the BMI difference between adults and children. Adult males have a BMI, which is 1.86 times six-year old boys. The body mass index adjusted mercury for children implies the mercury load for autistic children would be comparable to 16.05 mcg/24 hours if they had an adult BMI. So, this further suggests autistic children may have an average total burden of mercury 2.06 times greater than adults (including adults with occupational exposure to mercury). The maximum amount

for a female (age 9) was 56.4 mcg/24 hours, and for a male (age 9) was 238.9 mcg/24 hours. The BMI adjusted to adult female standards showed the maximum was 104.9 mcg/24 hours (13.4 times the adult norm) and for the males was 444.35 mcg/24 hours (57 times the adult norm).

Conclusions: For children with autism, 87% have measurable mercury during a DMSA provocation test. Of these children, the average mercury collected in a 24hour period represents more than double (2.06 times) the mercury burden of adults on a BMI adjusted basis. In a smaller group of children, mercury burdens were extremely high with a maximum of as much as 57 times the adult level. These data will require comparison to age-matched controls, but provides concern that thimerosal cannot be routinely given to children with autism. Further, since it now appears there is a 1 in 80 risk of boys developing autism, and since as we have demonstrated children with autism have on average higher mercury burden than adults, there is concern that thimerosal represents an added neurotoxic risk factor for a significant proportion of population.

Recommendations: It is recommended no child diagnosed with autism or other neurodevelopmental disorder receive thimerosal. It is further recommended children with autism be screened for mercury burden using DMSA. It is also advisable to develop a mercury reduction strategy for children with autism including restriction of dietary sources of mercury, dental amalgams and all other sources of mercury. In the autism population of children, DMSA should be researched as a tool for reducing total body burden of mercury. Mercury susceptibility is both genetically and environmentally determined. Metallothionein, glutathione and other mercury protective factors should be evaluated in children with autism in an attempt to establish risk indicators for mercury vulnerability. Other markers for mercury exposure include myelin basic protein autoantibodies. This has previously been published as a marker for many children with autism. The exact relationship of anti-MBP to thimerosal and autism symptoms remains an etiologically unclear, but consistent finding worthy of additional research.

2) Study of DMSA Urine Provocation in a New Jersey Family with a Child with Autism. J.J. Bradstreet, International Autism Research Center, Palm Bay, Florida.

Previously, we reported to Congress the findings of a family in New Jersey. This family consisted of a mother: age 31, father: age 30, a boy age six with autism, and his younger brother age 4. All we tested in late September or early October of 2000. The family is unique in that the mother is a nurse who has had numerous vaccinations for her employment and she also has numerous amalgam fillings. The father has less exposure but has some amalgams, and the younger brother has received only a single hepatitis B vaccine at birth, but is otherwise not vaccinated. The entire family underwent DMSA provocation using 10 mg/kg three times daily for three days. Urine was collected on the first morning void on the fourth day. The response to DMSA was measured as mcg/g of creatinine using induction coupled plasma mass spectrometry and creatinines were measured using the Jaffe method.

The lab reports are included in JPG scanned format.

This New Jersey Family is certainly interesting. I do not intend to take the implications of this too far, but again we see in children with autism, it would be unwise to add ANY mercury to the child so affected. The lead and mercury levels are concerning and likely causing symptoms. Lead and mercury are co-toxic to the central nervous system. This child has completed a 19-day standard lead detoxification DMSA program and several three-day DMSA cycles. He is showing significant cognitive gains and decreasing autistic symptoms. There was no apparent contamination of the family water supply and it appears a potential genetic susceptibility to Hg/Pb, perhaps in the form of metallothionein defects could be responsibly for this child's heavy metal overload.

3) Findings Regarding the Occurrence of Heavy Metal Burden and Brain Autoimmunity In Indonesian Children with Autism Spectrum Disorders. Part 1. J.J. Bradstreet, R. Sutadi and D. Tanjung International Autism Research Center, Palm Bay, Florida and The Faculty of Medicine, University of Indonesia, Jakarta

Indonesia is a country with high environmental exposure to mercury from fish and lead from car exhaust (leaded gasoline is still used in Indonesia). The Indonesian form of the diphtheria, pertussis and tetanus vaccine also contains 50 mcg of thimerosal- double the amount used in previous U.S. vaccines. To determine the possible relationship to mercury and lead to autoimmunity in autism in the Indonesian population we investigated a sample population of 27 children ages 2 -12. This first part of the study looks at packed erythrocyte levels of toxic metals and brain autoimmunity. Part 2 will evaluate the chelatable mercury from the same population. Blood was obtained and couriered to U.S. for study of antibodies to endothelium at Washington University Hospital, St. Louis, Missouri, and anti-Myelin Basic Protein (anti-MBP) at Specialty Laboratory in Santa Monica, California. Additional blood was sent to Doctor's Data in Chicago for study of packed erythrocyte levels of toxic metals using the induction coupled plasma mass spectrometry technique. Results: Average anti-MBP and average mercury were high in the children, but not lead. Of the children studied, 18 of 27 (67%) showed positive anti-MBP titers, with an average anti-MBP titer of 12.15 EIA units (range = 4 to 23 EIA units) where 10 or greater would be considered positive. For IgM antibodies to brain endothelium 19 of 27 were positive (70.4%) and for IgG antibodies to endothelium, nine of 27 (33.3%) were positive. Overall, 22 of 27 children (81.5%) had either IgM or IgG to brain endothelium, which is significantly higher than previously reported by Connolly, et al (J Peds, May 1999). Only one child who was negative for anti-endothelial antibodies was further found positive to anti-MBP. The average mercury level was 0.014 mcg/g of erythrocytes (high by adult norms = 0.01mcg/g) with 19 of 27 (70.4%) positive for detectable mercury, with 8 of 27 (29.6%) exceeding adult normal levels. All children had detectable lead with the average lead level was 0.074 mcg/g of erythrocytes, (borderline for adult norms = 0.09mcg/g). Only 4 of 27 children (14.8%) exceeded adult normal levels of PRBC lead. Conclusions: Brain autoimmunity is a common finding among Indonesian children with autism. Excess mercury burden is also common in children with autism. A direct correlation between current mercury or lead burdens and brain autoimmunity could not be inferred from this study. We are, however concerned about the high titer of thimerosal used in the DTaP vaccine in Indonesia. These data do not

exclude total body mercury burden from contributing to the problem of brain autoimmunity, but other causes, such as a TH-2 immune inducers must be considered.

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Supporting Literature for All Studies: Diagnostic chelation challenge with DMSA: a biomarker of long-term mercury exposure? Environ Health Perspect 2001 Feb;109(2):167-71 Frumkin et al

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I also suggest viewing the video at <http://commons.ucalgary.ca/mercury/> from the University of Calgary , 2001.

I would also reference my submission to the House Reform Committee April 25, 2001.

Respectfully Submitted,

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