

# Facility Automation Management Engineering (FAME) Systems

33 Hoffman Avenue, Lake Hiawatha, NJ 07034

Friday, 21 October 2005

## To Whom It May Concern:

The review that follows this introductory letter is a critical assessment of an article, titled "Evidence Suggests Vaccines Do Not Cause Autism," by Linda Little dated 14 October 2005 that was published on-line in the MedScape Medical News at <http://www.medscape.com/viewarticle/514585>, which I visited as a part of my research in this area on 14 October 2005.

In general, to clearly separate my review comments and those of the article, the article's printed statements are quoted in a "Times New Roman" font followed by my remarks in an indented "**Nimrod**" font.

In cases where there is an important spelling or grammatical error, that error is noted by using a parenthesized "sic; *correction*" text "(sic; xxxx)" insertion placed immediately after the error.

Quotes from general reference articles and documents will be presented in an "Arial" font; and federal laws and statutes will be quoted in a "Lydian" font.

For those who have access to a color printer, this reviewer's comments are made in a **blue** color with original text needing correction in **red**.

Should anyone find any factual errors in these remarks, then this reviewer requests that the factual error along with the scientifically sound and appropriate documents that prove your point to this reviewer so that this reviewer can learn from you, incorporate that new knowledge into his understanding, and, where indicated, appropriately correct this document.

Respectfully,

A handwritten signature in black ink that reads "Paul G. King". The signature is written in a cursive style with a large, prominent "K".

Paul G. King, PhD, MS, BA  
Founder, **F.A.M.E. Systems**

## **A Critical Review of Medscape Medical News Article: “Evidence Suggests Vaccines Do Not Cause Autism”**

by Paul G. King, PhD, MS, BA

### **“Evidence Suggests Vaccines Do Not Cause Autism**

Linda Little

Oct. 14, 2005 (Washington) — A vaccine safety expert reiterated once again that there is no scientific proof linking vaccines to autism or other diseases such as diabetes or asthma.”

**Sadly, this doctor did not address the scientific proof linking the Thimerosal (49.55% mercury by weight), a known highly toxic, “all systems and organs” (systemic) poison<sup>1</sup> that is found in some vaccines, to the systemic mercury poisoning of the American public.**

**Thimerosal has been linked to instances where the clinical mercury-poisoning symptoms observed are diagnosed as “neurodevelopmental disorders” and labeled “ADHD,” “delayed speech,” “tics,” “Asperser’s” or, in the worst cases, “autism.”**

**As this reviewer reports in Appendix B<sup>2</sup>, there is also ample evidence that Thimerosal is implicated in damage to the organs and the immune system that affect the onset and severity of diseases like diabetes (via autoimmune destruction of the specialized cells that produce insulin) and asthma (see articles directly addressing asthma in Appendix B, including references: B-103, B-106 – B-109, B-111, B-113 and B-115).**

“Current scientific research does not implicate thimerosal-containing vaccines or the measles-mumps-rubella (MMR) vaccine with autism, asthma, or infection, according to Walter Orenstein, MD, professor of pediatrics and director of the Emory Vaccine Center at Emory University School of Medicine in Atlanta, Georgia. He spoke to a packed crowd here at a plenary session of the American Academy of Pediatrics National Conference and Exhibition.”

**Dr. Orenstein seems to be unaware of the body of evidence that clearly shows Thimerosal is a, if not the, major cause of the sub-clinical mercury poisoning of Americans.**

**Injecting Thimerosal into humans has been established to mercury poison all who are exposed (injected) to some degree, some to the point that they exhibit one or more of the symptoms of clinical mercury poisoning (including the mercury-poisoning symptom set that is diagnosed as “autism”), and a few to the point that they die.**

**Since Thimerosal has also been proven to be a powerful immune system suppressor and to induce autoimmune symptoms, it is a triggering agent that non-reversibly damages the immune system.**

**Thus, it is clear that Thimerosal has been implicated in the asthma and infections seen in the mercury-poisoned children diagnosed as having the causeless disease “autism.” [See Appendices B and C.]**

“Still, many parents are questioning the safety of such vaccines. Dr. Orenstein cited a 2004 survey of U.S. physicians in which 92% of pediatricians and 60% of family practitioners reported at least one parental refusal of one recommended vaccine.”

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<sup>1</sup> APPENDIX A.

<sup>2</sup> Information derived from postings on: <http://www.extremehealthusa.com/autism.html>

**This reviewer finds that the doctor's cited study does show that some parents are refusing to have their children vaccinated with some vaccines.**

**Moreover, this reviewer also notes it is that the parents and guardians, and not the doctors, who have the right and responsibility in our representative democracy to decide what is best for their minor children and wards.**

**It is also the failure of the medical community to educate themselves about, or even consider, the poisonous effects of the Thimerosal injected into infants, which should be a major concern to that community.**

**Yet, belief in the CDC's unverified statements that Thimerosal 'hasn't been proven to be unsafe' indicates the physicians are simply not reading the medical and scientific literature on the systemic mercury poisoning of biological processes and tissues by Thimerosal at levels below 20 ppb (0.000002%), levels more than a 5,000-fold lower than the nominal 100,000 ppb (0.01%) level in most of today's Thimerosal-preserved vaccines.**

"Parental concerns expressed to physicians included possible links between autism and thimerosal-containing vaccines, autism and the MMR vaccine, and the possible link between the use of multiple vaccinations and diabetes, asthma, and infection."

**Since sound science has clearly established (see Appendices B and C) "links between" the mercury poisoning hidden by the label (diagnosis) of "autism" and the Thimerosal (49.55% mercury) in "thimerosal-containing vaccines," this reviewer finds that the commenter's use of the phrase "possible links" is inappropriate.**

**Second, because some studies have implicated "the MMR vaccine" in the etiology of the development/worsening of "autism" symptoms in children after they are inoculated with the MMR, it is obvious that parents should have such concerns.**

**Finally, because of the established links between "diabetes, asthma, and infection" and the mercury poisoning caused by the repeated injection of Thimerosal-containing vaccines, this reviewer must also note that it is inappropriate to call the "link between the use of multiple vaccinations and diabetes, asthma, and infection" a "possible link"— as that Thimerosal linkage has been directly (for asthma and infection) and indirectly (for diabetes) established in the scientific literature.**

"It is imperative that the medical profession ensure the safety of vaccines, but it is equally important that the science behind studies is examined, Dr. Orenstein said."

**This reviewer must again remind Dr. Orenstein that, though required by law [21 CFR 610.15(a)<sup>3</sup>] to be proven safe, the medical profession has, for almost four decades, failed to prove that Thimerosal was safe for use as a preservative in vaccines at Thimerosal levels of from 30,000 ppm to 100,000 parts per billion (0.003 to 0.01 %) — the range of levels over which Thimerosal (49.55% mercury) is recognized for use as a vaccine preservative.**

**Independent studies have also repeatedly shown that, in human cell and tissue systems, Thimerosal is toxic at levels below 20 parts per billion<sup>4, C-1, C-18</sup>.**

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<sup>3</sup> Thimerosal has been illegally used as a preservative since 1968 when the FDA enacted regulations requiring a compound to be proven safe, (21 CFR 610.15(a): Ingredients, preservatives, diluents, adjuvants. ... Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, ..." before use as a preservative.

<sup>4</sup> Harry E. Morton, Leon L. North and Frank D. Engley, "THE BACTERIOSTATIC AND BACTERIOCIDAL ACTIONS OF SOME MERCURIAL COMPOUNDS ON HEMOLYTIC STREPTOCOCCI In Vivo and in Vitro Studies," *JAMA* 136(1), pp 36-41 (1948).

Although Thimerosal is known to cause severe adverse reactions, including anaphylaxis and death in “sensitive” individuals, the medical profession has again done nothing to demand its removal from vaccines under 42 U.S.C. 300aa-27, which, *since 1986*, has required the Secretary of HHS to do all that he or she can to reduce adverse reactions in vaccines.

This reviewer must also note the seminal 1948 *Journal of the American Medical Association* (J.A.M.A.) report of the Council on Pharmacy and Chemistry by Harry E. Morton et al<sup>4</sup>, which clearly established that Thimerosal was not suitable for use as a vaccine preservative because Thimerosal (49.55% mercury) is, at “preservative levels”:

- Only bacteriostatic and not, *as a preservative should be*, bactericidal,
- Much more toxic to human cells and tissues (5 to 35 times) than it was to bacteria, and
- Toxic at levels below 20 parts per billion in skin-cell studies (where the toxic effect levels in skin cells were similar to those for neurons).

Had the medical profession truly been concerned about the safety of vaccines, then, after the publication of that paper, it would have immediately and continually demanded that Thimerosal be banned from any use in vaccines or vaccine manufacture.

Even the reported<sup>5</sup> deaths of 10 of 13 infants whose umbilical stumps were treated with a topical “antiseptic” solution of Thimerosal in the mid-1970s seems to somehow have gone unnoticed — another lost opportunity for the medical establishment to proactively push to get mercury out of medicine.

Since the medical profession did not then demand, and has not, until this day, demanded, that Thimerosal be removed from all vaccines (and other drugs), it obvious to the parents and the scientists, who study in this area, that the medical profession has, for more than 50 years, been ignoring the doctor’s “imperative that the medical profession ensure the safety of vaccines.”

“One study in his review that raised parental fears of the connection between thimerosal and autism was a California ecological study that showed an apparent connection between children with autism in special education classes with estimated mercury exposure from vaccines. ‘This was an ecological study,’ Dr. Orenstein commented. ‘This could have been due to a change in diagnostic codes as well as the number of available educational services for autism. This would be easily studied in a better epidemiological study.’”

**As the study of which the doctor speaks is not explicitly identified and it deals with “estimated mercury exposures from vaccines” and “children with autism in special education classes,” this reviewer can only note that the California DDS has evaluated the issues raised by Dr. Orenstein and reported<sup>6</sup> that:**

- **Neither diagnostic code change (widening of diagnostic criteria),**
- **Nor number of available services,**

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<sup>5</sup> D. G. Fagan, J. S. Pritchard, Thomas W. Clarkson and M. R. Greenwood, “Organ mercury levels in infants with omphaloceles treated with organic mercurial antiseptic,” *Archives of Disease in Childhood*, 52, pages 962-964 (1977).

<sup>6</sup> Report to the California Legislature on the Principal Findings from, *The Epidemiology of Autism in California*, October 17, 2002” by Dr. Robert E. Byrd et al [Byrd RE, Sage AC, Keyzer J, Shefelbine R, Gee K, Enders K, Neufeld J, Do N, Heung K, Hughes T, Baron R, Moore A, Walbridge B, Samuels S, Tancredi D, He J, Calvert E, Chavez D, Elsdon A, Lee L, Wong D, Sigman M, Bono M, Beck C, Clavell S, Lizaola E, and Meyerkova V] published online at: <http://www.dds.ca.gov/autism/mindreport.cfm> by the M.I.N.D. Institute.

- **Nor the addition of inclusion criteria (designed to reduce number of cases included and having an estimated effect of reducing the confirmed cases that were included by only 1% of the confirmed cases), had any significant effect on the confirmed “autism” case reporting numbers for California’s DSM/CDER Category 1 “autism” cases.**

**Because the doctor did not attack the validity of the “estimated mercury exposure from vaccines,” this reviewer presumes that he agrees with those estimates.**

“He also pointed to a National Institutes of Health and Harvard study that compared the features of children with autism and nonautistic children with mercury poisoning. The study found few similarities between the groups in motor function, vision, speed, sensory perception, and psychology.”

**Again, since the doctor did not identify the specific study of which he is speaking, this reviewer can only state that an in-depth comparison of the “features” of mercury poisoning with the “features” reported being found in children having the diagnosis “autism,” found “similarities” in all instances.**

**A tabulation of that much more comprehensive comparison can be found in Appendix B.**

**In the initial portion of Appendix B, which addresses similar “traits,” the “traits” common to mercury poisoning and “autism” cases were:**

- **Psychiatric Disturbances (including, social deficits [shyness, social withdrawal]; repetitive, preservative and stereotypic behaviors; obsessive-compulsive tendencies; depression/depressive traits, mood swings and flat affect; impaired face recognition; anxiety; schizoid tendencies; irrational fears; irritability, aggression, and temper tantrums; lacks eye contact; and impaired visual fixation or problems in joint attention).**
- **Speech and Language Deficits (including, loss of speech, delayed language and failure to develop speech; dysarthria; articulation problems; speech comprehension deficits; and verbalizing and word retrieval problems or echolalia, word use and pragmatic errors).**
- **Sensory Abnormalities (including, abnormal sensation in mouth and extremities; sound sensitivity; mild to profound hearing loss; abnormal touch sensations; touch aversion; over-sensitivity to light; and blurred vision).**
- **Motor Disorders (including, flapping, myoclonal jerks, choreiform movements, circling, rocking, toe walking and unusual postures; deficits in eye-hand coordination; and limb apraxia, intention tremors, or problems with intentional movement or imitation).**
- **Cognitive Impairments (including, borderline intelligence or mental retardation which is reversible in some cases; poor concentration, attention and response inhibition or, in other words, shifting attention; uneven performance on IQ subtests; verbal IQ higher than performance IQ; poor short term, verbal, and auditory memory; poor visual and perceptual motor skills; impairment in simple reaction time or, in other words, lower performance on timed tests; deficits in understanding abstract ideas and symbolism; degeneration of higher mental powers or, in other words, problems with sequencing, planning & organizing; and difficulty carrying out complex commands).**

- **Unusual Behaviors (including, self injurious behavior [e.g., head banging]; ADHD traits; agitation, unprovoked crying, grimacing, and staring spells; and sleep difficulties).**
- **Physical Disturbances (including, hyper- or hypotonia; abnormal reflexes; decreased muscle strength [especially upper body]; incontinence; problems chewing and swallowing; rashes, dermatitis, eczema and itching; diarrhea; abdominal pain/discomfort, constipation and "colitis"; Anorexia; nausea and vomiting; and poor appetite or self-restricted diet).**

“There are major differences between traditional mercury poisonings and thimerosal, Dr. Orenstein said. ‘Not all mercuries are the same.’”

**This reviewer must agree with the doctor here.**

**However, based on this reviewer’s understanding, injected Thimerosal (49.55% mercury) is a much more poisonous form of mercury than the ingested protein-bound “methylmercury” in fish or contaminated bread of which the doctor seems to be speaking.**

**Furthermore, the applicable sound toxicological studies, which have evaluated the clinical toxicity of some “ethylmercury” compound versus some comparable “methylmercury” compound, have established that the gross toxicities of these two series are similar<sup>7,8,9</sup>.**

“Methyl mercury implicated in the usual mercury poisoning is quite different from the ethyl mercury contained in thimerosal, he explained. ‘Ethyl mercury has a shorter half-life and is less associated with poisoning.’”

**Here again, the doctor seems to confuse more rapid excretion of the initial metabolite, ethylmercurihydroxide, with the build up (through dealkylation) of the “bound inorganic mercury” responsible for the long-term poisoning observed.**

**In a recent study<sup>10</sup>, Burbacher et al performed a comparative dosing and half-life study using baby monkeys and studying low-dose injected Thimerosal in vaccines as compared to ingested methylmercurihydroxide solutions.**

**The most important finding in that study is that for the same doses, the level of residual “inorganic mercury” trapped in the brains of the Thimerosal-injected monkeys (ThHg) was, on average, more than twice<sup>11</sup> that found in the brains of the monkeys fed a methylmercurihydroxide (MeHg) solution.**

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<sup>7</sup> K. A. Winship, “Organic mercury compounds and their toxicity,” *Adverse Drug Reaction Acute Poisoning Review*, **3**, pages 141-180 (1986).

<sup>8</sup> Laszlo Magos, A. W. Brown, S. Sparrow, E. Bailey, R. T. Snowden and W. R. Skipp, “The comparative toxicology of ethyl- and methylmercury.” *Archives of Toxicology*, **57**, pages 260-267 (1985).

<sup>9</sup> Leander Tryphonas and N. O. Nielsen, “Pathology of Chronic Alkylmercurial Poisoning in Swine,” *American Journal of Veterinary Research*, **34**(3), pages 379-392 (1973).

<sup>10</sup> Thomas M. Burbacher, Danny D. Shen, Noelle Liberato, Kimberly S. Grant, Elsa Cernichiari, and Thomas Clarkson, “Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methylmercury or Vaccines Containing Thimerosal,” *Environ Health Perspect* **113**, pages **1015-1021** (2005).

<sup>11</sup> The level of inorganic mercury in 7 of the MeHg monkeys was below, the MeHg-inorganic (n=10) » 5.7 ng/g and the estimated level for the inorganic mercury was ThHg-inorganic (n=17) » 12.3 ng/g (estimated from the graphs since the values were not reported). The true “ThHg-inorganic / MeHg-inorganic” ratio is obviously larger, or a “ThHg-inorganic / MeHg-inorganic” ratio of ~ 2.2. If the missing values were taken to be 0 ng/g, then the ratio ThHg-inorganic / “MeHg-inorganic” would be about ~ 12.3 to “~ 3.69” or “~ 3.3.” Thus, the true “ThHg-inorganic / MeHg-inorganic” ratio is between “~ 2.2” and ~ 3.3.”

**On balance, the long-term clinical toxicity of Thimerosal's initial metabolite, ethylmercurihydroxide currently seems to be more than twice as toxic as the long-term toxicity of ingested methylmercurihydroxide.**

**Also, neither the article's writer nor, apparently, the doctor cited any study that proves this premise.**

**Based on the applicable reports this reviewer has studied, this reviewer must reject the unsubstantiated premise, "Ethyl mercury ... is less associated with poisoning."**

"Dr. Orenstein cited a study conducted in Sweden and Denmark that did not find a link between thimerosal and autism. When thimerosal was removed from the vaccines in Sweden and Denmark, there was no correlating change in the rates of autism reported in either country, he said."

**As far as this reviewer can ascertain, the studies deal with much lower maximum Thimerosal doses, delivered at later times as well as with studies that looked at "reporting rates" rather than true "incidence rates" in countries where the nominal incidence rates in Sweden and Denmark (between 5 and 6 DSM "autism" diagnoses per 10,000 are less than 20% of the U.S. incidence rate for diagnosed "autism" cases (30+ DSM "autism" diagnoses per 10,000).**

**For a more detailed rebuttal of the commenter's remarks, the reader should read Dr. Blaxill's review<sup>12</sup> of those studies because not only does he rebut Dr. Orenstein's view of these foreign studies but he also points out the significant, but undisclosed, conflicts of interest of the authors who conducted these apparently less than scientifically sound epidemiological studies.**

"In reviewing other pertinent studies, it was found that three studies showing a link between thimerosal and autism did not meet any of the eight established epidemiologic study quality criteria, while four studies finding no link met between five and seven of the quality criteria."

**Since neither the article's writer nor the doctor:**

- **Identified the "pertinent studies" or**
- **Enumerated "the eight established epidemiologic study quality criteria,"**

**this reviewer can only note that no independent study of the raw data and intermediate data files from any of the epidemiological studies that reported "no evidence of a link" has been permitted nor, for the CDC-sponsored American study<sup>13</sup>, are such independent studies currently possible because the researchers responsible for maintaining those datasets have *conveniently* "lost" them.**

**For the "discredited studies," which found evidence of a significant link between Thimerosal dose and the risk of being diagnosed with various neurodevelopmental disorders, including "autism," most have been independently reviewed and found to be epidemiologically sound by not only the peer-reviewed journals in which they were published but also outside reviewers who, *in some cases*, have been able to review the underlying data sets upon which the published studies rest.**

**Given the preceding realities, this reviewer must discount the article's rhetoric since the validity of remarks made has not been independently verified.**

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<sup>12</sup> Mark Blaxill, "Danish-Autism Study in *Pediatrics*: Misleading and Uninformative on Autism-Mercury Link," SafeMinds.com, pp. 4 (September 2, 2003).

<sup>13</sup> Thomas Verstraeten, Robert L. Davis, Frank DeStefano, Tracy A. Lieu, Philip H. Rhodes, Steven B. Black, Henry Shinefield and Robert T. Chen; for the Vaccine Safety Datalink Team, 'Safety of Thimerosal-Containing Vaccines: A Two-Phased Study of Computerized Health Maintenance Organization Databases,' *Pediatrics*, 112(5), pages 1039-1048 (2003)

“In addition, when an Institute of Medicine committee reviewed published and unpublished studies in 2004, the committee found no supporting evidence for a causal relationship between thimerosal-containing vaccines or the MMR vaccine and autism.”

**While this reviewer finds that the statements here are technically true, this reviewer must note that the Institute of Medicine (IOM) committee’s findings were conflicted by the initial instructions provided to the IOM by the Center of Disease Control and Prevention (CDC) when they entered into the contract.**

**Since the CDC’s initial charge to the IOM’s committee, *as reflected in the transcript of the 2001 IOM’s initial closed-door meeting*, clearly instructed the committee members to do essentially whatever necessary to debunk the link between Thimerosal dose and the form of mercury poisoning labeled “autism,” this reviewer is compelled to totally discount the findings stated in the reports issued by both the 2001 IOM and the follow-up 2004 IOM committees.**

**Finally, this reviewer would ask the doctor and the writer, *after having more than 60 years to find the “cause,”* how can it be that the medical establishment has been unable to find the cause of the disorder called “autism”?**

“Current vaccines given during the first six months of life have essentially no mercury, except trace amounts, Dr. Orenstein said. ‘There is virtually no mercury.’”

***The sanofi-aventis’ “Thimerosal Preserved” influenza vaccine, Fluzone®, which nominally contains 50 micrograms of mercury per milliliter of vaccine solution, is approved for use in 6-month-old children and the CDC/AAP childhood vaccination program recommends that babies 6 months to 2 years of age be vaccinated.***

**Thus, the doctor’s statement is simply not true for children vaccinated with the “Thimerosal Preserved” influenza vaccine, who, *based on the vaccines’ label claims*, will injected with nominally about 15.5 micrograms of mercury during the first 6 months of life and 28 micrograms during the first 7 months of life whenever their parents follow the current American childhood vaccination schedule.**

**Even ignoring the mode of administration differences and the fact that the ERA/FDA safe daily intake levels are based on *guesses* made on the ingestion of mercury-containing foods by adults, a nominal 12.5-microgram injected dose of mercury exceeds the EPA/FDA “daily dose” guideline for ingested mercury (which has been shown to be less toxic in animals than when it is injected) unless the 6-month-old baby weighs more than 125 kilograms (kg).**

**Based on the preceding facts, the doctor’s “There is virtually no mercury” statement is: a) obviously untrue and b), *since Dr. Orenstein is an expert in these matters*, he apparently knew<sup>14</sup> it was a misrepresentation.**

**Given the medical establishment’s ongoing and continual distortion of the level of mercury in Thimerosal-containing vaccines given to children and adults, it would also seem that the medical establishment knows full well that the Thimerosal (49.55% mercury by weight) is the “cause” of the knowing mercury poisoning of the American babies.**

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<sup>14</sup> Title 21 of the United States Code (U.S.C.) CHAPTER 9—FEDERAL FOOD, DRUG, AND COSMETIC ACT  
SUBCHAPTER II—DEFINITIONS

Sec. 321. Definitions; generally

For the purposes of this chapter—

(bb) The term “knowingly” or “knew” means that a person, with respect to information—

(1) has actual knowledge of the information, or

(2) acts in deliberate ignorance or reckless disregard of the truth or falsity of the information.

Moreover, the mercury poisoning of American babies has been an ongoing reality since the late 1800's when the previously concealed mercury poisoning, where the Calomel (84.98% mercury by weight, but not highly soluble in water) in teething powders was the mercury poisoning vector used for the mercury poisoning and, *according to the medical establishment*, "Pink Disease" was the prior causeless disease.

At the end of 1930s, it is just a "coincidence" that, *as the Calomel-laced teething powders were withdrawn from the market*, Eli Lilly introduced Thimerosal (a highly toxic, organic mercury compound that is 49.55% by weight mercury and highly soluble in water [1 gram per milliliter {mL}]).

Thimerosal's initial metabolite, ethylmercuri hydroxide, is also a highly toxic mercury compound, which

- Preferentially resides in the body's lipid-rich tissues,
- Crosses the blood-brain and the blood-placenta barriers, and
- Is metabolized in the body into some "bound inorganic mercury" species.

Though there is a body of in vitro evidence that Thimerosal is toxic at levels below 0.02 micrograms per gram [g] (or mL) {less than 0.000002%}, the doctor persists in claiming that injecting Thimerosal at levels of 1 to 100 micrograms per mL (0.0001% to 0.01%) is "safe" while the federal government is still putting off conducting<sup>15</sup> the requisite toxicological studies of Thimerosal, which were finally "scheduled" in 1999.

Please Dr. Orenstein, why haven't the requisite toxicology studies been conducted?

"Vaccines today are much more highly purified than in the past, he said. 'They are not being overloaded with antigenic proteins.'"

Given the apparent knowing misrepresentations in the prior statement and the *non sequitor* between "... are much more highly purified ..." and "... are not being overloaded with antigenic proteins," this reviewer cannot accept that the doctor's unsupported statement is factually accurate.

Moreover, a recent report from Germany<sup>16</sup> in which the introduction of a "six-disease vaccine" to replace a "five-disease vaccine" seemed to be connected to an increase in "SIDS" (sudden infant death syndrome) deaths would seem to indicate that simultaneous injection with vaccine components for multiple diseases does fatally overload the immune systems of some babies.

"In addition, Dr. Orenstein concluded, 'epidemiological evidence shows no relationship between those with multiple immunizations and asthma nor infections.'"

**Because the doctor:**

- Cites no studies to support his statements, and
- This topic has nothing to do with the stated topic, "vaccines and autism," this reviewer is at a loss to understand relevance of his statement here.

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<sup>15</sup> According to the web page [http://cerhr.niehs.nih.gov/CERHR\\_chems/index.html](http://cerhr.niehs.nih.gov/CERHR_chems/index.html), of mid-September 2005, containing Thimerosal, CAS 54-64-8, was not nominated by the FDA to have its toxicity appropriately studied until "11/99." However, that proposed study's status was changed to "Nomination Deferred" in "7/00" because there were "Chemicals with higher priorities" for, given the studies that were allowed to proceed, no scientifically sound reason.

<sup>16</sup> B. Zinka et al, "Unexplained cases of sudden infant death shortly after hexavalent vaccination," **Vaccine**, in press March 2005

"There have been enough studies done trying to link autism to vaccines," Carden Johnston, MD, past president of the American Academy of Pediatrics of Birmingham, AL, told Medscape.

**Ironically, this reviewer agrees with this statement because the current experimental evidence has clearly established that:**

- **The injuring agent is the Thimerosal in Thimerosal-containing drugs given to the children and adults and**
- **The resulting disease is mercury poisoning.**

**Thus, because it has been proven that Thimerosal causes mercury poisoning, there is no further need *per se* for epidemiological studies seeking to link “vaccines” and “autism.”**

“Ever since Ed Jenner started smallpox vaccinations, there have been public groups trying to link vaccines to morbidity.’ Research funds should be spent on more productive areas, he concluded.”

**This reviewer agrees with Dr. Orenstein that, *since Thimerosal has been proven to cause mercury poisoning in those injected with preparations containing Thimerosal*, research funds should be spent on areas other than doing epidemiological studies to establish this linkage.**

**Again, this reviewer notes that the government continues to hold off<sup>15</sup> on conducting the in-depth experimental toxicological studies needed to establish:**

- **Just how toxic Thimerosal is,**
- **The half-life of the tissue-localized bound “inorganic mercury” that forms from the intermediate Thimerosal metabolite, ethylmercuri hydroxide, and**
- **What are its modes and pathways for both the short-term and long-term mercury poisoning in the various organs and tissues.**

**Moreover, though case studies have clearly established that diet, dietary supplements, certain supportive drugs (e.g., bethanacol hydrochloride), detoxification using various preparations of certain chelating agents, DMSA and DMPS, as well as certain herbal supplements, and hyperbaric oxygen therapies have led to marked improvement in some who are the most severely mercury poisoned (the ones who are diagnosed with severe “autism”), this reviewer notes that there are no government- or pharmaceutical industry- funded studies in these areas.**

**Why is it, Dr. Orenstein, that the “curative” therapies that seem to work are not being researched?**

**Why are genetic research projects being funded in an attempt to blame the mercury poisoning on the children who have been mercury poisoned rather than those who are clearly responsible for the mercury poisoning?**

“AAP 2005 National Conference and Exhibition: Plenary Session. Presented Oct. 11, 2005.

Reviewed by Gary D. Vugin, MD”

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#### **About the Reviewer**

In addition to the information available on his web page<sup>17</sup>, this reviewer, Dr. Paul G. King, is the New Jersey Representative for the “Coalition for Mercury-Free Drugs” (CoMeD) [<http://www.mercury-freedrugs.org>], the current District 33 Democratic Committeeman for Township of Parsippany-Troy Hills, Morris County, NJ, a Taoist philosopher and a servant of Elohim.

As a scientist and student of the federal regulations and statutes governing drugs, Dr. King led CoMeD in the drafting and submission of a Citizen Petition, posted in the FDA Public Docket 2004P-0349 (and on the

CoMeD web site), and wrote and submitted CoMeD’s response to the FDA’s 180-day response letter.

[**Note:** A draft of article was reviewed by Mark R. Geier, MD, PhD, FABMG and by Boyd E. Haley, PhD, who provided some suggestions that were incorporated into this draft.]

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<sup>17</sup> <http://www.dr-king.com>

# APPENDIX A

## “Abbreviated Material Safety Data Sheet”

### SECTION 1. CHEMICAL IDENTIFICATION

NAME: THIMEROSAL

### SECTION 2. COMPOSITION/INFORMATION ON INGREDIENTS

CAS #: 54-64-8

Molecular Formula: C9H9HGNAO2S

EC NO: 200-210-4

#### SYNONYMS:

((O-CARBOXYPHENYL)THIO)ETHYLMERCURY SODIUM SALT, ETHYLMERCURITHIOSALICYLIC ACID SODIUM SALT, MERTHIOLATE SODIUM, MERTORGAN, MERZONIN, MERZONIN SODIUM, SODIUM ETHYLMERCURIC THIOSALICYLATE, SODIUM O-(ETHYLMERCURITHIO) BENZOATE, SODIUM ETHYLMERCURITHIOSALICYLATE, SODIUM MERTHIOLATE, THIMEROSAL, THIMEROSALATE, THIOMERSAL, THIOMERSALATE \*

### SECTION 3. HAZARDS IDENTIFICATION

#### LABEL PRECAUTIONARY STATEMENTS

**HIGHLY TOXIC (USA); VERY TOXIC (EU); VERY TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED; DANGER OF CUMULATIVE EFFECTS; MAY CAUSE SENSITIZATION BY INHALATION AND SKIN CONTACT, IRRITATING TO EYES; RESPIRATORY SYSTEM AND SKIN; CALIF. PROP. 65 REPRODUCTIVE HAZARD.**

**TARGET ORGAN(S):** NERVES, KIDNEYS, GUT, SKIN, LIVER, PANCREAS, SPLEEN, GLANDS, ETC.

**SENSITIZER;** CAUSES IRRITATION.

KEEP AWAY FROM FOOD, DRINK AND ANIMAL FEEDINGSTUFFS.

**AFTER CONTACT WITH SKIN, WASH IMMEDIATELY WITH PLENTY OF WATER.**

**IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF WATER AND SEEK MEDICAL ADVICE.**

WEAR SUITABLE PROTECTIVE CLOTHING.

IN CASE OF ACCIDENT OR IF YOU FEEL UNWELL, SEEK MEDICAL ADVICE IMMEDIATELY (SHOW THE LABEL WHERE POSSIBLE).

### SECTION 4. FIRST-AID MEASURES

**IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.**

**CALL A PHYSICIAN IMMEDIATELY.**

**IF INHALED, REMOVE TO FRESH AIR. IF NOT BREATHING GIVE ARTIFICIAL RESPIRATION; IF BREATHING IS DIFFICULT, GIVE OXYGEN.**

IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND SHOES. CALL A PHYSICIAN.

IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

### SECTION 5. FIRE FIGHTING MEASURES

...

### SECTION 6. ACCIDENTAL RELEASE MEASURES

WEAR SELF-CONTAINED BREATHING APPARATUS, RUBBER BOOTS AND HEAVY RUBBER GLOVES. SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL. AVOID RAISING DUST. VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE. EVACUATE AREA.

### SECTION 7. HANDLING AND STORAGE

**REFER TO SECTION 8.**

### SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

SAFETY SHOWER AND EYE BATH. USE ONLY IN A CHEMICAL FUME HOOD. WASH CONTAMINATED CLOTHING BEFORE REUSE. WASH THOROUGHLY AFTER HANDLING. DO NOT BREATHE DUST. DO NOT GET IN EYES, ON SKIN, ON CLOTHING. AVOID PROLONGED OR REPEATED EXPOSURE. NIOSH/MSHA-APPROVED RESPIRATOR. COMPATIBLE CHEMICAL-RESISTANT GLOVES. CHEMICAL SAFETY GOGGLES. KEEP TIGHTLY CLOSED. STORE IN A COOL DRY PLACE.

### SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

**APPEARANCE AND ODOR:** SOLID.

**PHYSICAL PROPERTIES:** MELTING POINT: 234 C, FLASHPOINT >482F (>250C)

**SOLUBILITY:** 1g in mL of water; 8 mL of ethanol; **SPECIFIC GRAVITY:** 0.5 G

# APPENDIX A

## “Abbreviated Material Safety Data Sheet”

### SECTION 10. STABILITY AND REACTIVITY

**STABILITY:** STABLE.

**CONDITIONS TO AVOID:** MAY DISCOLOR ON EXPOSURE TO LIGHT.

**INCOMPATIBILITIES:** STRONG OXIDIZING AGENTS, STRONG ACIDS, STRONG BASES.

**HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS:** CARBON MONOXIDE, CARBON DIOXIDE, MERCURY, MERCURY OXIDES, AND SULFUR OXIDES.

**HAZARDOUS POLYMERIZATION:** WILL NOT OCCUR.

### SECTION 11. TOXICOLOGICAL INFORMATION

#### ACUTE EFFECTS:

CAUSES SKIN IRRITATION.

MAY BE FATAL IF ABSORBED THROUGH SKIN.

CAUSES EYE IRRITATION.

MAY BE FATAL IF INHALED.

MATERIAL IS IRRITATING TO MUCOUS MEMBRANES AND UPPER RESPIRATORY TRACT.

MAY BE FATAL IF SWALLOWED.

POSSIBLE ALLERGIC REACTION TO DUST IF INHALED, INGESTED OR IN CONTACT

WITH THE SKIN. HYPERSENSITIVITY REACTIONS MANIFESTED BY ERYTHEMA,

PAPULAR OR VESICULAR ERUPTIONS OCCUR OCCASIONALLY. ALLERGIC

CONJUNCTIVITIS HAS BEEN REPORTED.

TO THE BEST OF OUR KNOWLEDGE, THE CHEMICAL, PHYSICAL, AND

TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

#### CHRONIC EFFECTS:

**TARGET ORGAN(S):** NERVES, KIDNEYS, *ETC.*

**RTECS #: OV8400000** MERCURY, ((O-CARBOXYPHENYL)THIO)ETHYL-, SODIUM SALT

**IRRITATION DATA:** EYE-RABBIT: 8 µg mild

AJOPAA 78,98,1974

#### TOXICITY DATA:

IAL-CHD LDLO: 60 mg/kg/4W-I

JOPDAB 104,311,1984

ORL-RAT LD50: 75 mg/kg

PCOC\*\* -,1130,1966

SCU-RAT LD50: 98 mg/kg

CTOXAO 4,185,1971

UNR-RAT LD50: 40 mg/kg

30ZDA9 -,290,1971

ORL-MUS LD50: 91 mg/kg

NYKZAU 58,235,1962

IPR-MUS LD50: 54 mg/kg

NYKZAU 58,235,1962

SCU-MUS LD50: 66 mg/kg

QJPPAL 12,212,1939

IVN-MUS LD50: 45 mg/kg

QJPPAL 12,212,1939

#### TARGET ORGAN DATA:

BRAIN AND COVERINGS (OTHER DEGENERATIVE CHANGES); BEHAVIORAL (ANOREXIA, HUMAN); BEHAVIORAL (CHANGE IN MOTOR ACTIVITY); BEHAVIORAL (ATAXIA); BEHAVIORAL (COMA); LUNGS, THORAX OR RESPIRATION (OTHER CHANGES); GASTROINTESTINAL (NAUSEA OR VOMITING); KIDNEY, URETER, BLADDER (CHANGES IN TUBULES); EFFECTS ON FERTILITY (POST-IMPLANTATION MORTALITY); EFFECTS ON FERTILITY (ABORTION); EFFECTS ON EMBRYO OR FETUS (FETAL DEATH); TUMORIGENIC EFFECTS (UTERINE TUMORS); NUTRITIONAL AND GROSS METABOLIC (CHANGES IN: METABOLIC ACIDOSIS); TUMORIGENIC (NEOPLASTIC BY RTECS CRITERIA); TUMORIGENIC (TUMORS AT SITE OF APPLICATION).

[NOTE: Note: ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS) DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.]

### SECTION 12. ECOLOGICAL INFORMATION: DATA NOT YET AVAILABLE.

### SECTION 13. DISPOSAL CONSIDERATIONS

CONTACT A LICENSED PROFESSIONAL WASTE DISPOSAL SERVICE TO DISPOSE OF THIS MATERIAL.

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE AND LOCAL ENVIRONMENTAL REGULATIONS.

# APPENDIX A

## “Abbreviated Material Safety Data Sheet”

### SECTION 14. TRANSPORT INFORMATION

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### SECTION 15. REGULATORY INFORMATION

#### EUROPEAN INFORMATION

EC INDEX NO: 080-004-00-7

VERY TOXIC

**R 26/27/28** VERY TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

**R 33** DANGER OF CUMULATIVE EFFECTS.

**R 50/53** VERY TOXIC TO AQUATIC ORGANISMS, MAY CAUSE LONG-TERM ADVERSE EFFECTS IN THE AQUATIC ENVIRONMENT.

**S 13** KEEP AWAY FROM FOOD, DRINK AND ANIMAL FEEDINGSTUFFS.

**S 28** AFTER CONTACT WITH SKIN, WASH IMMEDIATELY WITH PLENTY OF SOAP SUDS.

**S 36** WEAR SUITABLE PROTECTIVE CLOTHING.

**S 45** IN CASE OF ACCIDENT OR IF YOU FEEL UNWELL, SEEK MEDICAL ADVICE IMMEDIATELY (SHOW THE LABEL WHERE POSSIBLE).

**S 60** THIS MATERIAL AND ITS CONTAINER MUST BE DISPOSED OF AS HAZARDOUS WASTE.

**S 61** AVOID RELEASE TO THE ENVIRONMENT. REFER TO SPECIAL INSTRUCTIONS/SAFETY DATA SHEETS.

#### REVIEWS, STANDARDS, AND REGULATIONS

ACGIH TLV-TWA 0.1 MG(HG)/M3 (SKIN)

DTLVS\* TLV/BEI,1999

MSHA STANDARD-AIR:TWA 0.05 MG(HG)/M3

DTLWS\* 3,22,1973

OSHA PEL (GEN INDU):8H TWA 0.01 MG(HG)/M3

CFRGBR 29,1910.1000,1994

OSHA PEL (CONSTRUC):8H TWA 0.01 MG(HG)/M3 (SKIN)

CFRGBR 29,1926.55,1994

OSHA PEL (SHIPYARD):8H TWA 0.01 MG(HG)/M3 (SKIN)

CFRGBR 29,1915.1000,1993

OSHA PEL (FED CONT):8H TWA 0.01 MG(HG)/M3 (SKIN)

CFRGBR 41,50-204.50,1994

OEL-AUSTRALIA: TWA 0.05 MG(HG)/M3, SKIN, JAN1993

OEL-BELGIUM: TWA 0.05 MG(HG)/M3, SKIN, JAN1993

OEL-DENMARK: TWA 0.05 MG(HG)/M3, SKIN, JAN1999

OEL-FINLAND: TWA 1 MG(HG)/M3, JAN1999

OEL-FRANCE: VME 0.1 MG(HG)/M3, JAN1999

OEL-GERMANY: MAK 0.01 PPM (0.1 MG(HG)/M3), JAN1999

OEL-HUNGARY: TWA 0.02 MG(HG)/M3, STEL 0.04 MG(HG)/M3, JAN1993

OEL-JAPAN: OEL 0.05 MG(HG)/M3, JAN1999

OEL-THE NETHERLANDS: MAC-TGG 0.05 MG(HG)/M3, MAC-K 0.15 MG(HG)/M3, SKIN, JAN1999

OEL-NORWAY: TWA 0.05 MG(HG)/M3, JAN1999

OEL-THE PHILIPPINES: TWA 0.05 MG(HG)/M3, JAN1993

OEL-POLAND: MAC(TWA) 0.05 MG(HG)/M3, MAC(STEL) 0.15 MG(HG)/M3, JAN1999

OEL-RUSSIA: TWA 0.05 MG(HG)/M3, STEL 0.01 MG(HG)/M3, JAN1993

OEL-SWEDEN: NGV 0.05 MG(HG)/M3, SKIN, JAN1999

OEL-THAILAND: STEL 0.05 MG(HG)/M3, JAN1993

OEL-UNITED KINGDOM: LTEL 0.05 MG(HG)/M3, STEL 0.15 MG(HG)/M3, JAN1993

OEL IN ARGENTINA, BULGARIA, COLOMBIA, JORDAN, KOREA CHECK ACGIH TLV;

OEL IN NEW ZEALAND, SINGAPORE, VIETNAM CHECK ACGIH TLV

NIOSH REL TO MERCURY, ARYL AND INORGANIC-AIR:CL 0.1 MG/M3 (SK)

NIOSH\* DHHS #92-100,1992

NOHS 1974: HZD 84569; NIS 83; TNF 5617; NOS 30; TNE 242717

NOES 1983: HZD 84569; NIS 32; TNF 3695; NOS 41; TNE 152997; TFE 114190

#### EPA GENETOX PROGRAM 1988, POSITIVE: S CEREVISIAE GENE CONVERSION

EPA TSCA SECTION 8(B) CHEMICAL INVENTORY

EPA TSCA TEST SUBMISSION (TSCATS) DATA BASE, JANUARY 2001

#### U.S. INFORMATION

THIS PRODUCT IS SUBJECT TO SARA SECTION 313 REPORTING REQUIREMENTS - MERCURY COMPOUNDS.

THIS PRODUCT IS A CHEMICAL KNOWN TO THE STATE OF CALIFORNIA TO CAUSE DEVELOPMENTAL TOXICITY.

### SECTION 16. OTHER INFORMATION

## APPENDIX B

### Comparison Of: The Characteristics of “Autism” To Those For Mercury Poisoning

Information derived from postings on: <http://www.extremehealthusa.com/autism.html>

**“Table I: Summary Comparison of ‘Traits’ of Autism & Mercury Poisoning”**  
“(ASD references in **bold**; Mercury Poisoning references in *italics*)” **Part A**

<b>Psychiatric Disturbances</b>
Social deficits, shyness, social withdrawal ( <b>1,2,130,131</b> ; <i>21,31,45,53,132</i> )
Repetitive, preservative, stereotypic behaviors; obsessive-compulsive tendencies ( <b>1,2,43,48,133</b> ; <i>20,33-35,132</i> )
Depression/depressive traits, mood swings, flat affect; impaired face recognition ( <b>14,15,17,103,134,135</b> ; <i>19,21,24,26,31</i> )
Anxiety; schizoid tendencies; irrational fears ( <b>2,15,16</b> ; <i>21,27,29,31</i> )
Irritability, aggression, temper tantrums ( <b>12,13,43</b> ; <i>18,21,22,25</i> )
Lacks eye contact; impaired visual fixation (HgP)/ problems in joint attention (ASD) ( <b>3,36,136,137</b> ; <i>18,19,34</i> )
<b>Speech and Language Deficits</b>
Loss of speech, delayed language, failure to develop speech ( <b>1-3,138,139</b> ; <i>11,23,24,27,30,37</i> )
Dysarthria; articulation problems ( <b>3</b> ; <i>21,25,27,39</i> )
Speech comprehension deficits ( <b>3,4,140</b> ; <i>9,25,34,38</i> )
Verbalizing and word retrieval problems (HgP); echolalia, word use and pragmatic errors (ASD) ( <b>1,3,36</b> ; <i>21,27,70</i> )
<b>Sensory Abnormalities</b>
Abnormal sensation in mouth and extremities ( <b>2,49</b> ; <i>25,28,34,39</i> )
Sound sensitivity; mild to profound hearing loss ( <b>2,47,48</b> ; <i>19,23-25,39,40</i> )
Abnormal touch sensations; touch aversion ( <b>2,49</b> ; <i>23,24,45,53</i> )
Over-sensitivity to light; blurred vision ( <b>2,50,51</b> ; <i>18,23,31,34,45</i> )
<b>Motor Disorders</b>
Flapping, myoclonal jerks, choreiform movements, circling, rocking, toe walking, unusual postures ( <b>2,3,43,44</b> ; <i>11,19,27,30,31,34,39</i> )
Deficits in eye-hand coordination; limb apraxia; intention tremors (HgP)/problems with intentional movement or imitation (ASD) ( <b>2,3,36,181</b> ; <i>25,29,32,38,70,87</i> )
Abnormal gait and posture, clumsiness and incoordination; difficulties sitting, lying, crawling, and walking; problem on one side of body ( <b>4,41,42,123</b> ; <i>18,25,31,34,39,45</i> )

**APPENDIX B**  
**Comparison Of:**  
**The Characteristics of “Autism” To Those For Mercury Poisoning**

**“Table I: Summary Comparison of Traits of Autism & Mercury Poisoning”**  
 (ASD references in bold; Mercury Poisoning references in italics) **Part B**

<b><i>Cognitive Impairments</i></b>
Borderline intelligence, mental retardation - some cases reversible ( <b>2,3,151,152;</b> <i>19,25,31,39,70</i> )
Poor concentration, attention, response inhibition (HgP)/shifting attention (ASD) ( <b>4,36,153;</b> <i>21,25,31,38,141</i> )
Uneven performance on IQ subtests; verbal IQ higher than performance IQ ( <b>3,4,36;</b> <i>31,38</i> )
Poor short term, verbal, and auditory memory ( <b>36,140;</b> <i>21,29,31,35,38,87,141</i> )
Poor visual and perceptual motor skills; impairment in simple reaction time (HgP)/ lower performance on timed tests (ASD) ( <b>4,140,181;</b> <i>21,29,142</i> )
Deficits in understanding abstract ideas & symbolism; degeneration of higher mental powers (HgP)/sequencing, planning & organizing (ASD); difficulty carrying out complex commands ( <b>3,4,36,153;</b> <i>9,18,37,57,142</i> )
<b><i>Unusual Behaviors</i></b>
Self injurious behavior, e.g. head banging ( <b>3,154;</b> <i>11,18,53</i> )
ADHD traits ( <b>2,36,155;</b> <i>35,70</i> )
Agitation, unprovoked crying, grimacing, staring spells <b>3,154;</b> <i>11,23,37,88</i> )
Sleep difficulties ( <b>2,156,157;</b> <i>11,22,31</i> )
<b><i>Physical Disturbances</i></b>
Hyper- or hypotonia; abnormal reflexes; decreased muscle strength, especially upper body; incontinence; problems chewing, swallowing ( <b>3,42,145,181;</b> <i>19,27,31,32,39</i> )
Rashes, dermatitis, eczema, itching ( <b>107,146;</b> <i>22,26,143</i> )
Diarrhea; abdominal pain/discomfort, constipation, "colitis" ( <b>107,147-149;</b> <i>18,23,26,27,31,32</i> )
Anorexia; nausea (HgP)/vomiting (ASD); poor appetite (HgP)/restricted diet (ASD) ( <b>2,123;</b> <i>18,22</i> )
Lesions of ileum and colon; increased gut permeability ( <b>147,150;</b> <i>57,144</i> )

**APPENDIX B**  
**Comparison Of:**  
**The Characteristics of “Autism” To Those For Mercury Poisoning**

**“ Table II: Summary Comparison of Biological Abnormalities in Autism & Mercury Exposure” Part A**

<b>Mercury Exposure</b>	<b>Autism</b>
<b>Biochemistry</b>	
Binds -SH groups; blocks sulfate transporter in intestines, kidneys (40,93)	Low sulfate levels (91,92)
Reduces glutathione availability; inhibits enzymes of glutathione metabolism; glutathione needed in neurons, cells, and <b>liver</b> to detoxify heavy metals; reduces glutathione peroxidase and reductase (97,100,161,162)	Low levels of glutathione; decreased ability of liver to detoxify xenobiotics; abnormal glutathione peroxidase activity in erythrocytes (91,94,95)
Disrupts purine and pyrimidine metabolism (10,97,158,159)	Purine and pyrimidine metabolism errors lead to autistic features (2,101,102)
Disrupts mitochondrial activities, especially in brain (160,163,164)	Mitochondrial dysfunction, especially in brain (76,172)
<b>Immune System</b>	
Sensitive individuals more likely to have allergies, <b>asthma</b> , autoimmune-like symptoms, especially rheumatoid-like ones (8,11,18,24,28,31,111,113)	More likely to have allergies and <b>asthma</b> ; familial presence of autoimmune diseases, especially rheumatoid arthritis; IgA deficiencies (103,106-109,115)
Can produce an immune response in CNS; causes brain/MBP autoantibodies (18,111,165)	On-going immune response in CNS; brain/MBP autoantibodies present (104,105,109,110)
Causes overproduction of Th2 subset; kills/inhibits lymphocytes, T-cells, and monocytes; decreases NK T-cell activity; induces or suppresses IFNg & IL-2 (100,112,117-120,166)	Skewed immune-cell subset in the Th2 direction; decreased responses to T-cell mitogens; reduced NK T-cell function; increased IFNg & IL-12 (103,108,114-116,173,174)
<b>CNS Structure</b>	
Selectively targets brain areas unable to detoxify or reduce Hg-induced oxidative stress (40,56,161)	Specific areas of brain pathology; many functions spared (36)
Accumulates in amygdala, hippocampus, basal ganglia, cerebral cortex; damages Purkinje and granule cells in cerebellum; brain stem defects in some cases (10,34,40,70-73)	Pathology in amygdala, hippocampus, basal ganglia, cerebral cortex; damage to Purkinje and granule cells in cerebellum; brain stem defects in some cases (36,60-69)
Causes abnormal neuronal cytoarchitecture; disrupts neuronal migration, microtubules, and cell division; reduces NCAMs (10,28,57-59,161)	Neuronal disorganization; increased neuronal cell replication, increased glial cells; depressed expression of NCAMs (4,54,55)
Progressive microcephaly (24)	Progressive microcephaly and macrocephaly (175)

## APPENDIX B

### Comparison Of: The Characteristics of “Autism” To Those For Mercury Poisoning

“Table II: Summary Comparison of Biological Abnormalities in Autism & Mercury Exposure” Part B

<b>Neuro-chemistry</b>	
Prevents presynaptic serotonin release and inhibits serotonin transport; causes calcium disruptions (78,79,163,167,168)	Decreased serotonin synthesis in children; abnormal calcium metabolism (76,77,103,179)
Alters dopamine systems; peroxidine deficiency in rats resembles mercurialism in humans (8,80)	Either high or low dopamine levels; positive response to peroxidine, which lowers dopamine levels (2,177,178)
Elevates epinephrine and norepinephrine levels by blocking enzyme that degrades epinephrine (81,160)	Elevated norepinephrine and epinephrine (2)
Elevates glutamate (21,171)	Elevated glutamate and aspartate (82,176)
Leads to cortical acetylcholine deficiency; increases muscarinic receptor density in hippocampus and cerebellum (57,170)	Cortical acetylcholine deficiency; reduced muscarinic receptor binding in hippocampus (83)
Causes demyelinating neuropathy (22,169)	Demyelination in brain (105)
<b>Neurophysiology</b>	
Causes abnormal EEGs, epileptiform activity, variable patterns, e.g., subtle, low amplitude seizure activities (27,31,34,86-89)	Abnormal EEGs, epileptiform activity, variable patterns, including subtle, low amplitude seizure activities (2,4,84,85)
Causes abnormal vestibular nystagmus responses; loss of sense of position in space (9,19,34,70)	Abnormal vestibular nystagmus responses; loss of sense of position in space (27,180)
Results in autonomic disturbance: excessive sweating, poor circulation, elevated heart rate (11,18,31,45)	Autonomic disturbance: unusual sweating, poor circulation, elevated heart rate (17,180)

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## APPENDIX B

### Comparison Of:

### The Characteristics of “Autism” To Those For Mercury Poisoning

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- B-176 Carlson M. L. Hypothesis: is infantile autism a hypoglutamatergic disorder? Relevance of glutamate - serotonin interactions for pharmacotherapy. *J Neural Transm* 1998; 105(4-5): 525-535.
- B-177 Gillberg C., Svennerholm L. CSF monoamines in autistic syndromes and other pervasive dev. disorders of early childhood. *Br J Psychiatry* 1987; (151): 89-94.
- B-178 Ernst M., Zametkin A. J., Matochik J. A., Pascualvaca D., Cohen R. M. Low medial prefrontal dopaminergic activity in autistic children. *Lancet* 1997; 350(9078): 638.
- B-179 Leboyer M., Philippe A., Bouvard M., et al. Whole blood serotonin and plasma beta-endorphin in autistic probands and their first-degree relatives. *Biol Psychiatry* 1999; 45(2): 158-163.
- B-180 Ornitz E. M. Neurophysiologic studies of infantile autism. *Handbook of Autism and Pervasive Developmental Disorders*. John. 02-60773, 5th Cir.

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### “Updated Publications List That Supports The Proposition: Thimerosal Causes Mercury Poisoning”

#### Part A: Important Publications Including Those Found After July 2004

- C-1 Frank B. Engley, Jr. Mercurials as Disinfectants Evaluation of mercurial antimicrobial action and comparative toxicity. Soap and Chemical Specialties, 1956 Dec.:200, 201, 203, 205, 223, 224 and 225.**

[Note: This is an excellent article that was fashioned from a presentation at the Chemical Specialties Manufacturing Association Meeting by Dr. Frank Engley earlier in 1956.] In the published paper, Dr. Engley comments:

**"The problems involving the use of chemicals as anti-bacterial agents have been of particular interest to me as a bacteriologist ... Some ten years or more ago with Morton and North we were asked to carry out a study on mercurials for the Council on Pharmacy and Chemistry of the American Medical Association which was published in its journal in 1948. This report suggested that mercurials did not fulfill all the conditions expected of antiseptics...Unlike the theatrical or political figure who once said that it didn't matter what was written about him so long as they wrote something and spelled his name correctly-we in the field of scientific investigation would rather be quoted correctly than not at all. In this regard the report might not be the most misquoted or maligned report from certain quarters but it is in there with the best or the worst depending upon your point of view or the source of your income."**

Then, he proceeds to describe the ineffectiveness of Thimerosal as a preservative in vaccines and other pharmaceuticals products by stating:

**"The use of mercurials as preservatives in vaccines and antisera is of considerable interest. These chemicals are added to protect against the introduction of organisms in multi-use containers in particular. We have always wondered about their efficacy in that both vaccines and antisera contain reactive groups to tie up these compounds. In a series of continuing experiments over the past several years we have begun to evaluate various preservatives in serum and vaccines under conditions of use. Employing stock vaccines and serum with and without preservatives and stored at varying lengths of time a contaminating dose of representative sporeformer (Bacillus subtilis) in the spore stage gram negative rod (E. coli) and gram positive coccus (S. aureus) were added. While the mercurial preservatives had good activity on initial addition, after storage of three, six or more months decreasingly less to negligible residual activity appeared to be left, indicating that the chemical was tied up by the protein of the biological of otherwise inactivated. A check on a series of over one thousand bottles of various biologicals from clinics obtained after use revealed that up to five percent contained micro-organisms. This would suggest that once these biologicals are in the hands of users a problem still exists. Regarding preservatives, one of the real problems existing in hospitals and clinics is the need for good preservatives in the routine eye dilators and nasal preparations of the decongestant type. Routine checks of these indicate a high percentage of contaminated solutions. In one instance we had direct evidence of upper respiratory cross-infection from the use of a common nasal dropper preparation in a clinic."**

Dr. Engley then comments about the toxicity of mercurials such as Thimerosal by stating:

**"The toxicity of chemicals used as drugs on or in the body has been of considerable interest since man first began exposing himself to various chemicals many years ago. Unfortunately there have not been good techniques for toxicity determinations of certain types of chemicals which might be really indicate of toxicity for humans...Graph 15 compares mercurial compounds and shows how they fit in with other compounds in toxicity...Mercurochrome appears to be the least toxic ranging down through Merthiolate" (Merthiolate is another name for Thimerosal) "...One point should be made here. Bichloride of mercury has always been pointed out as an extremely toxic mercurial and the organic mercurials were supposed to be much less toxic, but according to these data, we find bichloride right in the middle of the organic mercurials in regard to cell toxicity...mercurial antiseptics proved to be more toxic than the antibiotics in common usage..."**

Also, Dr. Engley observed (see Graph 15) toxic effects for Thimerosal in his human tissue skin culture cell system at levels from 1 ppm of Thimerosal down to less than 15 parts-per-billion of Thimerosal. Specifically, he was able to show toxicity from Thimerosal at levels comparable to those in recent studies that have shown low parts-per-billion levels of Thimerosal are toxic (at 10 to 20 parts-per-billion of Thimerosal) to human cells almost 50 years before many of the current studies

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were published. Furthermore, the low parts-per-billion levels of Thimerosal that Dr. Engley observed to be toxic to human tissue culture cells are many-fold lower than the levels recently demonstrated by Burbacher et al (see reference C-24) to be present in the brain following injection of Thimerosal-containing vaccines (age- and weight-adjusted) mirroring the US childhood vaccines schedule). One additional important point is that in Graph 16, Dr. Engley compares the relative toxicity of mercurials to various organs in the body including: cord, heart, spleen, and skin. He found that, among the organs of the body he tested, the cord (i.e. nervous system tissue) is, as we know, most sensitive organ to mercury (i.e. mercury was more toxic for the cord than for heart or spleen), and that the skin had a similar sensitivity to mercury intoxication as the cord.]

- C-2** Undated, 7-page 1991 Merck memo: From: “Maurice R. Hilleman WP 26-200B”; To: “DR. DAVID GORDON RY 33-76”; Regarding: “VACCINE TASKFORCE ASSIGNMENT THIMEROSAL (MERTHIOLATE) PRESERVATIVE – PROBLEMS, ANALYSIS, SUGGESTIONS FOR RESOLUTION,” which: **a)** was discovered in a recent court case and **b)** clearly indicates that Merck had been aware of the excessive level of mercury being injected into babies for some time. This memo ends with the following two telling paragraphs in the postscript:
- “The seasoned conclusion Wigzell gives is, “Our opinion, however, is that the problems associated with the spread of mercury via vaccination are so minor that there is no reason to push a hastened solution.
- Note, however, that Wigzell mentions only Thimerosal-reserved DTP or DT given in at least 3 doses since the 1950s. Even with such small exposures, Sweden is moving as expeditiously as feasible to achieve a zero input of mercury from Thimerosal.”
- C-3** Digar A, Sensharma GC, Samal S. Lethality and teratogenicity of organic mercury (Thimerosal) on the chick embryo. *J Anat Soc India* 1987;36:153-9.
- C-4** Gasset AR, Itoi M, Ishii Y, Ramer RM. Teratogenicities of Ophthalmic Drugs II. Teratogenicities and Tissue Accumulation. *Arch Ophthalmol.* 1975 Jan;93:52-55.
- C-5** Oliver WT, Platonow N. Studies on the pharmacology of N-(ethylmercuri)-p-toluenesulfonanilide. *Am J Vet Res.* 1960 Sep;21:906-16.
- “This article shows dose dependent and outcomes specific to dosing level and repetition frequency. The apparent lack of clinical symptoms and non-lethality (within the 38-day period these animals were monitored) of a single 140 µg/Kg dose coupled with the rapid appearance of clinical symptoms and swift lethality (6 hours) after a single 224 µg/Kg dose indicates to this informed reviewer that humans and animals have varying abilities to intercept and protect critical systems from the clinical mercury poisoning and lethal effects of N-(ethylmercuri)-p-toluenesulfonanilide, which, when exceeded, lead to observable mercury-poisoning symptoms and animal death within 6 hours of dosing. Finally, this article clearly establishes that, outside of the “medical profession,” where various terms are used to disguise the disease, these researchers clearly recognized the disease as mercury poisoning.
- Another key finding was that, though the gross effects are the same, mercury poisoning, each compound has a slightly different modus operandi with respect to its specific pattern of poisoning.”
- C-6** Withrow TJ, Brown NT, Hitchins VM, Strickland AG. Cytotoxicity and Mutagenicity of Ophthalmic Solution Preservatives and UVA Radiation in L5178Y Cells. *Photochem Photobiol.* 1989 Sep;50(3):385-9.
- C-7** Westphal GA, Asgari S, Schulz TG, Bunger J, Muller M, Hallier E. Thimerosal induces micronuclei in the cytochalasin B block micronucleus test with human lymphocytes. *Arch Toxicol.* 2003 Jan;77(1):50-5.
- C-8** Kiffe M, Christen P, Arni P. Characterization of cytotoxic and genotoxic effects of different compounds in CHO K5 cells with the comet assay (single-cell gel electrophoresis assay). *Mutat Res.* 2003 Jun 6;537(2):151-68.

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#### Part B: Additional Key Publications From Mid-2004 To Mid-September 2005

- C-9** Gosselin NH, Brunet RC, Carrier G, LeBouchard M, Feeley M. Reconstruction of methylmercury intakes in indigenous populations from biomarker data, *J. Exposure Analysis and Environmental Epidemiology*. 2005 Jun 29;advance online publication: 1-11.

“Significant amounts of methylmercury (MeHg) can bioaccumulate in fish and sea mammals. To monitor MeHg exposure in individuals, organic and inorganic mercury are often measured in blood samples or in hair strands, the latter being by far the best integrator of past exposure. With knowledge of the MeHg kinetics in humans, the levels of both biomarkers can be related to MeHg body burden and intakes. In the present study, we use the toxicokinetic model of Carrier et al. (2001) describing the distribution and excretion of MeHg in humans, to reconstruct the history of MeHg intakes of indigenous women of the Inuvik region in Canada starting from total mercury concentrations in hair segments. From these reconstructed MeHg intakes, the corresponding simulated mercury blood concentrations are found to be good predictors of the concentrations actually measured in blood samples. **An important conclusion of this study is that, for almost all subjects, the reconstructed history of their MeHg intakes provides much lower intake values than intakes estimated from questionnaires on food consumption and estimated MeHg levels in these foods; the mean value of the reconstructed MeHg intakes is 0.03 mg/kg/day compared with the mean value of 0.20 mg/kg/day obtained from questionnaires.** The model was also used to back-calculate the MeHg intakes from concentrations in hair strands collected from aboriginals of the Amazon region in Brazil, a population significantly more exposed than the population of the Inuvik region.”

- C-10** Havarinasab S, Haggqvist B, Bjorn E, Pollard KM, Hultman P. Immunosuppressive and autoimmune effects of thimerosal in mice. *Toxicol Appl Pharmacol*. 2005 Apr 15;204(2):109-21.

This paper reports:

“With regard to the fraction of total mercury present as inorganic mercury after thimerosal treatment, Suzuki et al. (1973) reported 17–21% Hg<sup>2+</sup> in the kidneys 6 days after a single injection of thimerosal. A similar fraction of Hg<sup>2+</sup> was seen in the kidneys of our mice after 6 days continuous peroral treatment. **We found a maximum fraction of inorganic mercury (41%) after 14 days thimerosal treatment.** A comparable dose of Hg given as MeHg for up to 30 days caused a continuous increase in the fraction of inorganic mercury, which however reached only 22% after 30 days treatment (Haggqvist et al, unpublished observations). Finally, when equipotent doses of Hg were given as thimerosal or MeHg for up to 30 days, the maximum total kidney Hg concentration was higher after thimerosal as compared with MeHg treatment. **The presence of a substantial fraction of inorganic mercury in the tissues of thimerosal-treated mice, and the many similarities between the immunostimulation which develops after thimerosal treatment and primary treatment with inorganic mercury (Pollard and Hultman, 1997), indicates that inorganic Hg may be responsible for the immunostimulatory effect. The threshold for induction of HgIA using inorganic Hg is around 4 µg/g tissue (Hultman and Nielsen, 2001), a threshold which was rapidly reached in thimerosal-treated mice. However, this observation does not exclude the possibility that EtHg also contributed to the stimulatory effect.**

In conclusion, treatment of genetically metal-susceptible mice with the organic mercury compound thimerosal (EtHg) has initially a similar suppressive effect on the immune system as MeHg. However, **thimerosal treatment subsequently leads to strong immunostimulation and autoimmunity, which is at variance with only a weak autoimmune response after MeHg treatment.**

Suzuki, T., Takemoto, T.I., Kashiwazki, H., Miyama, T., 1973. Metabolic fate of ethylmercury salts in man and animal. In: Miller, M., Clarkson, T. (Eds.), *Mercury, Mercurials and Mercaptans*. Charles C. Thomas, Springfield, IL, pp. 209–232.

Pollard, K.M., Hultman, P., 1997. Effects of mercury on the immune system. In: Sigel, H., Sigel, A. (Eds.), *Mercury and Its Effects on Environment and Biology*. Marcel Dekker, Basel, pp. 421–440.

Hultman, P., Nielsen, J.B., 2001. The effect of dose, gender, and non-H-2 genes in murine mercury-induced autoimmunity. *J. Autoimmun.* 17, 27–37.”

#### Reviewer’s Observation:

This article clearly establishes that, unlike “MeHg” mercury poisoning, Thimerosal mercury poisoning includes a “strong immunostimulation and autoimmunity” component making it much less safe to use Thimerosal in drugs than it would be to use a “methylmercury”-releasing component in a drug formulation.

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- C-11** A Two-Phased Population Epidemiological Study of the Safety of Thimerosal-Containing Vaccines1.pdf in Adobe Acrobat Format Geier DA, Geier MR. A two-phased population epidemiological study of the safety of thimerosal-containing vaccines: a follow-up analysis. Med Sci Monit. 2005 Apr;11(4):CR160-70.

#### “Summary

**Background:** Thimerosal is an ethylmercury-containing preservative in vaccines. Toxicokinetic studies have shown children received doses of mercury from thimerosal-containing vaccines (TCVs) that were in excess of safety guidelines. Previously, an ecological study showing a significant association between TCVs and neurodevelopmental disorders (NDs) in the US was published in this journal.

**Material/Methods:** A two phased population-based epidemiological study was undertaken. Phase one evaluated reported NDs to the Vaccine Adverse Event Reporting System (VAERS) following thimerosal-containing Diphtheria-Tetanus-acellular-Pertussis (DTaP) vaccines in comparison to thimerosal-free DTaP vaccines administered from 1997 through 2001. Phase two evaluated the automated Vaccine Safety Datalink (VSD) for cumulative exposures to mercury from TCVs at 1-, 2-, 3-, and 6-months-of-age for infants born from 1992 through 1997 and the eventual risk of developing NDs.

**Results:** Phase one showed significantly increased risks for autism, speech disorders, mental retardation, personality disorders, and thinking abnormalities reported to VAERS following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. Phase two showed significant associations between cumulative exposures to thimerosal and the following types of NDs: unspecified developmental delay, tics, attention deficit disorder (ADD), language delay, speech delay, and neurodevelopmental delays in general.

**Conclusions:** This study showed that exposure to mercury from TCVs administered in the US was a consistent significant risk factor for the development of NDs. **It is clear from these data and other recent publications linking TCVs with NDs that additional ND research should be undertaken in the context of evaluating mercury-associated exposures and thimerosal-free vaccines should be made available.”**

#### Reviewer’s Observation:

Given the clear central-nervous-system-related mercury poisoning effects found for a single 50-microgram dose of Thimerosal, it should be obvious that the mercury-poisoning effects are stronger and more systemic when, as is the case, multiple 25- and 50- microgram doses were given in the period from the late 1980’s to, for some U.S. children and most children in some developing countries, the present (mid-2000’s).

- C-12** Geier DA, Geier MR. Neurodevelopmental disorders following thimerosal-containing childhood immunizations: a follow-up analysis. Int J Toxicol. 2004 Nov-Dec;23(6):369-76.

#### “CONCLUSIONS

The present study provides additional epidemiological evidence linking thimerosal with neurodevelopmental disorders. From the late 1980s to the late 1990s, the level of thimerosal in childhood vaccinations based on the recommended vaccination schedule within the first 6 months of life increased from 75  $\mu$ grams of ethylmercury starting at 2 months (3 DTP vaccines at 25  $\mu$ grams of ethylmercury each) to approximately 200  $\mu$ grams of ethylmercury (three DTP vaccines [25  $\mu$ grams of ethylmercury each], three Hib vaccines [25  $\mu$ grams of ethylmercury each], three hepatitis B vaccines [12.5  $\mu$ grams of ethylmercury each], and in many children influenza vaccine [12.5  $\mu$ grams of ethylmercury]). ... It is clear that the results of the present study mandate that additional research should be undertaken, not only for autism, but (sic; but also) other childhood neurodevelopmental disorders, by evaluating childhood mercury-associated exposures, especially from thimerosal-containing childhood vaccines.”

#### Reviewer’s Observation:

Like the CDC, the author’s repeat the oft-made mistake of confusing the percentage of mercury by weight in Thimerosal, 49.55% (see Footnote 5), with the weight percentage of ethylmercury in Thimerosal, which is actually 56.73%. Otherwise, the authors’ conclusions as to the need for clinical research is right n the mark because **a)** the evidence of harm is clear and **b)** the requisite appropriate scientifically sound toxicology studies required by law (21 CFR 610.15(a)) have, as yet, not been conducted and/or published.

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- C-13** James SJ, Cutler P, Melnyk S, Jernigan S, Janak L, Gaylor DW, Neubrandner JA. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. *Am J Clin Nutr.* 2004 Dec;80(6):1611-7.

**“ABSTRACT**

**Background:** Autism is a complex neurodevelopmental disorder that usually presents in early childhood and that is thought to be influenced by genetic and environmental factors. Although abnormal metabolism of methionine and homocysteine has been associated with other neurologic diseases, these pathways have not been evaluated in persons with autism.

**Objective:** The purpose of this study was to evaluate plasma concentrations of metabolites in the methionine transmethylation and transsulfuration pathways in children diagnosed with autism.

**Design:** Plasma concentrations of methionine, S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), adenosine, homocysteine, cystathionine, cysteine, and oxidized and reduced glutathione were measured in 20 children with autism and in 33 control children. On the basis of the abnormal metabolic profile, a targeted nutritional intervention trial with folinic acid, betaine, and methylcobalamin was initiated in a subset of the autistic children.

**Results:** Relative to the control children, the children with autism had significantly lower baseline plasma concentrations of methionine, SAM, homocysteine, cystathionine, cysteine, and total glutathione and significantly higher concentrations of SAH, adenosine, and oxidized glutathione. This metabolic profile is consistent with impaired capacity for methylation (significantly lower ratio of SAM to SAH) and increased oxidative stress (significantly lower redox ratio of reduced glutathione to oxidized glutathione) in children with autism. The intervention trial was effective in normalizing the metabolic imbalance in the autistic children.

**Conclusions:** An increased vulnerability to oxidative stress and a decreased capacity for methylation may contribute to the development and clinical manifestation of autism. ...

**TABLE 1**

**Comparison of methionine cycle and transsulfuration metabolites between autistic children and control children<sup>1</sup>**

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

<sup>1</sup> All values are  $\bar{x} \pm SD$ ; range in parentheses. SAM, S-adenosylmethionine;

SAH, S-adenosylhomocysteine; tGSH, total glutathione; GSSG, oxidized glutathione.

<sup>2-5</sup> Significantly different from control children: <sup>2</sup> P < 0.001, <sup>3</sup> P < 0.01, <sup>4</sup> P < 0.05, <sup>5</sup> P < 0.002.”

**Reviewer’s Observations:**

While this article points out the effects observed, it does not address the specific causal agent for the outcomes observed choosing instead to characterize it broadly as “oxidative stress.” Based on what this reviewer understands, the major cause of this “oxidative stress” is mercury poisoning of the enzymatic pathways that regulate the production and utilization of these key biochemicals.

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- C-14** Boris M, Goldblatt A, Galanko J, James SJ. Association of MTHFR gene variants with autism. J Am Phys Surg 2004;9:106-8.

#### “ABSTRACT

Autism is a complex neurodevelopment disorder with numerous possible genetic and environmental influences.

We retrospectively examined the laboratory data of 168 children sequentially referred to our facility with a confirmed diagnosis of autism or pervasive developmental disabilities (PDD). Since folate and methylation (single carbon metabolism) are vital in neurological development, we routinely screened children for the common mutations of the methylenetetrahydrofolate reductase gene (MTHFR), which regulates this pathway. All children had polymerase chain reaction (PCR) DNA evaluation to determine the frequency of the 677 and 1298 common polymorphisms in the MTHFR gene.

We observed a significantly increased frequency of the homozygous mutation 677CT allele (TT): 23% in the autistic children compared to 11% in the control population ( $P < 0.0001$ ). Additionally, the heterozygous 677CT allele (CT) was present in 56% of the autistic children compared to 41% in the control population ( $P < 0.0001$ ). Somewhat paradoxically, the normal 1298AA allele was significantly higher in the autistic group, 55%, compared to the controls, 44% ( $P < 0.05$ ). Despite the increased frequency of normal 1298AA alleles, the compound 677CT/1298AC heterozygous mutations were more prevalent in the autistic population, 25%, than in controls, 15% ( $P = 0.01$ ).

Overall, the data show an increased risk of autism spectrum disorder (ASD) associated with common mutations affecting the folate/methylation cycle. These associations by themselves may provide a partial explanation for a subgroup of children genomically at risk for ASD disorders. Increased folic acid during pregnancy and early development may offset the genomic risk factors, and this deserves further study. Further, since folate-dependent methylation provides, in part, the methyl group for inactivation of monoamine neurotransmitters via the catecholamine-O-methyltransferase (COMT) system, this observation may help to further differentiate subtypes within the broad phenotype of ASD. A search for additional genomic and environmental risk factors should be undertaken. In particular, the methylation/transsulfation and COMT pathways should be investigated.”

#### Reviewer’s Observations:

While this article points out the genomic variabilities that may have some association with the causeless symptoms currently diagnosed as “autism,” it does not address the specific causal agent for the “autism.” Based on what this reviewer understands, the unstated cause of the “causeless” disorder, “autism,” is mercury poisoning and the correlations point to differences in the ability to resist being poisoned by the Thimerosal mercury in the vaccines injected into them from the day they were born.

- C-15** Environmental Working Group. Overloaded? New Science, New Insights about Mercury and Autism in Susceptible Children. Washington, DC: EWG Action Fund; Issued 13 December 2004. Published to the Internet on 3 march 2005 at:  
[http://www.ewg.org/reports/autism/execsumm.php?print\\_version=1](http://www.ewg.org/reports/autism/execsumm.php?print_version=1)

#### “Findings

An eighteen-month investigation by Environmental Working Group concludes that scientists have identified a signature metabolic profile or “biomarker” in autistic children that may indeed characterize a “small subset” of susceptible children. These findings represent a potential milestone in our understanding of individual vulnerability to toxic substances, including, but not limited to, mercury. This science turns on its head the IOM’s judgment that research into the thimerosal/autism link be abandoned, and instead strengthens significantly the case for additional research in this area. We found that:

- Newly published research and follow-up testing by former FDA senior research scientist Dr. Jill James, now of the University of Arkansas for Medical Sciences, has uncovered a unique and consistent metabolic imbalance in autistic children when compared to normal healthy children... This impairment manifests as a severe deficit in the body’s most important antioxidant and metals detoxifier, glutathione. When compared to normal health children, autistic children showed a significant impairment in every one of five measurements of the body’s ability to maintain a healthy glutathione defense. These findings are strong evidence that if these children were exposed to a potentially toxic dose of mercury or other compound they would be much less able to mount an effective defense...

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- The finding of a significant glutathione deficit in autistic children provides a biological basis for integrating many facets of autism that have baffled researchers attempting to pin the autism epidemic on a single gene or chemical exposure.
- The implications of these findings extend well beyond thimerosal and autism. Reduced antioxidant defense may characterize a group of individuals who are demonstrably more sensitive to the effects of a range of toxic chemical exposures, and shed light on increasing rates of related learning and behavioral disorders.
- These findings raise serious concerns about the studies that have allegedly proven the safety of mercury in vaccines. While Dr. James' results do not prove that mercury causes autism, they significantly strengthen this possibility. The epidemiologic studies used to dismiss a causal relationship between mercury and autism assumed that all children have the same resistance to chemical exposure. Given James' finding that autistic children would be much more sensitive to certain chemical contaminants, studies that do not acknowledge these vulnerabilities cannot be used to dismiss the relationship between environmental chemicals, including mercury, and the disease.
- When James' results are considered together with the existing body of science, including other recently published research, the weight of the evidence now strongly supports increased research into the relationship between thimerosal and autism as well as other neurodevelopmental and neurodegenerative disorders.

#### Recommendations

##### Research

The findings by James significantly strengthen the science supporting a connection between mercury and autism. Contrary to the recommendation of the Institute of Medicine, that research on the relationship between mercury and autism essentially be abandoned, the weight of the evidence in the basic biological sciences now supports accelerated funding and research into the biological pathways and genetic mechanisms that may make some individuals more vulnerable to mercury and a host of other environmental toxins. We recommend increased federal support for research in this area.

A small follow-up group of children in this study have benefited markedly when their impaired antioxidant defense was restored. This provides important clues about treatments that could derive from increased funding for research in this area...

Several studies are underway to explore the relationship between thimerosal-containing vaccines and autism in greater detail—including a follow-up study underway by the CDC ... The power of these studies would be dramatically enhanced if they included Dr. James' simple blood test to examine the antioxidant capacity of autistic and healthy children as a factor that modifies an individual's sensitivity to mercury toxicity.

##### Policy Reform: Environmental Health

James' findings also have major implications for public health protections and pollution control. They potentially identify a subgroup of people with dramatically increased risk of harm from industrial chemicals, and provide important new evidence that policies designed to protect the average person, or even the average child, from chemical exposure, are insufficient to fully protect the public health. Children with the metabolic profile James has identified may be more susceptible to a vast number of common pollutants, from arsenic in drinking water and pressure-treated wood, to air pollution from cars and power plants. Environmental and health officials must evaluate the adequacy of current laws and policies to protect individuals with a heightened sensitivity to chemicals exposure.

##### Policy Reform: Immunizations

The Environmental Working Group strongly supports the standard battery of childhood immunizations recommended by the American Academy of Pediatrics and the CDC. Clearly, vaccinations have led to many major advances in public health. At the same time, EWG recommends the removal of thimerosal and all mercury-based preservatives from all vaccines in the United States, as is currently required by law in California and Iowa.

As individual states and many industrialized countries have phased out or banned the use of the mercury-based preservative in vaccines, the use of immunizations preserved with thimerosal continues unabated in the developing world. Precisely because of the clear public health benefits of vaccinations, the limited access to refrigeration, and the need to deliver vaccines in multiple dose containers in these countries, we urge the World Health Organization and multinational drug companies to move quickly to develop and adopt an alternative, low cost, effective preservative that is safer than mercury-based thimerosal.”

##### Reviewer's Observation:

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In general, this reviewer agrees with the findings and recommendations except that the long-term relationship that needs to be studied is the “relationship between Thimerosal-containing vaccines” and the mercury intoxication (poisoning) of all of those who are given any such Thimerosal-containing vaccines.

**C-16** McGinnis WR. Oxidative stress in autism. *Altern Ther Health Med.* 2004 Nov-Dec;10(6):22-36.

“If we learn that oxidative stress is an important mechanism in autism, then our search for the genetic and environmental causes becomes much more focused. From the oxidative wounds, our science may more rapidly deduce the cause, treatment and prevention of autism.”

**Reviewer’s Observations:**

When these researchers recognize that mercury poisoning is the major cause of this “oxidative stress,” then perhaps, like this reviewer, they will understand that mercury poisoning is the “disease” and start studying all of the metabolic pathways damaged or corrupted by mercury. Hopefully, that day will come soon.

**C-17** Vojdani A, Pangborn JB, Vojdani E, Cooper EL. Infections, toxic chemicals and dietary peptides binding to lymphocyte receptors and tissue enzymes are major instigators of autoimmunity in autism. *Int J Immunopathol Pharmacol.* 2003 Sep-Dec;16(3):189-99. DG-IV-1

“Similar to many complex autoimmune diseases, genetic and environmental factors including diet, infection and xenobiotics play a critical role in the development of autism. In this study, we postulated that infectious agent antigens such as streptokinase, dietary peptides (gliadin and casein) and ethyl mercury (xenobiotic) bind to different lymphocyte receptors and tissue enzyme (DPP IV or CD26). We assessed this hypothesis first by measuring IgG, IgM and IgA antibodies against CD26, CD69, streptokinase (SK), gliadin and casein peptides and against ethyl mercury bound to human serum albumin in patients with autism. A significant percentage of children with autism developed anti-SK, anti-gliadin and casein peptides and anti-ethyl mercury antibodies, concomitant with the appearance of anti-CD26 and anti-CD69 autoantibodies. These antibodies are synthesized as a result of SK, gliadin, casein and ethyl mercury binding to CD26 and CD69, indicating that they are specific. Immune absorption demonstrated that only specific antigens, like CD26, were capable of significantly reducing serum anti-CD26 levels. However, for direct demonstration of SK, gliadin, casein and ethyl mercury to CD26 or CD69, microtiter wells were coated with CD26 or CD69 alone or in combination with SK, gliadin, casein or ethyl mercury and then reacted with enzyme labeled rabbit anti-CD26 or anti-CD69. Adding these molecules to CD26 or CD69 resulted in 28-86% inhibition of CD26 or CD69 binding to anti-CD26 or anti-CD69 antibodies. The highest % binding of these antigens or peptides to CD26 or CD69 was attributed to SK and the lowest to casein peptides. We, therefore, propose that bacterial antigens (SK), dietary peptides (gliadin, casein) and Thimerosal (ethyl mercury) in individuals with pre-disposing HLA molecules, bind to CD26 or CD69 and induce antibodies against these molecules. In conclusion, this study is apparently the first to demonstrate that dietary peptides, bacterial toxins and xenobiotics bind to lymphocyte receptors and/or tissue enzymes, resulting in autoimmune reaction in children with autism.”

**Reviewer’s Observations:**

While this reviewer understands the validity of the researchers’ findings, he hopes that, in future studies, these researchers will do similar studies on: **a)** a matched group of comparably Thimerosal-containing-vaccine vaccinated children that are not children with autism, and **b)** a matched control group of unvaccinated children to separate out the issues as to which is the major causative factor or factors for the immune responses observed. Based on the existing body of evidence, Thimerosal in Thimerosal-containing vaccines seems to be the primary immune/autoimmune triggering agent.

**C-18** Parran DK, Barker A, Ehrich M. Effects of Thimerosal on NGF Signal Transduction and Cell Death in Neuroblastoma Cells. *Toxicol Sci.* 2005 Jul;86(1):132-40.

“Signaling through neurotrophic receptors is necessary for differentiation and survival of the developing nervous system. The present study examined the effects of the organic mercury compound thimerosal on nerve growth factor signal transduction and cell death in a human neuroblastoma cell line (SH-SY5Y cells). Following exposure to 100 ng/ml NGF and increasing concentrations of thimerosal (1 nM–10 mM), we measured the activation of TrkA, MAPK, and PKC-d. In controls, the activation of TrkA MAPK and PKC-d peaked after 5 min of exposure to NGF and then decreased but was still detectable at 60 min. Concurrent exposure to increasing concentrations of thimerosal and NGF for 5 min resulted in a concentration-dependent decrease in TrkA and MAPK phosphorylation, which was evident at 50 nM for TrkA and 100 nM for MAPK. Cell viability was assessed by the LDH assay. Following 24-h exposure to increasing

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concentrations of thimerosal, the EC50 for cell death in the presence or absence of NGF was 596 nM and 38.7 nM, respectively. **Following 48-h exposure to increasing concentrations of thimerosal, the EC50 for cell death in the presence and absence of NGF was 105 nM and 4.35 nM, respectively.** This suggests that NGF provides protection against thimerosal cytotoxicity. To determine if apoptotic versus necrotic cell death was occurring, oligonucleosomal fragmented DNA was quantified by ELISA. Control levels of fragmented DNA were similar in both the presence and absence of NGF. With and without NGF, thimerosal caused elevated levels of fragmented DNA appearing at 0.01 mM (apoptosis) to decrease at concentrations >1 mM (necrosis). These data demonstrate that thimerosal could alter NGF-induced signaling in neurotrophin-treated cells at concentrations lower than those responsible for cell death. ...

In light of the proclivity of thimerosal to bind any protein containing sulfhydryl groups, it is likely that the effects of thimerosal on differentiation are the result of multiple sites of action. A comparison of the effective concentration at these various sites will be necessary to determine the critical actions of thimerosal, which ultimately result in the disruption of differentiation.”

#### Reviewer’s Observations:

While this reviewer supports the validity of the researchers’ findings here, this reviewer finds that to put things in perspective, the researchers could have also expressed their findings in terms of that relate the level at which significant toxicity were found to the level of Thimerosal in “Thimerosal Preserved” vaccines so that the average reader could more easily see the relative toxicity levels for the experiments to the vaccine levels. Since, in the absence of added nerve growth factor (NFG), the researchers reported, *after 48-hours of incubation*, a calculated “**EC50 for cell death**” Thimerosal concentration of “**4.35 nM**” or  $4.35 \times 10^{-9}$  moles of Thimerosal per liter of solution [ $4.35 \times 10^{-12}$  ~~moles of Thimerosal~~ (x 404.82 g of Thimerosal per ~~mole of Thimerosal~~) per milliliter (mL) of solution] or  $1.76 \times 10^{-9}$  g of Thimerosal per mL [1.76 parts-per-billion Thimerosal or 0.872 ppb mercury from Thimerosal. Thus, these researchers have established a 48-hour toxicity to the cell system for levels less than (<) 2 ppb Thimerosal or less than (<) 1 ppb mercury. Since, in ng per mL (ppb), the nominal level of Thimerosal in a “Thimerosal Preserved” vaccine containing 0.01% Thimerosal is 100,000 ppb, the level in such vaccines is > 56,800 times the toxic level found by these researchers. For a 0.5-mL dose, 50,000 ng of Thimerosal are injected into each person. Even assuming a uniform distribution in the person receiving the vaccine, to reduce the dose to below the toxic level found here, the recipient would have to weigh more than 28.4 kg (62.6 pounds). In the real-world case where the Thimerosal injected accumulates in brain and other lipid-rich cells, the probable minimum recipient weight for a 50,000 ng bolus of Thimerosal to be safe is at least 5 times the modeled level or 142 kg (313 pounds). In any case, injecting 25,000 ng (in the 0.25-mL dose given to babies 6-months and younger) into young children only begins to be truly safe when their weight significantly exceeds 14.2 kg (31.3 pounds) and most 6-month-old and younger children weigh less than half this value – clearly indicating that a single 0.25-mL injection of a Thimerosal-preserved vaccine significantly mercury poisons those to whom it is given. Based on this data, at birth, where babies weighing as little as 1 kg (2.2 pounds), the safe level of Thimerosal, setting a 10-x safety factor, in such vaccines would be less than 0.17 microgram of Thimerosal in a 0.5-mL dose of vaccine or, < 0.3 ppm Thimerosal (< 0.15 ppm mercury).

- C-19** Humphrey ML, Cole MP, Pendergrass JC, Kiningham KK. Mitochondrial Mediated Thimerosal-induced Apoptosis in a Human Neuroblastoma Cell Line (SK-N-SH). *Neurotoxicology*. 2005 Jun;26(3):407-16.

“Environmental exposure to mercurials continues to be a public health issue due to their deleterious effects on immune, renal and neurological function. Recently the safety of thimerosal, an ethyl mercury-containing preservative used in vaccines, has been questioned due to exposure of infants during immunization. Mercurials have been reported to cause apoptosis in cultured neurons; however, the signaling pathways resulting in cell death have not been well characterized.

Therefore, the objective of this study was to identify the mode of cell death in an in vitro model of thimerosal-induced neurotoxicity, and more specifically, to elucidate signaling pathways which might serve as pharmacological targets.

Within 2 h of thimerosal exposure (5  $\mu$ M) to the human neuroblastoma cell line, SK-N-SH, morphological changes, including membrane alterations and cell shrinkage, were observed. Cell viability, assessed by measurement of lactate dehydrogenase (LDH) activity in the medium, as well as the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay, showed a time- and concentration-dependent decrease in cell survival upon thimerosal exposure. In cells treated for 24 h with thimerosal, fluorescence microscopy indicated cells undergoing both apoptosis and oncosis/necrosis. To identify the apoptotic pathway

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associated with thimerosal-mediated cell death, we first evaluated the mitochondrial cascade, as both inorganic and organic mercurials have been reported to accumulate in the organelle. Cytochrome c was shown to leak from the mitochondria, followed by caspase 9 cleavage within 8 h of treatment. In addition, poly(ADP-ribose) polymerase (PARP) was cleaved to form a 85 kDa fragment following maximal caspase 3 activation at 24 h. Taken together these findings suggest deleterious effects on the cytoarchitecture by thimerosal and initiation of mitochondrial-mediated apoptosis. ...

In summary, we have shown that thimerosal can cause mitochondrial-mediated apoptosis in a human neuroblastoma cell line. To our knowledge, this is the first study to chronologically show the mitochondrial, cytosolic and nuclear events associated with thimerosal-mediated toxicity in a non-differentiated neuronal system. Although thimerosal has been shown to alter redox status, further evaluation will be required to determine the effect, if any, these alterations have on the cascade of events reported in this study.”

#### **Reviewer’s Observation:**

**This article has shed more light on the cellular pathways by which this systemic mercury poison, Thimerosal, poisons intracellular components and reinforces how insidious mercury poisoning is at the cellular level.**

- C-20** James SJ, Slikker W 3rd, Melnyk S, New E, Pogribna M, Jernigan S. Thimerosal Neurotoxicity is Associated with Glutathione Depletion: Protection with Glutathione Precursors. *Neurotoxicology*. 2005 Jan;26(1):1-8.

“Thimerosal is an antiseptic containing 49.5% ethyl mercury that has been used for years as a preservative in many infant vaccines and in flu vaccines. Environmental methyl mercury has been shown to be highly neurotoxic, especially to the developing brain. Because mercury has a high affinity for thiol (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 glioblastoma cells that have higher basal levels of intracellular GSH. Thimerosal-induced cytotoxicity was associated with depletion of intracellular GSH in both cell lines. Pretreatment with 100 mM glutathione ethyl ester or N-acetylcysteine (NAC), but not methionine, resulted in a significant increase in intracellular GSH in both cell types. Further, pretreatment of the cells with glutathione ethyl ester or NAC prevented cytotoxicity with exposure to 15  $\mu$ M Thimerosal. Although Thimerosal 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 as possible adjunct therapy to individuals still receiving Thimerosal-containing vaccinations. ...

In summary, we have shown that human glioblastoma cells are more resistant to Thimerosal cytotoxicity than neuroblastoma cells at doses in the low micromolar range and that the resistance is correlated with higher intracellular levels of intracellular glutathione. The significant protection by NAC and glutathione ethyl ester against Thimerosal cytotoxicity suggests the possibility that supplementation with glutathione precursors might be protective against mercury exposures in vivo. Numerous clinical studies have demonstrated the efficacy of NAC in increasing intracellular glutathione levels and reducing oxidative stress in humans ... Since cytotoxicity with both ethyl- and methylmercury have been shown to be mediated by glutathione depletion, dietary supplements that increase intracellular glutathione could be envisioned as an effective intervention to reduce previous or anticipated exposure to mercury. This approach would be especially valuable in the elderly and in pregnant women before receiving flu vaccinations, in pregnant women receiving Rho D immunoglobulin shots, and individuals who regularly consume mercury-containing fish.”

#### **Reviewer’s Observations:**

This reviewer supports the scientific conclusions reached by the authors with respect to Thimerosal cytotoxicity and immediate protection by glutathione and glutathione precursors. This reviewer has reservations about the supplementation strategy unless it is long term and coupled with supplements that promote the “sequestering” and “elimination” of the protein-bound inorganic mercury that forms from the metabolism of the “ethylmercurihydroxide” metabolite of Thimerosal and, to a lesser extent, from the metabolism of the methylmercury compound present in fish and other ingested foods. Furthermore, this reviewer finds the authors’ statement, “Although Thimerosal 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,” to be inaccurate because it fails to note that Thimerosal, at some level, is present in most of the doses of the flu vaccine that given to children as well as more than a half-dozen other in-date U.S.-licensed vaccines that are or may be

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given to children under the age of 18 on the US, including at least three (3) “Thimerosal Preserved” vaccines.

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- C-21** Mutkus L, Aschner JL, Syversen T, Shanker G, Sonnewald U, Aschner M. In Vitro Uptake of Glutamate in GLAST- and GLT-1-Transfected Mutant CHO-K1 Cells Is Inhibited by the Ethylmercury-Containing Preservative Thimerosal. *Biol Trace Elem Res.* 2005 Summer;105(1-3):71-86.

“In summary, we detail the effects of thimerosal on mRNA and protein expression of the predominately astrocytic glutamate transporters GLAST and GLT-1 in a transfected mutant CHO-K1 cell line DdB7. The results indicate that thimerosal is a potent inhibitor of transport activity as measured by D-aspartate uptake. This effect is more pronounced in GLT-1-transfected cells, and it occurs in the presence of selective changes in mRNA and protein expression of GLAST and GLT-1. Given the differential effects on transporter expression, the most likely explanation for the potent inhibitory effects of thimerosal on glutamate transport in CHO cells is a direct inhibitory effect of ethylmercury on transporter activity. Overall, the study provides direct evidence for the potential of thimerosal to alter glutamate homeostasis ...”

**Reviewer’s Observation:**

The importance of this article is that it again shows that “Thimerosal” is disruptive to processes in the central nervous system.

- C-22** Morita M, Higuchi C, Moto T, Kozuka N, Susuki J, Itofusa R, Yamashita J, Kudo Y. Dual Regulation of Calcium Oscillation in Astrocytes by Growth Factors and Pro-Inflammatory Cytokines via the Mitogen-Activated Protein Kinase Cascade. *J Neurosci.* 2003 Nov 26;23(34):10944-52.

“In response to neurotransmitters, astrocytes show various types of calcium increase (transient, oscillatory, and complex), the physiological significance of which is still controversial. To explore this variability, we examined factors affecting the calcium increase pattern in cultured astrocytes and investigated the consequences of the astrocytic calcium response in slice preparations. We found that growth factors (GFs) (EGF plus basic FGF) promoted calcium oscillation in response to glutamate, ATP, or thimerosal (which directly activates the inositol-1,4,5 triphosphate receptor) and that this effect was suppressed by pro-inflammatory cytokines (interleukin-1 $\beta$  or tumor necrosis factor- $\alpha$ ), lipopolysaccharide, or a MEK (mitogen-activated protein kinase) inhibitor, suggesting dual regulation of calcium oscillation in astrocytes by factors affecting brain function and pathology via the mitogen-activated protein kinase (MAPK) cascade. The calcium oscillation was accompanied by enlargement of the calcium store, cell proliferation, and the development of a hypertrophic morphology. The cytokines suppressed GF-induced MAPK-dependent immediate early gene promoter activation, but not phosphorylation of extracellular signal-regulated kinase (ERK), showing that they affected gene regulation by acting on the MAPK cascade downstream of ERK. In slice preparations, a metabotropic glutamate receptor agonist converted the spontaneous neuronal calcium increase, attributable to synaptic transmission, to an oscillatory response similar to that seen in astrocytes in culture, indicating that the calcium response in astrocytes acted as a feedback mechanism on the activity of neighboring neurons. This is the first evidence for a dual regulation of calcium oscillation by physiological factors and for the control of calcium dynamics actually being used in physiological processes.

...

It is reasonable to assume that the response of neurons to glutamate released by astrocytes is dependent on the subtype of glutamate receptor, which can vary outside synapses, and that the inhibitory effects are caused by inhibitory mGluRs (groups II and III). If this were the case, the physiological role of the calcium response and glutamate release by the astrocyte would vary, depending on the structure and topology of the glutamate release site on the astrocyte and the glutamate-receptive site on the neuron. In conclusion, we propose that the soluble factor-mediated regulation of astrocyte calcium dynamics is a novel mechanism for sensing the state of the CNS environment and responding to it by altering the physiology and pathology of the CNS. Additional studies on this regulatory mechanism should provide significant information on how the brain works.”

**Reviewer’s Observations:**

The importance of this article is that it shows that “Thimerosal” directly interferes with calcium-regulated neural processes by binding a key receptor site.

- C-23** Jin Y, Kim DK, Khil LY, Oh U, Kim J, Kwak J. Thimerosal decreases TRPV1 activity by oxidation of extracellular sulfhydryl residues. *Neurosci Lett.* 2004 Oct 21;369(3):250-5.

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“TRPV1, a receptor for capsaicin, plays a key role in mediating thermal and inflammatory pain. Because the modulation of ion channels by the cellular redox state is a significant determinant of channel function, we investigated the effects of sulfhydryl modification on the activity of TRPV1. Thimerosal, which oxidizes

sulfhydryls, blocked the capsaicin-activated inward current ( $I_{cap}$ ) in cultured sensory neurons, in a reversible and dose-dependent manner, which was prevented by the co-application of the reducing agent, dithiothreitol. Among the three cysteine residues of TRPV1 that are exposed to the extracellular space, the oxidation-induced effect of thimerosal on  $I_{cap}$  was blocked only by a point mutation at Cys621. These results suggest that the modification of an extracellular thiol group can alter the activity of TRPV1. Consequently, we propose that such a modulation of the redox state might regulate the physiological activity of TRPV1. ...

In summary, because TRPV1 has been implicated in the transmission of pain, and serves as a sensor for multimodal noxious stimuli ..., the modulation of  $I_{cap}$  by extracellular oxidizing agents reported here will contribute to revealing the mechanisms that regulate the activity of TRPV1 during pathologic conditions ...”

#### **Reviewer’s Observation:**

The importance of this article is that it shows that “Thimerosal” directly interferes with calcium transport and neural transmission by oxidizing sulfhydryls important to the activity of the TRPV1.

- C-24** Burbacher TM, Shen DD, Liberato N, Grant KS, Cernichiari E, Clarkson T. Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methylmercury or Vaccines Containing Thimerosal. “,” *Environ Health Perspect.* 2005;113:1015-21.

“Thimerosal is a preservative that has been used in manufacturing vaccines since the 1930s. Reports have indicated that infants can receive ethylmercury (in the form of thimerosal) at or above the Environmental Protection Agency (EPA) guidelines for methylmercury (MeHg) exposure, depending on the exact vaccinations, schedule, and size of the infant. This study compared the systemic disposition and brain distribution of total and inorganic mercury in infant monkeys following thimerosal exposure with infants exposed to MeHg. Monkeys were exposed to MeHg (via oral gavage) or vaccines containing thimerosal (via i.m. injection) at birth and 1, 2, and 3 weeks of age. Total blood mercury (Hg) levels were determined 2, 4 and 7 days after each exposure. Total and inorganic brain Hg levels were assessed 2, 4, 7 or 28 days after the last exposure. The initial and terminal half-life of Hg in blood following thimerosal exposure was 2.1 and 8.6 days, which are significantly shorter than the elimination half-life of Hg following MeHg exposure at 21.5 days. Brain concentrations of total Hg were significantly lower by ~3-fold for the thimerosal-exposed infants when compared to the MeHg infants, while the average brain-to-blood concentration ratio was slightly higher for the thimerosal-exposed infants ( $3.5 \pm 1.0$  vs.  $2.5 \pm 0.6$ ). A higher percentage of the total Hg in the brain was in the form of inorganic mercury for the thimerosal-exposed infants (34% vs 7%). The current study indicates that MeHg is not a suitable reference for risk assessment from exposure to thimerosal derived Hg. Knowledge of the toxicokinetics and developmental toxicity of thimerosal is needed to afford a meaningful assessment of the developmental effects of thimerosal-containing vaccines. ...

The key findings of the current study are the differences in the disposition kinetics and demethylation rates of thimerosal and MeHg. Consequently, MeHg is not a suitable reference for risk assessment from exposure to thimerosal derived Hg. Knowledge of the biotransformation of thimerosal, the chemical identity of the Hg-containing species in the blood and brain, and the neurotoxic potential of intact thimerosal and its various biotransformation products, including ethylmercury are urgently needed to afford a meaningful interpretation of the potential developmental effects of immunization with thimerosal-containing vaccines in newborns and infants. This information is critical if we are to respond to public concerns regarding the safety of childhood immunizations.”

#### **Reviewer’s Observations:**

The importance of this article is that it confirms that, in the timeframe of the study, the level of long-term mercury poison, bound “inorganic mercury,” accumulating in the Thimerosal-injected baby monkeys’ brains was, on average, more than twice the average level of found in the brain of the baby monkeys fed the same level of methylmercuri hydroxide. In addition, the variability of the level of this “inorganic mercury” in the brains of the Thimerosal-injected monkeys (from 1 to >20 ng/g) clearly indicates a variation in the excretion and metabolism of the monkeys in this treatment group in spite of the “sameness” of their treatment.