CITIZEN PETITION REQUESTING certain actions §
WITH RESPECT TO VACCINES AND OTHER DRUG §
PRODUCTS, CONTAINING ADDED MERCURY, §
IN ORDER TO REDUCE THE HEALTH RISK TO §
SUSCEPTIBLE FETUSES, NEWBORNS, CHILDREN, §
ADOLESCENTS AND ADULTS §

Docket No.: 2007P-

CITIZEN PETITION

I. ACTIONS REQUESTED

Petitioners request:

1. Until the federal government can prove that any and all Thimerosal-containing products have a 100X safety margin with respect to the risk of causing any level of neurological and other organ damage in newborns and children under 9 years of age, we request, under 42 U.S.C. Section 300aa-27, the Secretary of the Department of Health and Human Services or the Acting Commissioner of the Food and Drug Administration to immediately issue an order proscribing the use of disease-preventive Thimerosal-containing vaccines or other similarly preserved medical products in newborns, children under the age of 9 years, and pregnant women unless:

   a. The level of mercury in said vaccines, other pediatric drugs, and drugs administered during pregnancy is not more than 0.05 microgram (µg) per dose, or

   b. For other mercury-containing drugs, not more than 0.1 µg of mercury per milliliter (mL) for liquids or gram (g) for solid, semi-solid and other drugs.

2. Until the federal government can establish that any and all Thimerosal-containing products
have no less than a 100X safety margin\textsuperscript{1} with respect to the risk of causing any level of neurological damage to developing fetuses, newborns, children and adolescents, we request that the Commissioner of the Food and Drug Administration move to withdraw the approval (under 21 U.S.C. 355(e)) of any FDA-approved drug product (e.g., ophthalmic products) and revoke the license (under 42 U.S.C. 262(a)(2)(A)) of any FDA-licensed biological product (e.g., vaccines and other preserved serological preparations) that contains Thimerosal, or any other mercury-based neurotoxic compound, as a “preservative,” “adjuvant” or “impurity” unless the federal government and/or the manufacturer of said medical product can prove, at its maximum level, its safety and efficacy as a preservative, adjuvant or impurity in scientifically sound animal model studies using appropriate susceptible animal strains as the test subjects.

\textbf{Note:} We make this request because, as all parties (federal government, industry, academia, and the public) know, all such current products lack the appropriate safety studies. Despite the epidemiologically-based 2004 report by the Institute of Medicine (IOM), there is substantial inferential evidence, and a growing body of human toxicological exposure and animal data on Thimerosal and related-compounds, that has established Thimerosal and other mercury-based compounds can cause neurological and other tissue damage in susceptible individuals at levels of exposure above 0.01 microgram (µg) of mercury per kilogram (kg) \{0.01 parts-per-million\}. Furthermore, the concentration of 0.1 parts-per-million \{0.0001 mg / L\} has been established as a maximum ethylmercury concentration in water for human consumption.\textsuperscript{2} Similarly, for the other recognized hazardous alkyl mercury compound, methyl mercury, the current EPA (United States Environmental

\textsuperscript{1} McMillan DE. Risk assessment for neurobehavioral toxicity. \textit{Environmental Health Perspectives} 1987; 76; 155-161. [See Table 4. Guidelines for the use of uncertainty factors, article's page 157]

\textsuperscript{2} Arctic Council Action Plan to Eliminate Pollution of the Arctic (ACAP): Russian Federal Service for Environmental, Technological and Atomic Supervision, Danish Environmental Protection Agency. \textit{Assessment of Mercury Releases from the Russian Federation}. Copenhagen, Denmark: Danish Ministry of the Environment, 2005.
Protection Agency) consumption guideline, which has subsequently been shown to have, at best, no safety margin for "methyl mercury" from all sources for "infants" is not more than 0.1 µg mercury/kg/day. Finally, based on the findings in a well-controlled comparative study of "methylmercury" and "ethylmercury" given to swine, the ethylmercury compound was significantly more toxic than the methylmercury compound.

3. Issue:

a. Pursuant to the statutory authority set forth in 42 U.S.C. 262(d)(1) and the procedures set forth in 21 C.F.R. Section 7, governing recalls, an immediate Class I, or Class II, recall

3 Based on the information provided on the estimated safety limit for chronic toxicity effects arising from the intake of methyl mercury at http://www.epa.gov/ttn/atw/hltheflmercury.html including the following (bolding added for emphasis), "The RfD [oral reference dose: 'An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure of a chemical to the human population (including sensitive subpopulations) that is likely to be without risk of deleterious noncancer effects during a lifetime']) for methyl mercury is 0.0001 mg/kg/d [equivalent to 0.1 µg/kg/day] based on developmental neurologic abnormalities in human infants.(13)," and "EPA has medium confidence in the RfD due to: (1) medium confidence in the studies on which the RfD was based because the benchmark dose approach allowed use of the entire dose-response assessment, and the results of laboratory studies with nonhuman primates support the quantitative estimate of the no-observed-adverse-effect-level/lowest-observed-adverse-effect-level (NOAEL/LOAEL) range of the benchmark dose that was indicated by the human studies; and (2) medium confidence in the database.(13)," and its reproductive/developmental effects.


6 The recall classes are defined in 21 C.F.R. Sec. 7.3 Definitions which, in part, reads (with bolding for emphasis):
for, and order the destruction of, all batches of multi-dose vaccines and other mercury-containing drug products: i) containing a mercury level of more than 0.05 microgram per dose or 0.00001 % (0.1 part per million [ppm]; 0.1 µg per milliliter [mL] or 0.1 µg per gram [g]), whichever is higher, and ii) having approved alternatives that contain not more than 0.000005% mercury, and

b. If the “Class II recall” option is chosen, an open letter to all physicians advising them that they should destroy any of the drug products recalled in Point 3.a.

We make this request because:

- The current 0.01 % Thimerosal levels (equivalent to about 50 µg of mercury per mL or, for 0.5-mL-dose vaccines, 25 µg of mercury per dose) in drugs are now a proven health hazard to susceptible individuals of all ages,

- For a single dose, the current 0.01 % Thimerosal levels in multi-dose vaccine formulations (equivalent to about 50 µg mercury per 1-mL dose, 25 µg of mercury per 0.5-mL dose, or 12.5 µg of mercury per 0.25-mL dose):
  - Obviously exceed the total recommended mercury-equivalent daily intake level for infants and children under 13.3 kg (29.3 pounds) for the 0.25-mL dose

“(m) Recall classification means the numerical designation, i.e., I, II, or III, assigned by the Food and Drug Administration to a particular product recall to indicate the relative degree of health hazard presented by the product being recalled.

(1) Class I is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.

(2) Class II is a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

(3) Class III is a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences.”

[Note: Since 2004 subsequent animal studies and, in late 2006 and 2007, human studies have now clearly established that there is a definite link between the administration of 0.01%-Thimerosal-preserved vaccines and mercury poisoning in those diagnosed with neurodevelopmental disorders, including autism, that are recognized “serious adverse health consequences,” in susceptible individuals, the only issues remaining are whether, or not, these mercury-related “serious adverse health consequences” are “medically reversible adverse health consequences.” If deemed medically reversible, then a Class II recall is indicated; if not, then a Class I recall should be issued. Since the recent studies have proven causality, it is no longer permissible for any vaccine containing more than 0.000004 % Thimerosal (0.02 ppm mercury) to be left in commerce where it can be administered unless no “no Thimerosal” vaccine is currently licensed and the vaccine has been proven to be effective (not just have putative efficacy) in actual disease-outbreak situations.]
level, 26.9 kg (59.3 pounds) for the 0.5-mL dose and 53.3 kg (117.5 pounds) for the 1-mL dose.

➢ Have been **proven**, in one animal study using “susceptible” (autoimmune disease-sensitive) SJL/J mice exposed to similar relative levels and at similar relative developmental times matching those factors in humans⁷, to:

- **Elicit** the same etiology as “autism spectrum disorders” **and**
- **Alter** the brain structures in the exposed mice.

[Note: The study did **not** find either adverse effect in the two similarly treated mouse strains, C57BL/6J and BALB/cJ, used as controls. These control strains **obviously did not** have the same mercury-poisoning sensitivity.]

➢ Have been **proven**, in one animal model study using “susceptible” (autoimmune disease-sensitive) female (NZB x NZW)F1 (ZBWF1) mice exposed to similar relative levels that match those factors in humans⁸, to:

- **Elicit** the same etiology as “autoimmunity” **and**
- **Alter** the tissue structures in the exposed mice.

❖ Such a recall will reduce the risk of adverse reactions that, **under the authority conferred upon you by the National Childhood Vaccine Injury Act of 1986**, you have been mandated by Congress to minimize.

4. **Until medical products containing Thimerosal and other mercury-based preservatives can be removed from the market and be replaced by a suitable non-neurotoxic alternative, or, reformulated to contain not more than 0.05 microgram of mercury per dose of vaccine or, for other drugs, not more than 0.01 microgram of mercury per milliliter or gram, or said current**

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⁸ Havarinasab S, Hultman P. Alteration of the spontaneous systemic autoimmune disease in (NZB x NZW)F1 mice by treatment with thimerosal (ethyl mercury). *Toxicol Appl Pharmacol* 2006; 214: 43-54.
products can be proven to have not less than a 100X safety margin to protect mercury-poisoning-susceptible individuals, we request that the Commissioner of the U.S. Food and Drug Administration issue orders requiring:

a. All such medical products, including all OTC products, to contain a clear "Black Box" warning of the potential risk for neurological damage to susceptible fetuses, newborns, and children on all of said medical product's labeling,

b. For prescription medical products, including vaccines, preserved with mercury-based compounds that are administered to newborns, children, and all women of child bearing age, informed written consent be obtained, as appropriate, from all such patients or their guardians before any such medical product is administered to any covered patient, and that the consent forms used should: i) clearly state the possibility of neurological injury and ii) permit patients or their guardians, as appropriate, to postpone, for any reason, or decline, for religious or other stated health reasons, the administration of said medication, and

c. All vaccines remaining in commerce after 1 July 2008 that contain more than 0.05 micrograms of mercury per dose of drug product and all other drugs containing more than 0.1 microgram of mercury per milliliter or gram to be recalled and destroyed.

5. Finally, on the grounds that the manufacturer must prove drug safety for whomever may be treated with each drug product, we request the Commissioner of the Food and Drug Administration issue a policy that requires any preservative or other component of a vaccine, Rho(D) injection, flu shot, or other FDA-regulated product administered to humans or animals to be a substance that either:

a. Is not mercury based, or

b. When the manufacturer of such medical products provides proof that said preservative or other component must be mercury-based because, for multi-dose vials, there is no
other less-bioaccumulative preservative system or, for the manufacturing process, no less-bioaccumulative process sterilant that can be used, the level of mercury-based preservative or other mercury-containing component in the formulation must be proven (in scientifically sound repetitive acute and/or intermediate-term chronic-toxicity studies using “susceptible” animals [e.g., SJL/J mice and female (NZB x NZW)F1 (ZBWF1) mice]) to be sufficiently nontoxic:

i. At levels not less than one hundred (100) times the maximum component level of that mercury-based compound in any medical product that is intended to be administered to, or taken by, women of child-bearing age, newborns and children under the age of 15 years or, for any person, is intended to be taken for extended periods of time (e.g., ophthalmic eye drops approved for the treatment of a chronic eye condition), or

ii. At levels not less than thirty (30) times the maximum component level of that mercury-based compound in any medical product that is intended to be administered to or taken by adults and children 15 years of age or older, other than women of child-bearing age, at widely separated intervals (e.g., vaccines) or for short periods of time (e.g., prescription post-operative eye drops).

II. PETITIONERS

The representatives for the Coalition for Mercury-free Drugs (CoMeD), a group of individuals who support the withdrawal of drug products containing added mercury-based compounds unless they have been unequivocally proven safe for all susceptible individuals, bring this petition.

CoMeD is a broad-based advocacy group dedicated to:

a. The immediate removal of drug products whose formulations contain more than 0.05-µg-per-dose levels of mercury from the medical products approved or licensed for use in the
United States because of the proven harm which higher levels of mercury have now been established to cause and

b. **Longer term**, banning the addition of: i) mercury or ii) mercury-based materials and components to the formulation of all medical products unless the presence of said added mercury is proven, in appropriate toxicological testing panels requiring at least a 100-fold safety margin, to be safe for administration to susceptible individuals.

CoMeD's current position on mercury is based on the proven harm that Thimerosal (mercury) causes at Thimerosal levels of less than one (1) part-per-billion (1,000,000,000) [< 0.001 ppm; < 0.001 µg/mL, < 0.0000001 %] (mercury levels of less than 0.5 parts per billion [< 0.0005 ppm; < 0.0005 µg/mL, < 0.00000005 %]) to growing neurological structures and cellular genetic material.9

In addition, in comparative studies, ionic mercury was proven to cause damage to and to destroy growing neurological structures at concentrations of approximately twenty (20) parts per billion (1,000,000,000) [0.02 ppm; 0.02 µg/mL] when comparable levels of other ionic heavy metals (i.e., cadmium, lead, and manganese) and ionic aluminum have been shown to cause no observable harm.10

Finally, for bioaccumulative poisons that are also teratogens, mutagens, carcinogens, and immune-system poisons with tissue (e.g., brain and kidney) half-lives that may or do exceed 15 years,11 like Thimerosal and other organic mercury compounds, prudence dictates that the testing safety factor for such should be **not less than** 100.

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III. **STATEMENT OF GROUNDS**

A. **Introduction**

We urge you to honor our requests because:

❖ They arise out of our experience- and science- based concerns for the public health.

❖ *Based on the body of scientifically sound evidence we will cite*, these actions are required to guarantee the uncompromised development of **all** children before, at, and after their birth in this generation and future generations.

Therefore, we implore you to:

❖ Review the issues that we herein identify.

❖ Carefully consider the information and documentation submitted with this petition.

❖ Act to remove all mercury-containing compounds from all medical uses un**less**, with a 100X safety margin, there are scientifically sound and appropriate toxicological studies to prove that the usage of a given mercury-containing drug product formulation is "**sufficiently nontoxic**" when administered at the highest dose at the highest frequency for the longest time permitted to the most susceptible humans for whom the drug is intended— the "**Safety Proven**" case.

B. **Safety Not Proven**

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12 21 C.F.R. "Sec. 610.15 Constituent materials. [With bolding added for emphasis.]

(a) Ingredients, preservatives, diluents, adjuvants. All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. **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**, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Poliovirus Vaccine Live Oral; viral vaccines labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume in volume (v/v) glycerin. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or
1. Introduction

One of the fundamental tenets of the statutes governing drugs is that the manufacturer of a drug has an absolute duty to prove that a given drug is safe.

Moreover, given the U.S. Supreme Court's unanimous 1988 decision\(^\text{13}\) that rested on an affirmation that the administrative discretion of the FDA and any other federal administrator is limited by the applicable governing policies, laws (regulations) and statutes, the FDA has no legal discretion to approve any drug, including any vaccine, where the manufacturer has failed to prove the drug’s safety to the standard minimums set forth by law.

Since the only currently approved use for Thimerosal in a drug formulation is as a "preservative,” the applicable minimum safety standard for all such is the safety standard set forth in the 21 C.F.R § 610.15(a), “...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, …”\(^\text{14}\)

\(^\text{13}\) Kevan Berkovitz, a Minor by his Parents and Natural Guardians Arthur Berkovitz, et ux., et al., Petitioners, v. UNITED STATES. Case No. 87-498. 108 S.Ct. 1954, 100 L.Ed.2d 531, 56 USLW 4549. (Cite as: 486 U.S. 531, 108 S.Ct. 1954.)

\(^\text{14}\) 21 C.F.R. “Sec. 610.15 Constituent materials. [With bolding added for emphasis.]
(a) Ingredients, preservatives, diluents, adjuvants. All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. 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, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Poliovirus Vaccine Live Oral; viral vaccines labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume in volume (v/v) glycerin. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. The amount of aluminum in the recommended individual dose of a biological product shall not exceed:
(1) 0.85 milligrams if determined by assay;
(2) 1.14 milligrams if determined by calculation on the basis of the amount of aluminum compound added; or
(3) 1.25 milligrams determined by assay provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Center for Biologics Evaluation and Research.”

Coalition for Mercury-free Drugs (CoMeD)  
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Given the preceding realities, unless drug product manufacturers can provide toxicological proof of safety to the standard “sufficiently nontoxic …” for each drug-product formulation to which, at any step in processing, Thimerosal or any other mercury-containing compound is added where the mercury-compound level present in the formulation used for the toxicological tests proving safety was at 100 times the nominal maximum level in the finished formulation to assure an adequate safety margin, then those drug product formulations, including vaccines and other biological products, failing to be proven “sufficiently nontoxic …” should have their approval and/or licensing revoked and all such products in commerce should be recalled and destroyed, on the grounds that “safety was not proven” by the drug product manufacturer to the applicable legal standard minimum established for the safety of all drug products containing any added mercury compound.

2. **General Background - Thimerosal**

The compound, ethyl(2-mercaptobenzoato-S)mercury sodium salt or, more commonly named, sodium ethylmercurithiosalicylate, patented as a topical anti-infective in 1928 and known by many trade names, including Thimerosal, Merthiolate, and Thiomersal, has been used since the 1930’s.

Subsequently, Thimerosal came to be widely accepted as a “preservative” component in some of the vaccines and other drugs intended for use in humans.

Moreover, though not labeled as such, Thimerosal (at levels from 0.01 % [100 ppm] down to “0.0002 % [2 ppm]” in some vaccine formulations) also appears to function as an immune-system “adjuvant.”

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(3) 1.25 milligrams determined by assay provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Center for Biologics Evaluation and Research.”


From the 1980’s to present, the Centers for Disease Control and Prevention (CDC) and the FDA have allowed: a) the administration of Thimerosal-preserved Rho(D) and other biological preparations to pregnant women and b) the immunization of newborns and young children with Thimerosal-preserved vaccines that, in both instances, contain levels of Thimerosal that exceed EPA’s implicit safety guideline for mercury exposure.

Today, a range of multi-dose vaccines and related biological products that contain levels of Thimerosal above 0.001 % (> 10 ppm) are still produced, licensed or approved, and available for unrestricted use in humans.

3. Petitioners’ General Concerns

Of general concern to these petitioners are the facts that:

a. Today, Thimerosal’s mercury-containing metabolites, ethyl mercury and ionic mercury, are known toxins at levels below 1 part-per-billion (0.001 ppm; 0.001 µg/mL in liquids or 0.001 µg/g in solids; 0.0000001%) and

b. When Thimerosal is present at 0.01 %, as it commonly is in multi-dose vaccine formulations and other similarly preserved biological preparations, the effective level of “mercury” added to such formulations is about 50 parts per million (50 ppm; 50 µg/mL or 50 µg/g).

In spite of the preceding facts, the manufacturers have failed, as far as we have been able to ascertain, to establish the intrinsic safety of formulations containing added Thimerosal, a known neurotoxic compound, at the 0.01% level or, for that matter, at lower levels.

Petitioners find that the safety of each such formulation has not been scientifically established.


in the appropriate rigorous comparative toxicology studies (comparing the acute, chronic and reproductive toxicity of the formulation with added Thimerosal [at 100 times the finished formulation’s target level] to the toxicity of the same formulation without Thimerosal) using an appropriate mercury-susceptible cellular or animal model.

Inexplicably, the preceding safety-study data is deficient or non-existent even though the regulations for drugs, including vaccines and other biological preparations classified as drugs, explicitly require that all drugs (as that term is defined in 21 U.S.C. Section § 321(g)(1), including any component used in a drug [21 U.S.C. § 321(g)(1)(D)]) must be safe (based on the definition of safe in 21 U.S.C. § 321(u)) and effective in humans and animals.

In addition, the regulations governing “Preservatives in Vaccines” (contained in Section 610.15 of the Code of Federal Regulations [21 C.F.R. § 610.15]) explicitly require that “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”.

16 21 U.S.C. § 321(g)(1), “The term ‘drug’ means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). . .”

17 21 U.S.C. § 321(u), “The term ‘safe’ as used in paragraph (s) of this section and in sections 348, 360b, and 379e of this title, has reference to the health of man or animal.”

18 21 C.F.R. “Sec. 610.15 Constituent materials. [With bolding added for emphasis.]
(a) Ingredients, preservatives, diluents, adjuvants. All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. 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, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Poliovirus Vaccine Live Oral; viral vaccines labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume in volume (v/v) glycerin. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. The amount of aluminum in the recommended individual dose of a biological product shall not exceed:
(1) 0.85 milligrams if determined by assay;
(2) 1.14 milligrams if determined by calculation on the basis of the amount of aluminum compound added; or
Thus, as far as we have been able to ascertain, neither the maximum level of Thimerosal present in today’s Thimerosal-preserved drug products (0.01% [100 micrograms per milliliter or gram of drug product]) nor any lower Thimerosal level has been proven safe.

In contrast, we now know:

❖ Scientifically sound experimental studies have proven the toxicity of Thimerosal and its metabolites, ethyl mercury and mercuric ion, at “mercury” levels below 1 part-in-a-billion (< 0.001 ppm; < 0.001 µg per mL or g; < 0.00000001%), and

❖ There are NO properly designed experimental studies [using today’s science and animal models that, to the best of our understanding, mimic growth patterns and maturational changes in humans] that:

a. Address susceptible fetuses, newborns, children, adolescents and adults, and

b. Have proven the human safety (no acute or chronic effect) for Thimerosal at 10,000 ppm (1.0 %) in each biological product formulation so that the current 0.01 % level permitted in multi-dose formulations could be presumed, with a 100-fold safety margin, to be “sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to” any person who may be given such drug products, or

c. For that matter, have proven the human safety (no acute or chronic effect) for Thimerosal at 400 ppm (0.04 % [0.02 % mercury, 200 µg/mL]) in the product formulation so that the current maximum “trace” levels (0.0004% [0.0002% mercury, 2 µg/mL]) in the “single dose” and/or “trace Thimerosal” formulations (e.g., “trace Thimerosal” influenza vaccines produced for the 2006-2007 influenza season by GlaxoSmithKline and now Novartis’ Evans subsidiary) could be presumed, with a 100-

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(3) 1.25 milligrams determined by assay provided that data demonstrating that the amount of aluminium used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Center for Biologics Evaluation and Research.”
fold safety margin, to be “sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to” any person, including susceptible individuals of all ages, who may receive such drug products.

Today, in many cases, the level of Thimerosal has been reduced in, and, in several instances, eliminated from, pediatric “single dose” vaccine formulations.

However, in the case of drug products with the “trace” levels of Thimerosal (not more than 0.0004 % [4 ppm]), there is no scientifically sound or regulatory permissible justification for the continued use of Thimerosal, or any other, known, “sub-ppm-level” neurotoxin or bioaccumulative neurotoxin precursor as:

a. A “preservative” (Thimerosal’s only FDA-approved use in vaccines), or
b. An “adjuvant” (a clearly unapproved use) or
c. A “permissible contaminant carried over from a previous processing step” (an implicit claim for the current “mercury free” vaccines that contain Thimerosal at “trace” levels).

The preceding is the case because, at Thimerosal’s current maximum “trace” level (not more than 2 µg of Thimerosal [1 µg of mercury] per 0.5-mL dose [not more than 0.0004 %]) in “trace Thimerosal” vaccine formulations, Thimerosal does not meet the accepted United States Pharmacopeia’s (USP’s) definition of a preservative. [Note: The “0.01 % (100 µg per mL) Thimerosal” present in the current “multi-dose” vaccine formulations is represented to meet the USP’s definition even though some studies suggest that, at 0.01%, Thimerosal is, at best, a marginal preservative.]

Moreover, there are other suitable, less neurotoxic and non-bioaccumulative compounds that: a) are used as preservatives, b) have apparently been proven to be safe and effective for use, and c) are being used, in vaccines and other biological drugs (e.g., benzethonium chloride, phenol, and 2-phenoxyethanol).

4. Thimerosal Usage, Claimed Nontoxicity and Observed Toxicity — 1928 through the 1940s
Kharasch of College Park, Maryland, working in collaboration with Eli Lilly and Company (Lilly) at the University of Maryland, filed a patent in 1928 for an alkyl mercuric sulfur compound in Indianapolis, Indiana.19

In his patent, Kharasch claimed that compounds such as Thimerosal were, "...well-suited for intravenous injection...(and) effective therapeutically as germicides..."

Shortly thereafter, with the declaration that Thimerosal was "well-suited" for administration to humans and "effective" as a germicide, Lilly began to manufacture and market this new product.

In 1930, Smithburn and his colleagues recorded observations made during human clinical experiments using Thimerosal to try to treat meningitis victims.20

In this article, these researchers noted, "the treatment has remained essentially the same throughout the epidemic."

Smithburn and his colleagues then described the use of Thimerosal in an experimental effort to treat the disease.

Specifically, they stated:

"Intravenous administration of antiseptic solution was tried and found wanting despite the in vitro activity of the agent."

Smithburn and his colleagues also reported that efforts were made to combat positive nasopharyngeal cultures with Thimerosal.

They detailed a procedure to address this source of infection, applying ephedrine sulphate in each nostril followed by Merthiolate (1 part per 4000 strength) twice daily.

It was noted that, after the institution of this therapy, no nasopharyngeal cultures were positive.

However, Smithburn et al. also noted that the treatment was "symptomatic."

In light of this preliminary research, early concerns were raised about Thimerosal:

"...in view of our experience with the Merthiolate solution, we have to know pretty definitely what to expect from Merthiolate ointment and jelly before they are put on the market..."\textsuperscript{21}

Moreover, it was felt:

"Our experience with the solution ought to serve as a warning and certainly in the face of that warning we ought not to advocate the use...without some pretty definite evidence that we will not repeat our solution experience"\textsuperscript{22}.

Despite the preceding concern, \textit{commenting on the toxicity of Thimerosal}, in 1931, Eli Lilly researchers Powell and Jamieson reported:

"Toxicity in man. Merthiolate has been injected intravenously into 22 persons in doses up to 50 cubic centimeters of 1\% solution... The toleration of such intravenous doses indicates a very low order of toxicity of Merthiolate for man. This information has been supplied through the kindness of Dr. K.C. Smithburn of Indianapolis who has had occasion to use Merthiolate in a clinical way. Dr. Smithburn stated in these cases 'beneficial effect of the drug was not definitely proven. It did not appear, however, to have any deleterious action when used in rather large doses intravenously when all the drug entered the vein.'"\textsuperscript{23}

However, \textit{upon closer inspection}, these statements and the conclusions by Powell and Jamieson in 1931, reveal that significant information regarding their clinical trial experience with Thimerosal was \textit{not} published.

First, in their 1931 article, Powell and Jamieson failed to reveal that the subjects evaluated by Smithburn and his colleagues in 1930 had, \textit{in fact}, had meningitis, and were \textit{not} healthy, a revelation that would have called into question Powell and Jamieson's conclusions regarding the nontoxicity of Thimerosal.

It should also be noted that Powell and Jamieson provided a table in their 1931 article in which the 22 subjects injected with Thimerosal and their dosages were identified.

\textsuperscript{21} May 2003, Subcommittee on Human Rights & Wellness of the Government Reform Committee, US House of Representatives (Chairman Dan Burton -- following a 3 year congressional investigation), "Mercury in Medicine -- Taking Unnecessary Risks" pgs 1-80.

\textsuperscript{22} May 2003, Subcommittee on Human Rights & Wellness of the Government Reform Committee, US House of Representatives (Chairman Dan Burton -- following a 3 year congressional investigation), "Mercury in Medicine -- Taking Unnecessary Risks" pgs 1-80.

\textsuperscript{23} Powell HM, Jamieson WA. Merthiolate as a germicide. \textit{Am J Hyg} 1931; 13: 296-310.
These subjects, based upon the information provided in the table, received massive doses of mercury from intravenous administration of Thimerosal.

The table notes that approximately one-third of the patients were followed for only one day after the therapy.

However, the published table failed to note that, most probably, this follow-up period was so short because these patients died.

The table also noted only one patient was followed for 62 days.

This maximum follow-up length of 62 days was far too short to accurately discern any chronic damage produced by the mercury, because mercury toxicity manifests fully only several months after exposure.

The study was also flawed because any neurological and/or other damage observed was likely attributed to the meningitis rather than the Thimerosal exposure.

Additionally, Powell and Jamieson specifically commented in their 1931 paper that they evaluated patients, in particular, for shock or anaphylaxis-type immediate reactions to the administration of Thimerosal.

It is important to note that, though they do occur, these outcomes are not common initial-exposure symptoms for mercury toxicity in humans.

Second, it is also apparent that Powell and Jamieson failed to emphasize their disturbing animal toxicity data.

In fact, Powell and Jamieson had already determined that administration of low-mg doses of Thimerosal per kg of bodyweight in several different animals was acutely toxic and resulted in significant numbers of animals dying within days of exposure.

Regarding the reported conclusions reached by Powell and Jamieson in their 1931 paper, it was even commented that:
"Considering the type of patient involved, one might question these observations (the appearance of no deleterious action) as providing adequate indication of any harmful effects of high doses of Merthiolate in humans, in particular, more long term effects."24

In 1932, Kharasch filed a second patent application in an effort to acknowledge the potential dangers of the germicide/antiseptic he had developed.25

Kharasch stated in this second patent:

"...I will describe my invention more specifically in connection with that one of such compounds which is now in most general use. That is sodium ethyl mercuri-thiosalicylate, which is known on the market as Merthiolate..."

According to Kharasch, when Thimerosal:

"...is first made, it is entirely bland, both to the skin and mucous membrane. However, it is found that on standing... the solution loses its blandness and acquires certain burning properties; which make its use as an antiseptic and bactericide less desirable."

In describing the chemical basis for Thimerosal’s ability to acquire “certain burning properties,” Kharasch detailed an important discovery regarding the decomposition products of Thimerosal.

Kharasch recorded that if:

"...such for instance as for sodium ethyl mercuri-thiosalicylate, is allowed to stand, there is a dissociation of a few of the molecules at the bond between the sulphur and the ethyl mercury radical, producing a small quantity of resultant ions...”

and:

"However, on account of the invariable presence of oxygen, and of a catalyst such as copper, the sulphur-containing ion...is oxidized to the di-thio compound... The formation of the di-thio compound removes these sulphur-containing ions from the...mixture...so that progressively more ionization of the alky mercuric sulphur compound occurs... This process results in an excess of the mercuri ions such as C2H5–Hg++ -- which react with the hydroxyl ions present in the solution to form C2H5– Hg++ -- 'OH.'"

Furthermore, Kharasch also stated in the second patent that the C2H5– Hg++ -- 'OH breakdown product of Thimerosal might mediate adverse reactions in humans.

These observations are important because they demonstrate knowledge that, when dissolved in an aqueous environment, Thimerosal would break down, in fairly rapid order, to produce ethylmercury hydroxide and thiosalicylate, and that the ethylmercury breakdown product was the one mediating Thimerosal toxicity.

In 1935, Kharasch applied for a third patent for “organo-mercuri-sulfur compounds.”

In this third patent, Kharasch acknowledged Thimerosal’s ineffectiveness and adverse effects in clinical practice exceeded what he had reported in all of his previous statements:

“It is the object of my invention to stabilize more effectively than has heretofore been done certain antiseptic and bactericidal...compounds, which without such stabilization tend to form disassociation products and to thereby both lose their effectiveness as antiseptic germicides and to develop certain medicinally undesirable properties.”

In 1935, some of the first serious safety concerns were raised regarding Thimerosal.

Specifically, researchers reported:

“...reaction in about 50% of the dogs injected with serum containing dilutions of Merthiolate, varying in 1 in 40000 to 1 in 5000, and we have demonstrated conclusively that there is no connection between the lot of serum and the reaction. In other words, Merthiolate is unsatisfactory as a preservative for serum intended for use in dogs.”

They also noted, regarding the reactions observed in dogs following administration of Thimerosal-containing serums: “...in some instances, the reaction is extremely severe.”

These remarks concluded with:

“I might say that we have tested Merthiolate on humans and find that it gives a more marked...reaction than does phenol or tricresol”.

Additionally, in 1935, Salle and Lazarus determined Thimerosal was 35.3-times more toxic to embryonic cells than to the bacterial cells that Thimerosal was supposed to kill.

Soon after this 1935 publication by Salle and Lazarus, in 1937, Cummins documented the first

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reports of Thimerosal-induced poisonings in animal model systems.29

Specifically, he described:

"...two sets of 7 flasks each were treated with an amount of Merthiolate varying in dilution from 1 to 100 to 1 in 10 million of the medium in each series... The guinea pigs inoculated with 1 c.cm. of the mixtures after 24 hours all died; the first of Merthiolate poisoning..."

In 1939, Welch, working for the US FDA, expanded the evaluation of the toxic action of potential preservatives, including Thimerosal, in mammalian tissue culture experiments.30

By comparing the toxicity of Thimerosal with the toxicity of other germicide compounds such as phenol or iodine, Welch reported that Thimerosal was, by several orders of magnitude, the most toxic compound tested.

In addition, in 1940, Welch and Hunter, while employed by the US FDA, continued their toxicity research on germicides and reported the relative toxicity indices of germicides using human and guinea-pig blood.31

The researchers determined the toxicity index for each germicide tested by comparing the highest dilution producing inhibition in human cells or in guinea pig cells with the highest dilution that was bactericidal for Staphylococci.

Their experiments showed that Thimerosal was, in fact, considerably more toxic for human cells than bacterial cells (toxicity index = 5.7).

Furthermore, they observed, among the 10 germicides tested, that Thimerosal had the ninth worst toxicity index.

With regard to Thimerosal, the researchers concluded:

"It becomes obvious then that if any antiseptic destroys the function of the leukocyte much more readily than it kills bacteria there is little hope that it act efficiently as a chemotherapeutic agent."

In 1941, Kinsella described a cases-series of 13 patients with bacterial endocarditis that received Thimerosal treatment.\textsuperscript{32}

He observed that all patients receiving the Thimerosal treatment died, and that, following autopsy, some patients were found to have died of mercury poisoning from the Thimerosal treatment.

For example, one report stated:


In light of a determination that the treatment with Thimerosal produced mercury poisoning in humans, the suggestion was made to significantly limit Thimerosal exposure in humans because of Thimerosal's toxicity and other potential hazards.

Despite the aforementioned concerns, the United States Government purchased large amounts of Thimerosal in the 1940s (1941–1945) for use in the war effort.

During this time, the US Army evaluated the use of Thimerosal as a preservative in blood products.

On 20 February 1941, the National Institutes of Health issued minimum requirements for normal human plasma, indicating that a sufficient amount of a suitable preservative should be added to the product.\textsuperscript{33}

In the first of several meetings of the Subcommittee on Blood Substitutes of the US Army, it was noted that the Blood Transfusion Association of New York had found Thimerosal was unsatisfactory as a preservative for blood.

Specifically, Dr. Kendrick reported that the committee had considered the 1940 case in which

a large percentage of liquid plasma containing 1:10,000 Thimerosal, which had been collected in New York City, arrived in Britain, contaminated with viable microorganisms.\textsuperscript{34}

At that time, a publication that questioned Thimerosal as a "preservative" concluded:

"In a recent study of protein sulphhydryl groups Hellerman, Chinard and Deitz point out that organometallic compounds of the type R-Hg-X...form poorly dissociated protein mercaptides by combination of the organic mercurial with proteins and thiol groups. According to Fildes the formation of such mercaptides is the basis for the bacteriostatic action of mercury. Such sulphhydryl groups are present, however, not only in bacteria but in plasma and other proteins. Bacteriostatic action of such organomercuric compounds in the presence of serum is therefore largely prevented by competition of reactive groups on the serum proteins for the mercury. This presumably is the basis of the finding that the 'activity of a mercurial antiseptic in serum is reduced to 0.33-0.0007 percent of its activity in saline.' Ignoring these chemical facts can be responsible for very serious occurrences, such as the arrival in England of plasma 'preserved' with 1:10,000 Merthiolate containing viable microorganisms... In our experience 1:10,000 Merthiolate has not been able to insure the sterility of stored liquid plasma. The contaminations reported in this paper in plasma-saline mixture containing 1:10,000 Merthiolate are sufficient to be an argument against its use. The material found to be contaminated when tested after its arrival in England is further evidence that 1:10,000 Merthiolate cannot be considered the ideal preservative...\textsuperscript{35}

Weighing these concerns, some of the subcommittee members argued that plasma was best stored without any preservative at all.

However, a recommendation to this effect was waived when the subcommittee realized that commercial firms were not inclined to process plasma without a preservative.

Then, at the 3 November 1941 meeting of the subcommittee, Veldee reported on a review of the literature, which had been delegated to Weiss and himself.

He informed the subcommittee that Thimerosal apparently had some bacteriostatic value and possibly some bactericidal value.

Nonetheless, because of his toxicity concerns, Weiss was not willing to accept Thimerosal as a preservative unless a maximum limit was set on the amount of plasma that an individual patient could be administered.

He also stipulated that the symptoms of mercury poisoning must be published on the label of

\textsuperscript{34} Kendrick DB. Blood Program in World War II. Washington, DC: Office of the Surgeon General, Department of the Army, 1989.

\textsuperscript{35} Anonymous. Mercurials as "preservatives." \textit{JAMA} 1943; 122: 1253.
the can in which the plasma was packed.

In 1943, Ellis published an article on the possible danger of using Thimerosal in ophthalmic ointments.\(^{36}\)

In his report evaluating this use of Thimerosal, Ellis observed:

"Merthiolate is capable of causing an inflammation of the mucous membrane in patients..."

and made a very strong recommendation, based upon his clinical experience and that of several other physicians, to seriously consider the adverse effects of Thimerosal use.

He disputed the acceptance of Thimerosal in medicine, and referencing the potential ability of Thimerosal to produce permanent damage in the patient during clinical use, Ellis proposed:

"...it may be advisable to withdraw this product from the market..."

[Note: It is important to notice that this recommendation was made more than 6 decades ago, after Thimerosal had been on the market for only, approximately, 10 years.]

Tellingly, the Fifth Revision of Minimum Requirements for Liquid or Dried Plasma, 8 January 1945, stated:

"There is no preservative bactericidal to all probable contaminants in concentrations not dangerously toxic in the maximum human dose."\(^{37}\)

Ellis continued his work on Thimerosal, and, \textit{in 1947}, reported on an even larger case-series of patients experiencing adverse reactions following application of Thimerosal.\(^{38}\)

Based upon his further clinical experiences, as well as those of his medical colleagues, \textit{in 1947}, Ellis again strongly rebuked those advocating the continued use of Thimerosal in clinical medicine, stating: "...it may be dangerous to inject a serum containing Merthiolate into a patient..."

In 1948, Cogswell and Shown reported:

"We have had recently the occasion to observe a patient with a severe reaction to tincture of Merthiolate...which manifested a local and general reaction."\(^{39}\)

\(^{36}\) Ellis FA. Possible danger in use of Merthiolate ophthalmic ointment. \textit{Arch Ophthalmol} 1943; 30: 265-266.


The authors also stated: “The patient was warned never again to use Merthiolate solutions.”

Placing the experience of this patient in a larger perspective, the authors stated:
“Many severe reactions have been reported following the use of mercurial ointments and a lesser number due to antiseptics containing mercurials.”

In 1948, Cogswell and Shown even dared to condemn their colleagues for their myopia in wrongly evaluating the therapeutic effects of Thimerosal in the clinical setting:
“When a reaction does result, it is important that it be recognized and the application of the drug ceased. Many of the reported cases are similar in that in spite of a reaction to Merthiolate, its use was being continued as a means of therapy to alleviate the result of the application. Hollander reported on a nurse who had severe dermatitis venenata for over two years due to continuous self-medication with tincture of Merthiolate. Improvement was noted on discontinuing its use...reaction should be recognized to prevent further applications of the drug which would exacerbate or accentuate the illness.”

In 1948, Morton et al., under a grant from the Council on Pharmacy and Chemistry of the American Medical Association, published an article on the bacteriostatic and bactericidal actions of some mercurial compounds on hemolytic streptococci.40

They reported:
“...the label on a bottle of ‘Solution Merthiolate, 1:1,000, Stainless’ purchased as recently as June 1947 states that it is ‘a stable, stainless, organic mercury compound of high germicidal value, particular in serum and other protein media.’ It is not highly germicidal and especially does not possess high germicidal value in the presence of serum and other protein mediums. The loss of antibacterial activity of mercurials in the presence of serum proves their incompatibility with serum... The comparative in vitro studies on mercurochrome, metaphen and Merthiolate on embryonic tissue cells and bacterial cells by Salle and Lazarus cannot be ignored. These investigators found that metaphen, Merthiolate and mercurochrome were 12, 35 and 262 times respectively more toxic for embryonic tissue cells than for Staphylococcus aureus. Nye and Welch also found the same three mercurial compounds more toxic for leukocytes than for bacterial cells. Not only is there direct toxic action of the mercurial compounds on the cellular and humoral components of the animal body, but there is also the possibility of sensitization.”

Subsequently, the Sixth through Ninth Revisions of Minimum Requirements for Liquid or Dried Plasma (15 April 1949 through 15 May 1952) prohibited use of a preservative.41

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5. **Thimerosal Usage, Claimed Nontoxicity and Observed Toxicity — 1950s through 1960s**

In 1950, Engley, working in the Biological Department, Chemical Corps, Camp Detrick, published an evaluation of mercury compounds as antiseptics and judged these to be inadequate:

"Mercurial compounds have not enjoyed a peaceful career as antibacterial chemicals since their popularization as germicides over sixty years ago (Kock, 1891) . . . During the ensuing years, other workers, using various techniques, have also shown that the antibacterial activity of mercurials is only slowly bactericidal and mainly bacteriostatic. This bacteriostasis is even nullified by the presence of many types of sulfur-containing compounds, including sulﬁdes (Geppert, 1889), (Hunt, 1937), thioglycollate (Marshall, Gunnison, and Luxen, 1941), body ﬂuids such as plasma (Johnson and Meleney, 1942), and other organic matter (Green and Birkeland, 1944)."

Further, and of greater concern, was Engley’s conclusion that mercurials, such as Thimerosal:

"...are ineffective in vivo and may be more toxic for tissue cells than bacterial cells, as shown in mice (Nungester and Kempf, 1942) (Saber, 1942) (Spaulding and Bondi, 1947), tissue culture (Salle and Catlin, 1947), and embryonic eggs (Witlin, 1942) (Green and Birkeland, 1944), and with leucocytes (Welch and Hunter, 1940).\(^{42}\)

Early in 1956, Davisson et al., from the Lilly Research Laboratories, reported on a molecular mechanism for Thimerosal induced cellular toxicity.\(^{43}\)

Specifically, they described that the cellular toxicity of Thimerosal was the result of:

"...partial ionization of the compound to go give a low but effective level of ethyl mercuri ion (C\(_2\)H\(_3\)Hg\(^+\)), which blocks enzymatic processes by combining with sulphydryl groups on the enzymes."

Shortly thereafter, Engley also presented his Camp Detrick group’s research findings in 1956 to the 42\(^{nd}\) midyear meeting of the Chemical Specialties Manufacturer's Association in Chicago, Illinois.\(^{44}\)

Here, Engley overtly questioned the acceptance of Thimerosal as a preservative in vaccines and other pharmaceuticals products by stating:


\(^{44}\) Engley FB. Mercurials as disinfectants – evaluation of mercurial antimicrobial action and comparative toxicity for skin tissue cells. *Soap & Chemical Specialties* 1956, pgs. 199, 201, 203, 205, 223-5.
"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 or 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.”

Engley then discussed the relative 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 indicative 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... 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...”

Finally, it should be noted, with respect to the toxicity experiments undertaken by Engley, that he determined Thimerosal was significantly toxic to human tissue culture cells at a concentration of 10 parts-per-billion.

6. **Removal Of Thimerosal And Other Mercury-based Compounds From OTC Drugs**

In 1982, a scientific panel, convened by the FDA to review the over-the-counter (OTC) use of Thimerosal, concluded:

“... thimerosal is not safe for [over-the-counter] topical use because of its potential for cell damage if applied to broken skin and its allergy potential.” 45

[Note: This FDA-sponsored panel only addressed the epidermal and dermal effects of Thimerosal.]

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45 47 FR 436, Jan 5, 1982.
Based on the results of their review, that scientific panel recommended the removal of Thimerosal from over-the-counter products.

Sixteen years later, in 1998, the FDA finally banned the use of:

a. Thimerosal and any other ingredient containing mercury in OTC “topical antimicrobial” products, and

b. Phenylmercuric acetate, phenylmercuric nitrate, and any other ingredient containing mercury in “vaginal contraceptive” products. [See 21 C.F.R. § 310.545.]

7. FDA's Published Call-For-Data Notices And Announcements

In December of 1998 and April of 1999, the FDA announced, pursuant to Section 413 of the Food and Drug Modernization Act of 1997 (FDAMA)"

"a call-for-data to identify food and drug products that contain intentionally introduced mercury compounds, e.g., mercurous chloride, mercuric chloride, phenylmercuric acetate, Thimerosal. The agency is seeking both quantitative and qualitative information about the mercury compounds in these food and drug products."

[Note: In November of 1999, the FDA posted a notice of the availability of a document, entitled “Mercury Compounds in Drugs and Food,” that discussed drugs (including biologics) and foods that contain intentionally introduced mercury compounds.]

In July of 1999, shortly after the FDA's second "call-for-data" notice, the CDC issued a press release (entitled “Thimerosal in Vaccines: A Joint Statement of the American Academy of Pediatrics and the Public Health Service50) that, in part, stated (with underlining added):

“... because any potential risk is of concern, the Public Health Service (PHS), the American Academy of Pediatrics (AAP), and vaccine manufacturers agree that thimerosal-containing vaccines should be removed as soon as possible. Similar conclusions were reached this year in a meeting attended by European regulatory agencies, European vaccine manufacturers, and FDA, which examined the use of thimerosal-containing vaccines produced or sold in European countries.”

46 63 FR 19799-19802, April 22, 1998.
49 64 FR 63323-63324, November 19, 1999.
50 Morbidity Mortality Weekly Report, 48(26), pages 563-565 (July 09, 1999 [original press release issued on July 7, 1999]) – can be found by searching the MMWR subsite (http://www.cdc.gov/mmwr/).
8. Thimerosal / Ethylmercury Toxicological Effects

[Note: Where appropriate, bolding has been added to the quoted passages for emphasis.]

In 1937, Sass reported on the histological and cytological pathology induced by ethylmercury poisoning in corn seedlings.\(^{51}\)

Sass described:

"The use of dusts in which the active ingredient is ethyl mercury...produces a characteristic malformation of the seedlings of corn and other cereals."

Based upon his series of experiments, he subsequently reported:

"In corn seedlings grown from nontreated seed, the leaf primordial and apical meristem of the coleoptile have the structure characteristic of meristematic tissues. The cells are small, polygonal, compactly arranged, and of uniform size. These cells are strictly uninucleate, and the nuclei are size... Seedlings from treated seeds exhibit varying degrees of distortion of cells, tissues and organs in proportion to the severity of the gross external symptoms... The formation of new cells and new leaf primordial cases, the existing cells continuing their excessive irregular enlargement... The cells of the hypertrophied tissues of corn seedlings were found to be multinucleate. The number of nuclei in a cell varies from one to more than 10... The 'giant nuclei' are clearly polyploid."

One of the earliest studies to evaluate the effects of ethylmercury on animals was published in 1950.\(^{52}\)

This study evaluated the toxicity of the ethylmercury compounds in mice.

White-mice were exposed to ethylmercury compound vapor, and the animals were subsequently observed for clinical signs of toxicity and mortality.

This study found:

"Acute exposure to the organic mercury compounds caused symptoms indicative of serious respiratory and nervous system disruption: labored respiration, cyanosis of the nose, tail and ears, and hind limb paralysis. All animals died 6 to 15 hours after exposure... In the chronic study, the central nervous system was the main site of involvement. Mice exposed to the organic compounds showed a hind limb paralysis that gradually spread to the front limbs. Death occurred by day 38."

Subsequently, others reported adverse outcomes for an ethylmercury compound in animals.\(^{53}\)

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\(^{52}\) Trakhtenberg IM. The toxicity of vapors of organic mercury compounds (ethlmercuric phosphate and ethylmercuric chloride) in acute and chronic intoxication (experimental data). *Gigienna Sanitariya* 1950; 6:13-17.

These researchers reported that ethylmercury exposure:

"...produced signs of central nervous system or gastrointestinal disturbance, or both in cattle... It caused progressive degenerative changes in the heart... It produced diffuse lesions in the cord, cerebellum, and cerebrum and caused glomerulonephritis."

The effects of ethylmercury poisoning were also observed in mass poisonings of swine.54

In this case, the researchers reported:

"On the October’ Collective Farm in Tatishchevo District, 383 of 414 swine of various ages were affected during August (1967), the acute period; 121 died and 145 in the agonal state had to be slaughtered. By November, another 44 animals had died. On the Fedorov’ State Farm in Marx District, 211 of 444 swine were affected... The first signs of poisoning appeared in suckling pigs and fatting gilts 20 to 25 days after beginning feeding on the treated grain; in sows, the signs appeared in 30 to 40 days. At first, the animals refused food and water and became restless. There was some nasal mucous secretion. Then weakness in the hind limbs appeared, with different types of movement coordination disorder. Some animals showed spinal involvement. Signs of neural disorders were quite clear, including muscular tremors, convulsional jerking of the extremities and titanic contractions of the pelvic musculature. As the conditions worsened, the animals lay on their stomachs or sides, developing varying degrees of paralysis with loss of pain sensation, rapid breathing, etc. The younger swine almost all died within 3 to 6 days after the symptoms started; the sows’ condition persisted longer until death (6 to 11 days) and 40 to 45% of the affected animals died. In some instances, the swine suffered the above symptoms, including partial or complete loss of vision, for 2 to 3 months. The autopsy findings were initially the same in all the animals, the most constant changes being noted in the intestines. The intestinal mucous membrane was covered with dryish, dirty yellow or brownish-green deposits connected to the underlying tissue... The fact of a delay in the appearance of symptoms following Granosan must be taken into account in diagnosing organomercury poisonings. The clinical symptoms and pathological-anatomical changes in mass poisonings of swine with Granosan to a great extent recall the course of infectious diseases... so that mercury poisoning should be eliminated during a differential diagnosis."

Additionally, heavy losses were reported to have occurred in a poultry yard due to feed treated with ethylmercury.55

The clinical symptoms observed in chickens on the last day before death were depression, spasm, paralysis of the limbs, swollen heads, and elevated temperature.

Moreover, mercury residues were detected in the kidneys, liver, muscles, skin, brains, lungs, hearts, ovaries, and eggs; and, depending on the duration and intensity of the exposure, mercury residues could be detected in the chicken tissues for as long as 120 days after the poisoning.

Oharazawa (1968) published a study examining the ability of ethylmercury exposure during pregnancy to induce fetal damage in mice.\(^{56}\)

He observed that injection of ethylmercury during pregnancy significantly reduced the weights of developing fetuses in utero and produced significant increases in fetal malformations and the incidence of unstable chromosomes characterized as polyploidy, chromatid gaps, or fragmented, in comparison to unexposed controls.

By 1971, researchers had become more sophisticated and started evaluating the effects of ethylmercury on several successive generations of offspring.

Goncharuk administered an ethylmercury compound to albino rats, and subsequently, these animals were mated.\(^{57}\)

Investigations were made of the sexual cycle, and the viability, physical development and fertility of the progeny of the first and second generations.

His 1971 paper reported that females that had been previously exposed to the ethylmercury compound became pregnant only on the 4\(^{th}\) or 5\(^{th}\) occasion when they were placed with males when in estrus, whereas non-exposed control females became impregnated on the 1\(^{st}\) or 2\(^{nd}\) mating.

The number of offspring per litter was significantly smaller in the animals treated with the ethylmercury compound than in controls.

Moreover, young rats from mothers that had been previously exposed to the ethylmercury compound died significantly more frequently than the controls.

Observations of the first-generation progeny revealed a lag in weight growth in comparison to controls, especially during the 1\(^{st}\) and 2\(^{nd}\) months of extrauterine life.


In addition, the first-generation progeny had birth weights that exceeded those of the control group, and studies of skeletal ossification in the young rats found a number of cases with retardation of the appearance and development of ossification centers in the bones of the fore and hind paws.

Studies of the organs and the tissues of the first generation progeny revealed mercury in the stomach and intestine at birth and in the first week of life, apparently through the entry of mercury: a) across the placental barrier, and b) by way of their mother's milk, respectively.

Subsequently, the paper noted that the first generation progeny of mothers that had been previously exposed to the ethylmercury compound had significantly reduced fertility in comparison to the controls.

The second-generation progeny also had low viability, lagged in their weight growth, and were retarded with respect to ossification in several cases.

Finally, the researcher reported, when mating the second-generation progeny, that there was a significant decrease in fertility in comparison to the control group.

A later study on pheasants by the U.S. Bureau of Sport Fisheries and Wildlife, Patuxent Wildlife Research Center, concluded that ethylmercury compound exposure at a level equivalent to 12.5-ppm mercury was lethal to adult animals and, at 4.2-ppm mercury, impaired reproduction in the species.58

These researchers also reported:

"Ethyl mercury p-toluene sulfonanilide (active ingredient of Ceresan M) at a dietary concentration of 30 parts per million (12.5 parts of mercury per million) was lethal to adult ring-necked pheasants. Egg production and survival of third-week embryos were sharply reduced when breeders were maintained on feed containing 10 parts of this compound per million (4.2 parts of mercury per million)... Since similar residues of mercury have been found in eggs of wild pheasants and several species of aquatic birds, we conclude that mercury pollution may be sufficiently high in some areas to affect avian reproduction."

In 1972, Mukai, working under a grant from the U.S. National Institutes of Health, reported on an animal model of ethylmercury-cysteine induced encephalopathy using mice.\textsuperscript{59}

Mukai observed:

"Mice injected intraperitoneally with EMC (Ethyl Mercuri-S-Cysteine) labeled with tritium showed the typical neurologic symptoms of mercury poisoning. Administration of EMC in a concentration of 0.3 mg/0.5 mL saline per day for at least eight days was a prerequisite for significant accretion of EMC in the central nervous system. The extent and distribution of cell damage were highly predictable, and selective necrosis of the small granular neurons in the koniocrotex, and neostriatum was a constant finding. Autoradiographic study has suggested that the astroglial cell compartment plays a role in conveying the mercury complex into neurons."

Subsequent research by Tryphonas and Nielsen, which was sponsored by the Medical Research Council of Canada, not only showed that ethylmercury produced a consistent and predictable pattern of encephalopathy, but also that it induced severe developmental toxicity at very low doses.\textsuperscript{60}

In 1973, these researchers reported:

"... ethylmercuric chloride (EMC) was used to produce chronic alkylmercurial poisoning in young pigs. A dosage of 0.19 to 0.76 mg, of Hg / kg of body weight per day was used... The resulting toxicosis was primarily related to the nervous system, in which neuronal necrosis followed by secondary gliosis, capillary endothelial proliferation, and additional neuronal necrosis due to developing degenerative arteriopathy in the blood vessels supplying injured gray matter were seen. In other systems, degeneration of hepatocytes and renal tubular cells were commonly occurring lesions in pigs...edema of the mesocolon, necrosis of the epithelium, and degenerative arteriopathy in the submucosa were seen most consistently in the esophagus and large intestine of pigs... The results proved that...EMC, if fed at low concentrations...were highly poisonous... Finally, since the alkylmercurial moiety is absorbed and stored as such for considerable lengths of time in...cells, the public health implications...cannot be overlooked."

Furthermore, Wright et al.\textsuperscript{61} from the US Department of Agriculture evaluated the toxicokinetics of mercury in the tissues of cattle and sheep administered ethylmercury.

In 1973, these researchers reported that significant levels of mercury were detectable in multiple organs including the blood, kidney, liver, and muscle for significant lengths of time following exposure to ethylmercury.

Additionally, these researchers found that mercury crossed the blood-brain barrier, and resulted in significant levels of mercury in the brain for more than 20-weeks (> 140 days) following administration of the last dose of this ethylmercury compound.

In another study that examined swine-administered ethylmercury, Saley found that significant levels of mercury were detectable for more than 8 months (> 240 days) following administration of the last dose of the ethylmercury.62

Yonaha et al., working at the National Institute of Hygienic Sciences, also evaluated the uptake, retention, and toxicity of ethylmercury in several organs, when administered to mice.63

In the cited 1975 publication, these researchers reported:

"Ethylmercury chloride was highly incorporated into the brain... It may be presumed that manifestations of symptoms after exposure of organic mercury compounds is not merely related to mercury levels and not always in need of organic forms in the brain... The clinical signs and pathological findings caused by methylmercury compounds in animal experiments were known to be similar to Minamata disease manifested in human. At the same time, the symptoms in cats, calves, and mice poisoned by ethylmercury compounds were similar to those in methylmercury compounds. Further, as reported by Sebe, et al., alkylmercury compounds having short carbon chains (C₁-C₃) bring about the specific neurotoxicity and the signs of poisoning in rats..."

Spanning the 1950’s and 1970’s, a series of population poisoning outbreaks, involving ethylmercury and other mercury compounds and tens of thousands of people, occurred worldwide.64

A population outbreak of ethylmercury poisoning occurred in Iraq, following ingestion of Granosan M, an antifungal that was used to prevent plant root disease in grain products.
Beginning in 1955, the Iraqi Ministry of Agriculture supplied farmers with seeds treated with this fungicide.

Farmers had been given frequent warnings against using the treated seed for food, and as a result, most of them were aware of the highly lethal effect of eating treated seed.

Out of ignorance or, for other reasons, some unfortunate farmers and their families consumed the seed and became the victims of mercury poisoning.

Consequently, these farmers developed a number of serious mercury-related conditions.65

Specifically, one paper reported:

"Poisoning by a fungicide used for seed-borne diseases of cereals, ethyl mercury p-toluene sulphonanilide (Granoson M, Dupont) is described. It affected a large number of farmers and their families who used the dressed seed in the preparation of homemade bread. Many systems were involved, including the kidneys, the gastrointestinal tract, the skin, the heart, and the muscles, but involvement of the nervous system was the most constant with disturbance of speech, cerebellar ataxia, and spasticity. Mental abnormalities were occasionally observed...In 1956 many cases of mercury poisoning were observed in the North of Iraq, and more than 100 cases were admitted to Mosul Hospital with 14 deaths. In 1960, many farmers from the central part of Iraq were affected and 221 patients were admitted to one hospital in Baghdad. Other patients went to other hospitals."

Later, a significant series of patients in Russia was observed to suffer from serious toxic outcomes following ingestion of ethylmercury and occupational exposure to ethylmercury.67

Early signs of exposure included: general weakness, pains, tachycardia, and headache.

Thereafter, it was observed that appetite decreased until, at last, food was refused; there was also nausea, liquid stool, disordered sleep, decreased memory, and pain in the extremities.

Most of the patients recovered, but death was observed following exposure in some of the patients.

Such case studies clearly demonstrate the severe toxicity of this compound to humans and document its effect on multiple systems of the human body due to acute exposure.

Not only acute exposure, however, but also low-dose exposure has produced significant impairment in human beings, a fact documented by Mukhtarova (1977).\(^6\)

Mukhtarova examined the late after-effects upon the nervous system following chronic low-dose exposure to ethylmercury.

In 1977, this researcher reported:

"A total of 25 persons exposed to multiple effects of low ethyl-mercuric-chloride concentrations were subjected to a clinical examination in dynamics 1 ½ and 3 years after exposure to the compound. In investigations clinico-physiological (EEG, Asschner-Dagnini reflexes, etc) and biochemical (catecholamines, sugar, mercury, DDT, DDE in the urine, etc) methods were employed. The pathology of the nervous system presented certain peculiarities by comparison with early period. In evidence were changes in the simpatico-adrenal system function, vascular lesions of the brain after the type of transient derangements of the cerebral circulation in the vertebro-basilar basin and angiospasms, diffuse changes in the nervous system with predominant involvement of the hypothalamic cerebral structures and in some cases psychiatric disturbances were on record."

Over time, additional incidents of mercury poisonings by ethylmercury compounds continued to offer substantial evidence for, and disclose a pattern of, extreme toxicity produced by ethylmercury in humans.

For example, in 1980, Cinca et al. reported on accidental ethylmercury poisoning with nervous system, skeletal muscle, and myocardium injury, and stated:

"Four case reports are presented of patients who ate the meat of a hog inadvertently fed seed treated with fungicides containing ethyl mercury chloride. The clinical, electrophysiological, and toxicological, and in two of the patients the pathological data, showed that this organic mercury compound has a very high toxicity not only for the brain, but also for the spinal motor neurons, peripheral nerves, skeletal muscles, and myocardium."\(^6\)

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\(^6\) Mukhtarova ND. Late sequelae of nervous system pathology caused by the action of low concentrations of ethyl mercury chloride. *Gig Tr Prof Zabol*. 1977; (3): 4-7.

As another example, Zhang evaluated clinical symptoms observed in patients with ethylmercury chloride poisoning and, in 1984, reported:

“Forty-one patients in the Peoples Republic of China were poisoned by ethyl mercury chloride, caused by the ingestion of rice that had been treated with the chemical. A dose-response relationship was found. Five months after the onset of the intoxication, the patients were still in poor condition.”

In 1974, Derban even reported on clinical symptoms observed in children following ethylmercury poisoning of 144 people in a rural Ghana village:

“Four children developed disturbance of speech which led to stammering and scanning. Mental abnormality was observed in one boy who showed occasional outburst of anger unrelated to circumstances. A girl developed encephalitis and became completely paralyzed in both upper and lower limbs, with incontinence of urine and feces and complete loss of speech.”

Of key importance in the historical scientific record of exposures to ethylmercury compounds are the first reports of human fetal poisonings.

In study on a human fetal poisoning, in 1968, Bakulina reported:

"...granosan (ethylmercury chloride) is capable of passing through the placental barrier and penetrating into the fetus, causing in the organs of the latter grave pathological changes. The permeability of the placental barrier for organic mercury compounds finds its confirmation in the presence of mercury in the placenta and organs of the fetus... Breast feeding was found to be conducive to accumulation of mercury in the organism of newborns, since the mothers' milk, as a rule, disclosed the presence of this element. A very important point was that fetal intoxication was possible for as long as 3-4 years after the mother poisoned."

By the early 1970s, researchers developed an overall clinical picture of ethylmercury poisoning in fetuses following large-scale ethylmercury poisoning episodes.

In 1973, Ramanauskayte and Baublis stated that, after exposure to ethylmercury-treated seeds:

"Intrauterine poisoning in infants was observed... Children on the whole are more susceptible to mercury than adults... Serious functional disorders of the central nervous system, hydrocephalus, cerebral paralysis, and spasms were observed in infants. Toxic encephalomyeloradiculoneuritis with prevalence of the syndromes of lesions of the cerebral cortex, brain stem, cerebellum, myelitis, peripheral neurites, lesions of the motor centers, of the pyramidal tracts, and encephalitis with..."
irregular alpha-rhythm were observed... Epilepsy lasting up to 2 years was observed in 10% of all cases. Prevalence of vegetoneurotic syndromes, tachycardia, bradycardia, arrhythmia, acrocyanosis, liability of the arterial pressure, and reduction of the blood cholinesterase activity were found in older children with chronic poisoning. The lesions of the liver, kidney, heart and gastrointestinal tract were much less pronounced than those of the central nervous system. Sodium thiosulfate, glutamic acid, vitamin B and C complexes, glucose, and diuresis are essential for detoxification.74

Confirming the tremendous danger of ethylmercury compounds to children, Mal'tsev had reported, in 1972, that, in cases of children poisoned with ethylmercury, the onset of the symptoms of their poisoning usually occurred many weeks following exposure.75

The first symptoms of ethylmercury poisoning in children included asthenia, fatigability, loss of appetite, followed by nausea, vomiting, liquid feces, abdominal pains, and elevated temperature.

Subsequently, the neurological syndrome developed and consisted of symptoms such as ataxia, dysarthria, psychomotor disturbances, and sleep disturbances.

Tellingly, the researcher reported that damage to the nervous system may be irreversible even following low-dose exposure.

Mal'tsev also commented that, upon autopsy of children who died of ethylmercury exposure, degenerative, inflammatory, and necrotic alterations were seen, as well as hemorrhages in the central nervous system, kidney, liver, heart, and intestines.

Importantly, Mal’tsev also reported that ethylmercury appeared to be the most dangerous to the embryos during the third and four months of pregnancy.

Addressing the issue of vaccine toxicity and adverse reactions to vaccines, in 1967, Nelson and Gottshall from the Division of Biologic Products, Bureaus of Laboratories, Michigan Department of Public Health published:

"Pertussis vaccines preserved with 0.01% Merthiolate are more toxic for mice than unpreserved vaccines prepared from the same parent concentrate and containing the same number of organisms..."

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An increase in mortality was observed when Merthiolate was injected separately, before or after an unpreserved saline suspension of pertussis vaccine.76

From 17-19 June 1971, an international conference and its associated advisory committee reviewed the environmental toxicity of mercurials.77

One of the key areas examined at this conference was the metabolic fate of ethylmercury salts, with a specific emphasis on Thimerosal, in humans.

That committee reported:

"The toxic nature of ethylmercury has been considered to be fairly similar to that of methylmercury salts. In the recommendations of the international committee on Maximum Allowable Concentration for mercury and its compounds, ethylmercury was grouped with methylmercury. Reports on human intoxication with ethylmercury salts have usually reported symptoms similar to those of methylmercury, which is accentuated by the typical neurological symptoms, although there have been a few reports that noted slightly different symptoms from the typical features of methylmercury poisoning. In acute experiments on animals, ethylmercury has an LD50 similar to that of methylmercury salts and a high neurotoxicity similar to that of methylmercury." In addition, its report stated, "(b) by using methods for estimating the inorganic and total mercury content of biological specimens, the metabolism of ethylmercury salts was studied in man and animals. The (carbon-mercury bond) C-Hg of ethylmercury salts was able to break fairly rapidly and to a great extent in men, who were patients and were transfused with a commercial product of human plasma containing 0.01% (Thimerosal) sodium ethylmercurithiosalicylate, and also in mice injected subcutaneously or intravenously with ethylmercurithiosalicylate solution. The increasing level of inorganic mercury and its percentage to total mercury content in the brain were quite distinguishable with post-injection time in mice, which resulted in longer biological half-time of total mercury than that reported for methylmercury injection."

Itoi and his colleagues conducted a series of experiments to evaluate the reproductive toxicity of Thimerosal in rabbits.78

In 1972, they reported that injection of increasing doses of Thimerosal (from 0.02 to 0.2% solutions) into pregnant rabbits resulted in significantly increased numbers of dead fetuses (up to 18% of fetuses died following exposure) and increased fetal congenital anomalies (up to 9.1% of...
fetuses developed congenital anomalies following exposure) in comparison to rabbits injected with physiological saline.

Axton also reported on a series of 6 patients (4 children and 2 adults), 5 of whom died following injection with chloramphenicol preserved with abnormally high levels of Thimerosal.79

In 1972, he reported that there was something wrong with the chloramphenicol injections.

This problem was first suspected on 23 October 1969, after the appearance of skin necrosis over the injection sites in 4 children, and the drug was withdrawn from the pediatric wards.

Preliminary investigation of the vials used, for pH, concentration of chloramphenicol, and bacteriology, revealed no abnormality.

Heavy metal contamination was not considered at this stage.

Case 1 was the first to die (6 November 1969) and on the morning of his death, the combination of albuminuria and glycosuria with mental symptoms suggested poisoning, possibly by a heavy metal.

The suspicion was supported by the necropsy findings later in the day (large swollen kidneys).

The local manufacturers of the chloramphenicol were again contacted, and it was discovered that 0.51 Kg of Thimerosal was used in the preparation of 1,000, 1-g vials of chloramphenicol.

The correct amount should have been 0.51 g and, therefore, the amount of Thimerosal in each vial was 1,000 times too much.

In 1975, Gasset et al., working under a grant from the US National Institutes of Health (NIH), reported on their examination of mercury distribution following administration of Thimerosal to animals.80

They stated:

“A comparison of topical and subcutaneous administration of Thimerosal to rabbits shows that a substantial concentration of mercury was present in blood and tissues of the treated animals and their offspring. Thimerosal was found to cross the blood-brain and placenta barriers.”

These researchers also determined that administration of Thimerosal caused a significant dose-dependent increase in fetal mortality.

Blair et al. also examined the distribution, and chemical form, of the mercury in the body following administration of Thimerosal to animals.\(^8\)

In 1975, the authors reported that squirrel monkeys were dosed intranasally with saline or Thiomersal (sodium ethylmercurithiosalicylate, 0.002% w/v) daily for 6 months.

The total amounts of Thiomersal given during the 6-month period were 418 µg (low dose group) and 2280 µg (high dose group).

These were equivalent to 207 µg of mercury and 1125 µg of mercury, respectively.

The dose differential was achieved by more frequent administration to the high dose group.

Mercury concentrations were significantly raised over control values in brain, liver, muscle and kidneys, but not blood.

Concentrations were highest in kidneys, moderate in liver and lowest in brain and muscle.

Much of the mercury was present in the inorganic form (37-91%).

Regarding mercury toxicity, these authors commented:

“...it is conceivable that insidious damage may occur at lower concentrations. Nothing is known about the mercury concentration which can cause irreversible damage to single brain cells. Damage to only a few cells may not be detected in the clinical investigation because other cells take over. Clinical effects do show up early when too many cells have been damaged in a short time. However, over a long period, even a low frequency of brain cell damage, above the natural inactivation rate of these cells, has an effect on the organism as the number of available cells for each brain function is limited. Such damage may have serious effects in the later stages of life. These considerations must be kept in mind when the toxicological evaluation of alkyl mercury compounds is made. Perhaps any increase in brain mercury should be viewed as potentially hazardous... The mercury present in the brain was mainly ionic which may be the more toxic form of mercury... The chronic use by patients of formulations containing thiomersal as a preservative may therefore result in accumulation of some mercury in the brain and other tissues.”

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The authors concluded:

"... accumulation of mercury from chronic use of thiomersal-preserved medicines is viewed as a potential health hazard for man."

The US Veterans Administration and the US National Institutes of Health funded research, published by Van Horn et al., which examined the toxic effects of Thimerosal on human cells grown in tissue culture.\textsuperscript{82}

In 1977, these authors commented (with underlining added for emphasis):

"Widespread use of the mercurial-containing preservative Thimerosal as an antibacterial agent in ophthalmic drugs and solutions warranted an investigation into its possible cytotoxic effects on the functional and ultrastructural integrity of the corneal endothelium...(scanning electron microscopy) SEM and (transmission electron microscopy) TEM of the endothelium of corneas perfused with 0.0005 percent Thimerosal for 5 hours revealed condensed mitochondria, cytoplasmic vacuoles, and cytoplasmic flaps at the apical end of the cellular junctions. Perfusion of higher concentrations (0.001 and 0.005 percent) of Thimerosal in (glutathione bicarbonate Ringer's solution) GBR resulted in increases in corneal thickness after 2 hours and irreversible ultrastructural damage to the endothelial cells by 5 hours. Corneas perfused with 0.01 and 0.1 percent Thimerosal in GBR showed a rapid and immediate increase in corneal thickness and endothelial cell death and necrosis within 1 hour. It is postulated that the mercury in Thimerosal becomes bound to the cell membrane protein sulfhydryl groups, causing an increase in cellular permeability. These results suggest that the prolonged exposure of the corneal endothelium to Thimerosal in the accepted antimicrobial dosage of 0.005 to 0.001 percent may result in functional and structural damage to the endothelium... It is therefore concluded that ophthalmic solutions containing Thimerosal should not be used..."

Parry utilized yeast cultures for the detection of environmental mutagens using a fluctuation test.\textsuperscript{83}

In 1977, he reported:

"(a) microbial fluctuation test, modified for the detection of environmental mutagens has been evaluated using a number of strains of the yeast \textit{Saccharomyces cerevisiae}. Auxotrophic diploid cultures of yeast which produce prototrophic colonies by both mitotic gene conversion and mutation have been extensively utilized for the detection and evaluation of chemicals showing genetic activity. A number of the yeast strains utilized were shown to be suitable for use in the fluctuation test... The yeast strains respond to doses of mutagens at least a 100-fold lower than that required in a conventional short exposure treat and plate experiment. In experiments involving the induction of mitotic gene conversion at the tryptophan-5 and histidine-4 loci in the fluctuation test significant increases in prototrophic cells were produced in the presence of...the preservative Thiomersal (0.0001 µg/mL)... The results demonstrate that the fluctuation test provides an extremely sensitive


assay for the detection of chemicals which show genetic activity in yeast at non-toxic concentrations."

Importantl, Parry observed Thimerosal induced significant genetic alterations in yeast cells at a level of less than 1 part-per-billion (< 0.5 ng of mercury per gram or mL).

In 1977, Fagan et al. published a case-series of children who had apparently been poisoned by Thimerosal.84

In this study, funded by the National Institute of Environmental Health Sciences [NIEHS] of the US National Institutes of Health, Fagan et al. reviewed 13 cases of exomphalos that were treated by Thimerosal between 1969 and 1975.

The authors analyzed the mercury content in tissues from the 10 patients who had died.

Upon reviewing the test results, the researchers stated:

"The results showed that Thiomersal can induce blood and organ levels of organic mercury which are well in excess of the minimum toxic levels in adults and fetuses... Although Thiomersal is an ethyl mercury compound, it has similar toxicological properties to methyl mercury and the long-term neurological sequelae produced by the ingestion of either methyl or ethyl mercury-based fungicides are indistinguishable."

The authors also emphasized:

"...the fact that mercury readily penetrates intact membranes and is highly toxic seems to have been forgotten. Equally effective and far less toxic broad-spectrum antifungal and antibacterial...antiseptics are currently available."

Also published in 1977 were the results of a large-scale prospective human epidemiological study (the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke, the US Public Health Service, and the US FDA) on drug exposures during pregnancy and their association with birth defects.

This collaborative study85 reported:

"Between 1958 and 1965, under the auspices of the National Institute of Neurological and Communicative Disorders and Stroke, a prospective study of over 50,000 pregnancies was

undertaken with the main objective of determining whether there are factors during pregnancy or delivery that are related to the risk of cerebral palsy or other neurological outcomes. This study ultimately became known as the Collaborative Perinatal Project. Among many items of data obtained, drug use was recorded during pregnancy, and birth defects identified in the children were recorded subsequently. With the growing realization that drugs are sometimes teratogenic, it became mandatory to evaluate the data from the perspective... The purpose of this book is to present data on drugs used by 50,282 gravidae in relation to birth defects identified in children.' The conclusion of these researchers with regard to Thimerosal, '(t)he measure of association presented is a standardized relative risk (SRR) with its 95% confidence limits. The SRR is the ratio of the observed number to the expected number of malformed children. Since the SRR takes into account potential confounding variables, it represents the best estimate of the relationship between a drug and a malformation...’ Finally, thiomersal...was associated with malformations overall and with uniform malformations.'

Specifically, the study found that Thimerosal exposure during the first 4 months of pregnancy was associated with a statistically significant increased risk (SRR = 2.69) for birth defects.

In 1979, Anundi et al. described a molecular mechanism by which exposure to Thimerosal rapidly induced cellular oxidative stress and subsequent cellular lysis following glutathione depletion, and that the addition of cysteine could reverse the cellular toxicity of Thimerosal. 86

Specifically, they determined:

“Compounds are known which interact with lipids and proteins in such a way that both lipid peroxidation and protein alkylation have been considered a cause of toxicity... (I)t has become evidence that (glutathione) GSH protects against protein alkylation and that electrophilic compounds which deplete GSH may alkylate proteins. The main point in this communication is that cellular damage following GSH depletion can be explained by lipid peroxidation which destroys the cell before the alkylation of proteins, as a component of cellular damage, is expressed.”

9. Thimerosal & Other Mercurials At Multi-Dose-Vaccine, Or Lower, Levels
[Note: Where appropriate, bolding has been added to the quoted passages for emphasis.]

Heyworth and Truelove undertook a study to evaluate the potential adverse effects of Thimerosal-containing immune globulin preparations. 87

In 1979, these researchers reported:

“Merthiolate contains an ethyl group directly joined to a mercury atom. Organic compounds containing an alkyl radical directly attached to a mercury atom are more toxic to human subjects than are other types of mercury compounds. Considerable accumulation of mercury occurs in tissues of

mice injected with ethyl mercury compounds, and in 1 human subject receiving intravenous infusions of Merthiolate-containing plasma tissue accumulation of mercury was also observed."

The researchers went on to conclude:

"For many years, Merthiolate has been known to have anti-microbial activity. When it was first introduced as an anti-microbial preservative, little information about the fundamental biological effects of organic mercury compounds was available. We should like to suggest that Merthiolate should now be regarded as an inappropriate preservative for anti-lymphocytic globulin preparations and other materials which are intended for administration to human subjects."

In 1980, Matheson et al. published a case-report of mercury-poisoning induced by long-term injection of Thimerosal-containing gamma globulin.88

They reported that the patient developed pink, scaling pruritic palms and soles, flushed cheeks, photophobia, irritability, a fine tremor, altered sensation in his fingertips, and slowed nerve conduction velocity [the classical symptoms of “Pink Disease” and “Acrodynia,” medical diagnoses common in the era (1800s to mid-1900s) when Calomel (mercurous chloride) in teething powders and other drugs was the agent that was linked to the medical mercury poisoning of babies, young children, and adults].

These authors reported:

"Most commercially available gammaglobulin preparations contain Merthiolate (sodium ethylmercurithiosalicylate), a mercury-containing compound, which serves as a bacteriostatic agent. Thus, patients receiving regular injection of gammaglobulin are potentially at risk for the development of mercury toxicity... It would appear, therefore, that Merthiolate which is used as a preservative in a commercially available gammaglobulin preparation represents a potential hazard to patients..."

In 1980, Forstrom et al. also published warnings regarding the use of Thimerosal, this time in vaccines:

"...reactions can be expected in such a high percentage of Merthiolate-sensitive persons that Merthiolate in vaccines should be replaced by another antibacterial agent.»89

In 1982, Heyworth reported:

During a study of the properties of two antisera which had been prepared against human lymphoid cells, the present author found that one of the antisera was cytotoxic to lymphoid and non-lymphoid cells(1)... This effect was attributable to the organomercurial compound Merthiolate, which had been added to the (antilymphocyte serum) ALS as a preservative... In the opinion of the present author, Merthiolate should no longer be added to ALS or other materials which are intended for use in human subjects. Tissue accumulation of mercury has been observed...

In 1982, Takahashi also examined the cytotoxicity of two kinds of mercurial preservatives, Thimerosal and phenylmercuric acetate, using Chang's human conjunctival epithelia in cell culture. The cultured cells were exposed for 5 s, 2 min and 24 h to each of the two preservatives at various concentrations, obtained by serial dilution.

The cytopathic effect and cell desquamation from the wall of culture flask were observed with an inverted microscope and LD$_{50}$ was calculated by Van der Waerden's method.

The LD$_{50}$ values of Thimerosal were 291.6, 47.4 and 2.2 micrograms/mL at exposure times of 5 s, 2 min and 24 h, respectively.

Those of phenylmercuric acetate were 1,120.2, 227.5 and 2.6 microgram/mL at exposure times of 5 s, 2 min and 24 h, respectively.

In 1983, an article titled, "Mercury Poisoning in Child Treated with Aqueous Merthiolate," reported that the administration of Thimerosal resulted in a child dying from mercury toxicity.

The article stated:

"The Ohio Board of Pharmacy has received an investigative report from the Ohio Department of Health's Division of Epidemiology regarding the death of a 21-month old child due to mercury poisoning. The investigation strongly implicated the Thimerosal solution as 'the source of mercury' that subsequently resulted in the child's death since no other source could be identified."

In 1983, Kravchenko et al. questioned the use of Thimerosal in vaccines and its inexplicable acceptance in light of mounting scientific evidence demonstrating its inherent toxicity.

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93 Kravchenko AT, Dzagurov SG, Chervonskaia GP. Evaluation of the toxic action of prophylactic and therapeutic preparations on cell cultures. III. The detection of toxic properties in medical biological preparations by the degree of cell damage in the L132 continuous cell line. *Zh Mikrobiol Epidemiol Immunobiol* 1983; (3): 87-92.
These researchers found:

“Our experiments show that Merthiolate in 1:10,000 titer can not only damage cells in culture but also change their properties... Increased sensitivity to this mercury compound has been frequently noted in medical literature, and deserves particularly close attention. Although there are numerous clinical studies confirming Merthiolate’s damaging action on humans, (medical and biological preparations) MBP preservation with it continues and is even recommended by WHO.”

In regard to the use of Thimerosal in vaccines, the researchers concluded:

“All of the above show that Merthiolate usage for MBP manufacturing is inadmissible, especially in pediatrics.... Vaccines must contain only specific substances, free of ballast. There is no way that cell damage can cause not harmful sequelae in the body.”

Hekkens et al. undertook an evaluation of the effectiveness of some preservatives in inactivated human vaccines by application of the test described in the United States Pharmacopoeia (USP) XIX. 94

In the cited 1983 paper, these researchers reported that 5 recommended strains as well as 3 strains isolated from vaccines were used as the test strains.

They observed that vaccines preserved with Thimerosal did not fully meet the requirements for a vaccine preservative according to the criteria established by the then-current USP XIX.

In 1984, Rohyans et al. reported on mercury toxicity following pediatric Thimerosal ear irrigations. 95

With regard to the danger posed by mercurials, the researchers were expansive in stating:

“Although aqueous Merthiolate has been used for years as a topical antiseptic, a recent review of its use by the Food and Drug Administration resulted in its classification as ‘less than effective.’ Furthermore, two of the ingredients (Thimerosal and borate) in Merthiolate are toxic if absorbed or injected... Symptoms of organic mercury poisoning chiefly involve the central nervous system, including paresthesia of the mouth, lips, tongue, and extremities; speech disorders, with difficulty in articulating words; difficulty in swallowing; salivation; neurasthenia; inability to recall basic information; emotional instability; ataxia; clumsiness; stupor; and coma... Reactions to mercury depend to a large extent on the form of the chemical agent; its absorption, storage, and excretion; duration of exposure; and individual susceptibility. Both inorganic and dissociable organic mercurials appear to act by the same mechanism. Mercury ion reacts with sulfhydryl groups to form mercaptides, which inactivate sulfhydryl enzymes and interfere with cellular metabolism... The blood-brain barrier, is also more permeable to organic than inorganic mercury. There are definite individual

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differences in sensitivity to the effects of mercurials. Some patients tolerate prolonged exposure without symptoms; others have significant systemic signs and neurological disability with much less exposure. The mercury in Merthiolate is a thiosalicylate compound that is converted to inorganic mercury more rapidly than is methyl mercury. The organic compound itself is also easily absorbable, and undergoes widespread tissue distribution. Toxicity may be related both to the biotransformation into inorganic mercury and to the unchanged compound, both of which cause degenerative changes in the brain, especially in the visual cortex and cerebellum, and proliferative changes throughout the cerebellar cortex.

In 1985, Stetler et al. from the US CDC also evaluated the use of Thimerosal as a preservative in vaccines and found it to be unsatisfactory. The authors reported that: a) Thimerosal was ineffective as a vaccine preservative, and b) giving more mercury than was present in a single Thimerosal-containing vaccine dose might pose a health hazard to vaccine recipients.

Evaluating the effectiveness of Thimerosal as a preservative in vaccines, the authors stated:

“Laboratory experiments in this investigation have shown up to 2 weeks’ survival of at least one strain of group A Streptococcus in multidose DTP (Diphtheria-Tetanus-Pertussis) vials. The manufacturer’s preservative effectiveness tests showed that at 4°C, 4.5% of the challenge Streptococcus survived 14 days after inoculation into a multi-dose DTP vaccine vial. At currently used concentrations, Thimerosal is not an ideal preservative.”

The authors also made specific reference to the toxicity of Thimerosal:

“Howevers, because Thimerosal is an organic mercurial compound, higher concentrations might reduce vaccine potency or pose a health hazard to recipients.”

Their suggestions regarding the use of multi-dose vials with a Thimerosal preservative were:

“The Thimerosal preservative present in DTP vaccine requires substantial time to kill organisms and cannot be relied upon to prevent transmission of bacteria under conditions of practice when a vial is used over a short period. Instead, the most important means of preventing abscesses secondary to DTP vaccination is to prevent contamination by careful attention to sterile technique.”

The next year, 1986, Winship reported:

“Multi-dose vaccines and allergy-testing extracts contain a mercurial preservative, usually 0.01% Thimerosal, and may present problems occasionally in practice. It is, therefore, now accepted that multi-dose injection preparations are undesirable and that preservatives should not be present in unit-dose preparations.”


Furthermore, in 1988, Cox and Forsyth recommended:

"However, severe reactions to thiomersal demonstrate a need for vaccines with an alternative preservative."98

Digar et al. expanded the knowledge basis regarding the marked toxicity of Thimerosal to the developing fetus.99

In 1987, these researchers reported:

"A single dose of 0.1 mg of Ethyl-mercury-thiosalicylate (Thimerosal) was injected into the yolk sac of chick embryos... Embryos were collected... It was found that 0.1 mg dose of Thimerosal was lethal in 46.46%. Gross malformations like syndactyly, thinning of the abdominal wall, visceroptosis and scanty feather, during Organogenesis as well as in the later period, have been noted in 36.03%... Significant change in the weight of embryo, crown-rump length, body and wing lengths were also observed... However, there was no gross reduction in the size of brain as compared to that of the control. The high incidence of lethality and malformations prove that organic mercury was transmitted from the yolk sac to the embryo. The deleterious effects of mercurials on cells and tissues seem to be due to action on a wide spectrum of enzymes by the organic mercury both on the surface and within the cell. The enzymes particularly involved are – Na – K activated ATPase and also sulfhydryl groups. Goldwater reported that mercury disrupts the normal function of mitochondria and lysosomes.”

Simmons et al. investigated the effects of the ophthalmic preservatives Thimerosal on the proliferation and survival of rabbit corneal epithelial cells in tissue culture.100

In their 1988 paper, these researchers reported:

"Normally, explants of corneal epithelium grow vigorously during the first 7 days in culture. With 0.004% thimerosal present in the culture medium, the normal proliferation of corneal cells is suppressed completely... After a 1-h exposure to concentrations of thimerosal of 0.0005% or greater, virtually all corneal cells present in established cultures are killed. These results suggest that use of ophthalmic preparations containing these chemicals may affect the metabolic and proliferative capacity of the corneal epithelium adversely.”

Hakansson et al. evaluated the effect of Thimerosal used in nasal drops on phagocytosis by human granulocytes.101

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In 1989, these researchers reported that Thimerosal gave a dose-related reduction of phagocytosis down to zero.

A dilution of 1:10 of the Thimerosal solution used commercially (24 mg / L) was needed to get an almost normal phagocytic function and the authors concluded:

"These results together with previous studies indicate that the addition of preservatives in nasal drops should be questioned, excluded or replaced with other less harmful substances."

Hakansson et al. also evaluated the possible toxic effect of the components in nasal drops on chemotaxis by human granulocytes. 102

In 1989, they reported that Thimerosal was deleterious and produced chemotaxis at a concentration of 1 mg / L (1 ppm Thimerosal; 0.5 ppm mercury), which should be compared with a concentration of 24 mg / L (24 ppm; 0.0024%) used as a preservative in nasal drops.

These researchers concluded:

"Together with previous studies the present results indicate that the addition of preservatives in nasal drops should be questioned especially as they can be safely distributed without any risk of bacterial contaminations nowadays."

Withrow and his colleagues, from the US FDA, in keeping with the expanding circle of scientists and physicians expressing ever-increasing concerns in regard to the use of Thimerosal as a preservative, evaluated the cytotoxicity and mutagenicity of Thimerosal at preservative levels in a tissue culture system. 103

In 1989, these researchers reported:

"It is known that Thimerosal...present in lens care solutions sometimes cause(s) ocular irritation in contact lens users. For example, Coward et al. (1984) reported that 33% of patients using lens care solutions with Thimerosal...experienced solution intolerance... In vitro studies have shown that preservatives are toxic to cultured human and rat corneal epithelial cells and toxic to isolated rabbit corneas, and to intact rabbit eyes." Additionally, these researchers described the impact of Thimerosal at the cellular level, "(c)ell survival and mutagenesis were measured using the L5178Y mouse lymphoma (TK +/-) system. Cells were exposed to varying amounts of preservatives for 1 h at 37°C, and then aliquots were irradiated with UVA radiation (during the exposure to the preservative)."


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Cells were then assayed for survival, and for mutagenesis at the thymidine kinase (TK) locus. In concentrations commonly found in ophthalmic solutions... Thimerosal (was) toxic to cells, and Thimerosal was slightly mutagenic. When cells were exposed to preservative and UVA radiation... the mutagenic activity of Thimerosal was enhanced."

In 1990, Nascimento et al. not only reported on a death following Thimerosal ingestion but also warned of the widespread danger, which Thimerosal posed.104

Specifically, they reported:

"... (a) case of mercurial poisoning caused by ingestion of an organic mercurial compound, Thimerosal, found in local antiseptic solutions. The clinical picture consisted of grave neurological symptoms which were not reversed by penicillamine and resin administration despite rapid plasma level reduction of mercury. We call attention to this case because of the widespread availability of antiseptic solutions containing mercurial compounds..."

Aberer reviewed the continued use of mercury in medicine.105

In his 1991 article, Aberer was comprehensive in declaring the extent of the problem that Thimerosal represented in pharmaceutical products:

"The presence of mercury in over-the-counter drugs for the eye, ear, nose, throat, and skin; in bleaching creams; as preservative in cosmetics, tooth pastes, lens solutions, vaccines, allergy test and immuno-therapy solutions, in antiseptics, disinfectants, and contraceptives; in fungicides and herbicides; in dental fillings and thermometers; and many other products, makes it a ubiquitous source of danger."

He then went on to document the systemic failure to remove this toxin from drug products:

"Despite calls for abandonment and a general prohibition in 1967, mercury is still listed in many pharmacopoeias, including that of the United States... Thus mercury is still much more frequently used than is generally believed. This seems incomprehensible because side effects are not only potentially disastrous but also numerous and well documented."

In describing the numerous and well-documented side effects of the use of mercury in medicine, he stated that these included:

"(n)euroligic and psychiatric symptoms, renal toxicity, erythroderma, and other signs of poisoning...", and furthermore: "(k)nnowledge of all these side effects has been available for some time."

He concluded by arguing:

"Recommendations not to use mercury salts in children or only on prescription are insufficient. Removal from textbooks seems overdue. However, calls for their abandonment (as early as 1960) or restricted use have not sufficed. Only a general ban and their removal from the pharmacopoeias will be effective in stopping the use of these dangerous, outmoded substances."

Additionally, Seal et al., in their 1991 article on the case against Thimerosal, concluded:

"Thimerosal is a weak antibacterial agent that is rapidly broken down to products, including ethylmercury residues, which are neurotoxic. Its role as a preservative in vaccines has been questioned, and the pharmaceutical industry considers its use as historical."\(^{106}\)

In 1991, Hilleman a member of the Merck Vaccine Task Force expressed a newly initiated internal concern over the mercury exposure infants were receiving through standard immunizations.\(^{107}\)

This internal concern was expressed on the cited memo as:

"PROBLEM: The regulatory control agencies in some countries, particularly Scandinavia (especially Sweden), but also U.K., Japan, and Switzerland, have expressed concern for Thimerosal, a mercurial preservative, in vaccines... PUTTING THIS INTO PERSPECTIVE: For Babies: The 25 µg of mercury in a single 0.5 mL dose and extrapolated to a 6 lb. baby would be 25X the adjusted Swedish daily allowance of 1.0 µg for a baby of that size. The total mercury burden in a baby is unknown but it has been stated that the blood level of a newborn may exceed that of the mother. If 8 doses of Thimerosal-containing vaccine were given in the first 6 months of life (3 DPT, 2 HIB, and 3 Hepatitis B) 200 µg of mercury given, say to an average size of 12 lbs., would be about 87X the Swedish daily allowance of 2.3 µg of mercury for a baby of that size. When viewed in this way, the mercury load appears rather large."

Lowe and Southern evaluated the antimicrobial action of various preservatives for vaccines.\(^{108}\)

In 1994, they stated:

"The preservative most commonly used is Thiomersal. Other preservatives are being evaluated because: (i) this material has become difficult to obtain; (ii) the use of mercury-containing compounds in medicinal products is considered potentially harmful; and (iii) it has been found that some vaccine components are unstable in the presence of this material."

In light of these facts, the researchers undertook a series of experiments comparing the antimicrobial activity of phenoxyethanol with Thimerosal in a diphtheria, tetanus, and pertussis (adsorbed) vaccine.


They observed:

"Both chemicals were equally effective in inactivating challenge doses of Gram-negative and Gram-positive micro-organisms, as well as yeast."

In significant contrast to their concerns regarding the potentially harmful effect of mercury-containing compounds, Lowe and Southern noted:

"The low toxicity of phenoxyethanol in children has been reported..."

Lowell et al., from the Washington University School of Medicine, investigated the association between Thimerosal and mercury poisoning by evaluating the adverse effects resulting from administration of Thimerosal-containing hepatitis B immunoglobulin (HBIG) and, in 1996, reported:

"Preparations of HBIG use Thimerosal (a mercury derivative) as a preservative. We encountered mercury toxicity, in a patient who received high-dose immunoprophylaxis... HBIG preparations contain Thimerosal as a preservative, which contains 49% organically bound mercury. Previous reports have demonstrated that administration of Thimerosal-containing products may lead to mercury poisoning... Physicians should suspect mercury toxicity in patients receiving high-dose HBIG."

Overshadowing the recorded concerns of independent researchers and pharmaceutical representatives is the critical and unheeded recommendation that pregnant women and newborn children should be protected from the potential neurotoxic effect of the mercury-containing drug products, which was issued internally within the FDA.

In August of 1998, a US FDA internal "Point Paper" was prepared for the Maternal Immunization Working Group.

This document officially recommended:

"For investigational vaccines indicated for maternal immunization, the use of single dose vials should be required to avoid the need of preservative in multi-dose vials... Of concern here is the potential neurotoxic effect of mercury especially when considering cumulative doses of this component in early infancy".


10. Overview of Additional Research Evaluating Thimerosal, Ethylmercury, Phenylmercuric Acetate, & Mercury in General with Respect to Toxicity/Toxicokinetics


64. Lee CH, Lin RH, Liu SH. Distinct genotoxicity of phenylmercury acetate in human lymphocytes as compared with other mercury compounds. Mutat Res 1997; 392: 269-276.


11. *Toxicokinetic Observations of Thimerosal-Containing Vaccine Use in Humans & Animal Models*

   In 2001, Redwood et al. reported that U.S. infants who received multiple Thimerosal-containing vaccines probably had been exposed to cumulative mercury doses that were well in excess of the existing Federal safety guidelines for mercury exposure.111

   Based on the CDC's 2001 recommended immunization schedule, that study found infants could have been exposed to not less than 12.5 micrograms (µg) of mercury at birth, 62.5 µg of

mercury at 2 months, 50 µg of mercury at 4 months, 62.5 µg of mercury at 6 months, and 50 µg of mercury at approximately 18 months, for a total of **not less than** 237.5 µg of mercury during the first 18 months of life, provided:

- The infants' vaccinations were all given as scheduled and
- The vaccines given were Thimerosal-preserved multi-dose vaccines in every instance.

The authors estimated concentrations of mercury in hair expected to result from the recommended CDC schedule utilizing a one compartment pharmacokinetic model, and found that those modeled mercury concentrations in infants immunized with Thimerosal-preserved "multi-dose" vaccines were in excess of the Environmental Protection Agency's safety guidelines.

In addition, several of the modeled peak concentrations within this period were in excess of 4.5 times the EPA limit.

Recently, Marques et al. prospectively studied the impact of Thimerosal-containing vaccine administration on the total mercury (Hg) in hair of 82 breast-fed infants during their first 6 months.

In 2007, they reported the infants received three doses of the hepatitis-B vaccine (at birth, 1 and 6 months) and three DTP (diphtheria, tetanus, and pertussis) doses at 2, 4 and 6 months, according to the immunization schedule recommended by the Ministry of Health of Brazil.

The Thimerosal in vaccines provided a mercury (Hg) exposure of 25 µg Hg at birth, 30, 60 and 120 days, and 50 µg Hg at 180 days.

The exposure to vaccine-EtHg represents 80% of that expected from total breast milk-Hg in the first month but only 40% of the expected exposure integrated in the 6 months of breastfeeding.

However, the peak Hg exposure, corrected for body weight at the day of immunization, was much higher from Thimerosal-EtHg (5.7 to 11.3 µg Hg/kg b.w.) than from breastfeeding (0.266 µg Hg/kg b.w.).

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While mothers showed a relative average decrease (-57%) in total hair-Hg during the 6 months lactation there was substantial average increase in the infant's hair-Hg (446%).

These researchers concluded that dose and parenteral mode of Thimerosal-EtHg exposure modulated the relative increase in hair-Hg of breast-fed infants at 6 months of age, and reported that their observations were consistent with that modeled in 2001 by Redwood et al.

Marques et al. also recently investigated the impact of Thimerosal-containing hepatitis B vaccine exposure at birth and its association with neurodevelopmental outcome scores at 6 months in a relatively small cohort of children in Brazil.113

While not statistically significant, this 2007 study reported a trend towards increasing exposure from Thimerosal-containing vaccine exposure at birth / kg bodyweight and subsequent worse neurodevelopmental outcome scores at 6 months ($r = -0.1724; p = 0.1214$).

The researchers suggested that limited sample size and potential confounding may have minimized the effects observed.

Additionally, Stajich et al. examined total mercury levels before and after the administration of hepatitis B vaccine in 15 pre-term and 5 term infants.114

In 2000, these authors reported that there were statistically significant increased levels of mercury in the blood 48 to 72 hours following hepatitis B immunization in both pre-term (relative increase = 13.5, $p < 0.01$) and term (relative increase = 56, $p < 0.01$) infants.

In 2001, they also observed that some infants had blood levels of mercury in excess of the EPA blood mercury limits115, and subsequently reported, in 2005, some infants had blood levels of mercury at levels that the U.S. CDC considers to be diagnostic of mercury poisoning116.

Burbacher et al. evaluated infant monkeys following injection of doses of Thimerosal-containing vaccines comparable to the dosing schedule (weight- and age-adjusted) US children received during the 1990s.\footnote{117} In 2005, these researchers reported that blood levels of mercury induced by Thimerosal injection were in excess of the EPA blood mercury limit for several days, but that the half-life of mercury in the blood was short – about 7 days.

They determined that the maximum mercury content in the brains of the Thimerosal-treated infant monkeys averaged about 40-50 parts-per-billion. They also determined that the overall half-life of organic mercury in the brain of the infant monkeys examined was about 14 days.

In addition, post-dosing-schedule testing found the concentration of inorganic mercury (formed from the ethylmercury entering the brain) averaged about 16 parts-per-billion in the brains of the Thimerosal-treated infant monkeys.

Moreover, the half-life of inorganic mercury in the monkeys’ brains was too long to estimate from the available data (no significant measurable decline was detectable by 120 days).

It was previously estimated that the half-life of inorganic mercury in the human brain from autopsies was about 20 years.\footnote{118}

The overall importance of persistent inorganic mercury in the brain has been strengthened by the reality that a number of studies have shown that the dealkylation of mercury in the brain is not a detoxification process.\footnote{119}

\footnote{117} Burbacher TM, et al. Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing Thimerosal. \textit{Environ Health Persp} 2005; 113(8): 1015-1021.
After dosing monkeys with organic mercury, these researchers reported that the half-life of inorganic mercury in the brain was estimated to vary significantly across different regions of the brain, from 227 days to 540 days.

In other regions, the concentrations of inorganic mercury remained the same (in the thalamus) or doubled (in the pituitary) 6 months after mercury dosing had ended.120

Stereologic and autometallographic studies on the brains of these monkeys indicated that the persistence of inorganic mercury in the brain was associated with a significant increase in the number of microglia in the brain, whereas the number of astrocytes declined.

Notably, these effects were observed:

a. 6 months after organic mercury dosing had ended, when inorganic mercury concentrations were at their highest levels as well as

b. In animals solely exposed to inorganic mercury.121


In 2006, Orct et al. reported on the evaluation of the distribution pattern of Thimerosal or inorganic mercury (Hg2+) administered to rat pups subcutaneously, three times during the suckling period on days 7, 9, and 11 of life, imitating the "pre-hepatitis-B" vaccination of infants.122

Both groups of rats were administered an equimolar dose of mercury.

At 14 days of age, the animals were killed, and the total amount of mercury in blood and organs (kidney, liver, and brain) was evaluated.

The researchers observed that mercury was present in the blood and organs in both treatment groups, and that blood and organ levels were significantly higher in both treatment groups than in the unexposed controls.

The results showed the level of mercury was significantly higher in the liver (1.4-fold) and kidney (4.4-fold) of the inorganic mercury-exposed group than in the Thimerosal-exposed group.

However, the brain (1.5-fold) and blood (23-fold) concentration of mercury were significantly higher in the Thimerosal-exposed group in comparison to the inorganic mercury-exposed group.

In spite of the preceding realities and other studies, the FDA has, to date, failed to forbid the use of Thimerosal and other mercurials in all drugs.

It is apparent that, decades after an FDA advisory committee123 found, in 1982, that Thimerosal was not safe for use in topical drug products, new vaccines containing Thimerosal were, and are, being approved and added to the recommended childhood immunization schedule, including general-use vaccines (e.g., influenza) that are formulated to contain 0.01 % (100 ppm) Thimerosal. [Note: We have similar concerns because some of these Thimerosal-preserved, general-use vaccines and other Thimerosal-preserved biological drugs are recommended by the CDC for administration during pregnancy.]


12. Recent Comments of Federal Officials on Mercurials in Medicine

On 16 July 2001, Dr. George Lucier, National Toxicology Program, National Institute of Environmental Health Science made a presentation, “Comparative Toxicity of Ethyl & Methylmercury” to the Immunization Safety Review Committee of the US National Academy of Sciences.

Dr. Lucier concluded his presentation by stating:

“Ethylmercury exposure from vaccines (added to dietary exposures to methylmercury) probably caused neurotoxic responses (likely subtle) in some children.”

In 2003, after a three-year investigation, a Congressional report (prepared by the staff of the Subcommittee on Human Rights and Wellness, Committee on Government Reform of the United States’ House of Representatives) had this to say regarding the FDA, the CDC, Thimerosal in vaccines, and the “autism epidemic” (with bolding added for emphasis):

“II. FINDINGS AND RECOMMENDATIONS

A. Findings

Through this investigation of pediatric vaccine safety, the following findings are made:

1. Mercury is hazardous to humans. Its use in medicinal products is undesirable, unnecessary and should be minimized or eliminated entirely.

2. For decades, ethylmercury was used extensively in medical products ranging from vaccines to topical ointments as preservative and an anti-bacteriological agent.

3. Manufacturers of vaccines and thimerosal, (an ethylmercury compound used in vaccines), have never conducted adequate testing on the safety of thimerosal. The FDA has never required manufacturers to conduct adequate safety testing on thimerosal and ethylmercury compounds.

4. Studies and papers documenting the hyperallergenicity and toxicity of Thimerosal (ethylmercury) have existed for decades...

8. The FDA acted too slowly to remove ethylmercury from over-the-counter products like topical ointments and skin creams. Although an advisory committee determined that ethylmercury was unsafe in these products in 1980, a rule requiring its removal was not finalized until 1998.

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124 16 July 2001 (PowerPoint Slides), Dr. George Lucier, National Toxicology Program, National Institute of Environmental Health Science (NIEHS) presentation, “Comparative Toxicity of Ethyl & Methylmercury” to the Immunization Safety Review Committee of the US National Academy of Sciences.

9. The FDA and the CDC failed in their duty to be vigilant as new vaccines containing thimerosal were approved and added to the immunization schedule. When the Hepatitis B and Haemophilus Influenzae Type b vaccines were added to the recommended schedule of childhood immunizations, the cumulative amount of ethylmercury to which children were exposed nearly tripled.

10. The amount of ethylmercury to which children were exposed through vaccines prior to the 1999 announcement exceeded two safety thresholds established by the Federal government for a closely related substance - methylmercury. While the Federal Government has established no safety threshold for ethylmercury, experts agree that the methylmercury guidelines are a good substitute. Federal health officials have conceded that the amount of thimerosal in vaccines exceeded the EPA threshold of 0.1 micrograms per kilogram of bodyweight. In fact, the amount of mercury in one dose of DTaP or Hepatitis B vaccines (25 micrograms each) exceeded this threshold many times over. Federal health officials have not conceded that this amount of thimerosal in vaccines exceeded the FDA's more relaxed threshold of 0.4 micrograms per kilogram of body weight. In most cases, however, it clearly did.

11. The actions taken by the HHS to remove thimerosal from vaccines in 1999 were not sufficiently aggressive...

12. The CDC's failure to state a preference for thimerosal-free vaccines in 2000 and again in 2001 was an abdication of their responsibility. As a result, many children received vaccines containing thimerosal when thimerosal-free alternatives were available...

14. The CDC in general and the National Immunization Program in particular are conflicted in their duties to monitor the safety of vaccines, while also charged with the responsibility of purchasing vaccines for resale as well as promoting increased immunization rates. . .

17. To date, studies conducted or funded by the CDC that purportedly dispute any correlation between autism and vaccine injury have been of poor design, under-powered, and fatally flawed. The CDC’s rush to support and promote such research is reflective of a philosophical conflict in looking fairly at emerging theories and clinical data related to adverse reactions from vaccinations...

The Food and Drug Administration’s (FDA) mission is to ‘promote and protect the public health by helping safe and effective products reach the market in a timely way, and monitoring products for continued safety after they are in use.’ However, the FDA uses a subjective barometer in determining when a product that has known risks can remain on the market. According to the agency, ‘at the heart of all FDA’s product evaluation decisions is a judgment about whether a new product’s benefits to users will outweigh its risks. No regulated product is totally risk-free, so these judgments are important. FDA will allow a product to present more of risk when its potential benefit is great—especially for products used to treat serious, life-threatening conditions.’ This argument—that known risks of infectious diseases outweigh a potential risk of neurological damage from exposure to thimerosal in vaccines—is one that has continuously been presented to the Committee by government officials. FDA officials have stressed that any possible risk from thimerosal was theoretical: that no proof of harm existed. However, the Committee, upon a thorough review of the scientific literature and internal documents from government and industry, did find evidence that thimerosal did pose a risk...

Thimerosal used as a preservative in vaccines is likely related to the autism epidemic. This epidemic in all probability may have been prevented or curtailed had the FDA not been asleep at the switch regarding the lack of safety data regarding injected thimerosal and the sharp rise of infant exposure to this known neurotoxin. Our public health agencies’ failure to act is indicative of
institutional malfeasance for self-protection and misplaced protectionism of the pharmaceutical industry.”

On May 20, 2004, responding to public concern about the CDC’s apparently flawed epidemiological studies, the United States Office of Special Counsel (OSC), an independent federal agency, issued:

a. A press release\(^{126}\) and

b. A letter from Special Counsel Scott Bloch\(^{127}\) to Congress stating:

“I have recently received hundreds of disclosures from private citizens alleging a widespread danger to the public health, specifically to infants and toddlers, caused by childhood vaccines which include thimerosal, a mercury-containing preservative... The disclosures allege that thimerosal/mercury is still present in childhood vaccines, contrary to statements made by HHS agencies, HHS Office of Investigations and the American Academy of Pediatrics. According to the information provided, vaccines containing 25 micrograms of mercury and carrying expiration dates of 2005, continued to be produced and administered. In addition, the disclosures allege, among other things, that some datasets showing a relationship between thimerosal/mercury and neurological disorders no longer exist, that independent researchers have been arbitrarily denied access to the Centers for Disease Control and Prevention (CDC) databases, and that government-sponsored studies have not assessed the genetic vulnerabilities of subpopulations. Due to their heightened concern that additional datasets may be destroyed, these citizens urge the immediate safeguarding of the Vaccine Safety Datalink database, and other relevant CDC information, so that critical data are not lost. The disclosures also allege that the CDC and the Food and Drug Administration colluded with pharmaceutical companies at a conference in Norcross, Georgia, in June 2000, to prevent the release of a study which showed a statistical correlation between thimerosal/mercury exposure through pediatric vaccines and neurological disorders, including autism, attention-deficit/hyperactivity disorder (ADHD), stuttering, tics, and speech and language delays. Instead of releasing the data presented at the conference, the author of the study, Dr. Thomas Verstraeten, later published a different version of the study in the November 2003 issue of *Pediatrics,* which did not show a statistical correlation. No explanation has been provided for this discrepancy. Finally, the disclosures allege that there is an increasing body of clinical evidence on the connection of thimerosal/mercury exposure to neurological disorders which is being ignored by government public health agencies... I believe that these allegations raise serious continuing concerns about the administration of the nation's vaccine program and the government's possibly inadequate response to the growing body of scientific research on the public health danger of mercury in vaccines. The allegations also present troubling information regarding children's cumulative exposure to mercury and the connection of that exposure to the increase in neurological disorders such as autism and autism-related conditions among children in the US.”

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The following passage is from their “Statement of Criminal Charges”:

“We believe that the following charges can be brought against specific federal agencies and individuals at these agencies in their capacity as employees under the following statutes:

I. FDA: Criminal negligence in failure to regulate the safety and effectiveness of biological products under Title 42, Chapter 6A, Subchapter II, Part F., Subpart 1, Subsection 262, (C): The secretary shall approve biologics license application-(i) on the basis of demonstration that---(I) the biological product that is the subject of the application is SAFE, PURE, and POTENT;

II. HHS, CDC, and FDA: Criminal negligence in failure to regulate and promote vaccines as provided for under the National Vaccine Injury Compensation Program, Title 42, Chapter 6A, Subchapter XIX, Part 2, Subpart C, Section 300aa-27: Mandate for safer childhood vaccines (a) General rule: In the administration of this part and other pertinent laws under the jurisdiction of the Secretary, the Secretary shall-(1) promote the development of childhood vaccines that result in less serious adverse reactions than those licensed as of December 22, 1987, and promote the refinement of such vaccines, and (2) make or assure improvements in, and otherwise use the authority of the Secretary with respect to licensing, manufacturing, product testing, labeling, warning, use instructions, distribution, storage, administration, filed surveillance, adverse reaction reporting, and recall all reactogenic lots or batches of vaccines, and research on vaccines, in order to reduce the risks of adverse reactions to vaccines.

III. FDA: Criminal negligence in not instituting a Class I recall of all vaccines administered to infants containing Thimerosal in July of 1999 and again in June of 2000 when the results of VSD study were discussed at Simpsonwood. A class I recall under 21 CFR Section 7.4(a) may be imposed by FDA after taking into consideration the following factors: 1) whether any disease or injuries have already occurred from the use of the product; 2) whether an existing conditions could contribute to a clinical situation that could expose humans or animals to a health hazard; 3) assessment of the hazard to various segments of the population e.g. children...who are expected to be exposed to the particular product being considered, with particular attention paid to the hazard to those individuals who may be at greatest risk; 4) assessment of the degree of seriousness of the health hazard to which the populations at risk would be exposed; 5) assessment of the likelihood of occurrence of the hazard, and 6) assessment of the consequences (immediate or long range) of the occurrence of the hazard.

IV. HHS, FDA, CDC and ACIP employees and contractors: Criminal conspiracy to defraud the government by deception or artifice and to obstruct the wholesome administration of the laws and
affairs of the United States. Includes any conspiracy for the purpose of impairing, obstructing or defeating the lawful function of any department of government. See, e.g. Haas v. Henkel, 216 U.S. 462 (1910) (and progeny). Statutory reference, 18 USC Section 371, Part I Crimes, Chapter 19, Conspiracy: If 2 or more persons conspire to either commit any offense against the United States, or to defraud the United States, or any agency thereof in any manner or purpose and anyone or more of such persons do any act to effect the object of the conspiracy, each shall be fined under this title or imprisoned not more than five years or both.

V. HHS, FDA, CDC and ACIP employees and contractors: Criminal obstruction of justice: whoever corruptly, or be threats or force, or by any threatening letter or communication influences, obstructs, or impedes or endeavors to influence, obstruct, or impede the due and proper administration of law under which any pending proceeding is being had before any department or agency of the US, or the due and proper exercise of the inquiry is being had by either House or any committee of either house or joint committee of the Congress, shall be fined under this Title or imprisoned not more than five years or both. Statutory reference, Title 18, Part 1, Crimes, Chapter 73, Obstruction of justice, Section 1505.”

In April 2007, Dr. Larry Needham, Chief, Organic Analytical Toxicology Branch, National Center for Environmental Health, CDC made a presentation to the Institute of Medicine of the US National Academy of Sciences.

One of Dr. Needham’s “PowerPoint” slides was captioned, “Chemical Linked to ASD” and included “Thimerosal” as one of the items listed in that slide.”

13. “Confounded” and “Biased” Epidemiological Studies On Vaccinated Children?

a. Study Using HMOs’ Medical Records For American Children:
   The “Verstraeten” Studies

Among other things, the Congressional Subcommittee, Special Counsel Bloch, and former Congressional Counsel Birt discussed a CDC-commissioned epidemiological study on Thimerosal.

In that epidemiological study (begun in the fall of 1999), Thomas Verstraeten reported in a series of initial emails on the significant relationship that was observed between Thimerosal-containing vaccine administration and neurodevelopmental disorders (including autism).130

129 April 2007 (PowerPoint Presentation) by Dr. Larry Needham, Chief, Organic Analytical Toxicology Branch, National Center for Environmental Health, Centers for Disease Control and Prevention, “Exposure (To Stressors) and Autism Spectrum Disorders” to the Institute of Medicine of the US National Academy of Sciences.

130 a. 29 November 1999 (email) Verstraeten to Davis regarding, “Subject: Thimerosal Analyses”
   b. 17 December 1999 (email) Verstraeten to Davis regarding, “Subject: It just won’t go away…”

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For example, Thomas Verstraeten reported in an email with attachments ("Subject: It just won’t go away..."):

"Hi, Attach"[ed] “please find four tables with RRs [relative risks] and three SAS programs... As you’ll see some of the RRs increase over the categories and I haven’t yet found an alternative explanation... Please let me know if you can think of one.”

Thomas Verstraeten also admitted, “...harm is done...” by Thimerosal-containing vaccine administration.

The following is a summary of statistically significant increased risks observed for various outcomes reported in Thomas Verstraeten’s analyses:

- **Autism (2990) =** 11.35 (2.70-47.76), 7.62 (1.84-31.5)
- **Specific Disorders of Sleep of Nonorganic Origin (3074) =** 4.64 (1.12-19.25), 4.98 (1.55-15.94)
- **Attention Deficit Disorder (3140) =** 3.08 (1.09-8.35)
- **Mix = Coordination Disorder, Developmental Speech or Language Disorder, Attention Deficit Disorder, Specific Disorders of Sleep of Nonorganic Origin, Autism – whichever comes first) =** 2.38 (1.27-4.45)
- **Phase-Shift Disruption of 24-Hour Sleep-Wake Cycle (30745) =** 53.64 (3.23-892.10)
- **Somnambulism or Night Terrors (30746) =** 5.76 (1.38-24.05)
- **Attention Deficit Disorder without Mention of Hyperactivity (31400) =** 6.38 (1.56-26.09)
- **Attention Deficit Disorder with Hyperactivity (31401) =** 8.29 (2.03-33.89)
- **Developmental Speech or Language Disorder (3153) =** 2.09 (1.08-4.03)
- **Other Developmental Speech or Language Disorder (31539) =** 2.32 (1.20-4.48)
- **Coordination Disorder (3154) =** 18.26 (5.65-59.07)
- **Unspecified Delay in Development (3159) =** 2.08 (1.03-4.19)
Subsequently, Thomas Verstraeten, Frank DeStefano and Robert Davis, drafted a "02/29/00" Confidential – Do Not Release report, finding a significant relationship between Thimerosal-containing childhood vaccines and some types of neurodevelopmental disorders, including autism.

That draft report specifically stated:

"...we have found increasing risks of neurologic developmental disorders with increasing cumulative exposure to Thimerosal... increases were seen for the sub-group called specific delays (ICD9 code 315) and within this sub-group for the specific disorder developmental speech disorder (dyslalia, ICD9 code 315.39) and for autism (ICD9 code 299.0), stuttering (ICD9 code 307.0) and attention deficit disorder (ICD9 code 314.0)...."

In a "06/01/00" draft (the closest draft provided under the Freedom of Information Act [FOIA] to SafeMinds in 2001) to the exact documents discussed in a closed meeting held between government and industry at the Simpsonwood Retreat Center on June 7-8, 2000 in Norcross, Georgia), this "Confidential" report, titled, "Risk of neurologic and renal impairment associated with thimerosal-containing vaccines," reported:

"Background: Thimerosal is mercury-based preservative in vaccines. Theoretical concerns have been raised that, through vaccinations, infants were being exposed to mercury levels exceeding Environmental Protection Agency guidelines. We used automated data from two health maintenance organizations, prospectively collected for vaccine safety studies, to assess the risk of neurologic and renal impairment associated with exposure to Thimerosal-containing vaccines.

Methods: Cumulative exposure to mercury from Thimerosal was evaluated at 1, 2, 3 and 6 months of age for 213,185 infants born between 1992 and 1997. Using proportional hazards models, we compared the risk of 16 neurologic disorders and 1 renal disorder to cumulative exposure levels.

Results: We identified 3517 children with neurologic disorders, and 106 with renal disorders. We found a statistically significant positive correlation between the following measures of exposure and outcomes: the cumulative exposure at 2 months of age and unspecified developmental delay; the cumulative exposure at 3 months of age and tics; the cumulative exposure at 6 months of age and attention deficit disorder; the cumulative exposure at 1, 3, and 6 months of age and language and speech delay; and the cumulative exposure at 1, 3, and 6 months of age neurodevelopmental delays in general.

Conclusion: This analysis suggests that in our study population, the risks of tics, ADD, language and speech delays, and developmental delays in general may be increased by exposure to mercury from Thimerosal-containing vaccines during the first 6 months of life."

131 Verstraeten T, Davis R, DeStefano F. Thimerosal VSD study, phase I, update, 02/29/00. Obtained by SafeMinds under FOIA in 2001. [Note: This draft ends with 5 pages, having a footer notation of "LKLK03/28/00... Response.doc," and starting with a page heading of "Thimerosal VSD study- Follow-up on conference call 03/02/2000," that indicate the overall document dates to the end of March 2000.]

Even so, *principally because of a change in criteria and the inclusion of additional children*, the relationships reported in this June draft were different and less significant than those observed previously.

In the published version of that study, Verstraeten et al., *using further adjusted criteria and an altered dataset*, found even fewer significant relationships between the Thimerosal-containing childhood vaccines and some types of neurodevelopmental disorders.\(^{133}\)

In 2004, Verstraeten, *the lead author in the cited drafts and the prior publication*, reiterated that the *published* findings were *epidemiologically neutral* (i.e., could *neither* accept *nor* reject) with respect to a causal relationship between Thimerosal inoculation exposure and neurodevelopmental disorders (NDDs), in general, or diagnosed autism, in specific.\(^{134}\)

A version of the June 2000 report (that, *after further “adjustment”*, was used to generate the published article) was the subject of robust debate in the “Simpsonwood” closed meeting.\(^{135}\)

The following are some pertinent excerpts from a copy of a printed record of the “Simpsonwood” meeting. [Note: This record, obtained by SafeMinds under FOIA in 2001, sheds light on the underlying issues surrounding the June draft’s findings. *Where appropriate, bolding has been added to the quoted passages for emphasis.*]

Dr. Bernier (page 113): “We have asked you to keep this information confidential... So we are asking people who have done a great job protecting this information up until now, to continue to do that until the time of the ACIP meeting... That would help all of us to use the machinery that we have in place for considering these data and for arriving at policy recommendations.”

Dr. Verstraeten (page 31): “It is sort of interesting that when I first came to the CDC as a NIS officer a year ago only, I didn’t really know what I wanted to do, but one of the things I knew I didn’t want to do was studies that had to do with toxicology or environmental health. Because I thought it was too much confounding and it’s very hard to prove anything in those studies. Now it turns out that other people also thought that this study was not the right thing to do, so what I will present to you is the study that nobody thought we should do.”


\(^{134}\) Verstraeten T. Thimerosal, the Centers for Disease Control and Prevention, and GlaxoSmithKline. *Pediatrics* 2004; 113: 932.

\(^{135}\) A copy of the printed Simpsonwood-meeting record & PowerPoint Slides.
Dr. Verstraeten (pages 40 – 41): "...we have found statistically significant relationships between the exposures and outcomes for these different exposures and outcomes. First, for two months of age, an unspecified developmental delay, which has its own specific ICD-9 code. Exposure at three months of age, Tics. Exposure at six months of age, an attention deficit disorder. Exposure at one, three and six months of age, language and speech delays which are two separate ICD-9 codes. Exposure at three months of age, an unspecified developmental delay, which has its own specific ICD-9 code. Exposure at three months of age, the entire category of neurodevelopmental delays, which includes all of these plus a number of other disorders.”

Dr. Chen (page 151): "One of the reasons that led me personally to not be so quick to dismiss the findings was that on his own Tom independently picked three different outcomes that he did not think could be associated with mercury (conjunctivitis, diarrhea and injury) and three out of three had a different pattern across different exposure levels as compared to the ones that again on a priority basis we picked as biologically plausible to be due to mercury exposure.”

Dr. Johnston (pages 199 – 200): "This association leads me to favor a recommendation that infants up to two years old not be immunized with Thimerosal containing vaccines if suitable alternative preparations are available. My gut feeling? It worries me enough. Forgive this personal comment, but I got called out at eight o’clock for an emergency call and my daughter-in-law delivered a son by C-Section. Our first male in the line of the next generation, and I do not want that grandson to get a Thimerosal containing vaccine until we know better what is going on. It will probably take a long time. In the meantime, and I know there are probably implications for this internationally, but in the meantime I think I want that grandson to only be given Thimerosal-free vaccines.”

Dr. Weil (page 207): "The number of dose related relationships are linear and statistically significant. You can play with this all you want. They are linear. They are statistically significant. The positive relationships are those that one might expect from the Faeroe Islands studies. They are also related to those data we do have on experimental animal data and similar to the neurodevelopmental tox data on other substances, so that I think you can’t accept that this is out of the ordinary. It isn’t out of the ordinary.”

Dr. Brent (page 229): "The medical legal findings in this study, causal or not, are horrendous and therefore, it is important that the suggested epidemiological, pharmacokinetic, and animal studies be performed. If an allegation was made that a child's neurobehavioral findings were caused by Thimerosal containing vaccines, you could readily find a junk scientist who would support the claim with 'a reasonable degree of certainty'. But you will not find a scientist with any integrity who would say the reverse with the data that is available. And that is true. So we are in a bad position from the standpoint of defending any lawsuits if they were initiated and I am concerned.”

Dr. Clements (pages 247 – 248): "I am really concerned that we have taken off like a boat going down one arm of the mangrove swamp at high speed, when in fact there was not enough discussion really early on about which way the boat should go at all. And I really want to risk offending everyone in the room by saying that perhaps this study should not have been done at all, because the outcome of it could have, to some extent, been predicted, and we have all reached this point now where we are left hanging, even though I hear the majority of consultants say to the Board that they are not convinced there is a causality direct link between Thimerosal and various neurological outcomes. I know how we handle it from here is extremely problematic. The ACIP is going to depend on comments from this group in order to move forward into policy, and I have been advised that whatever I say should not move into the policy area because that is not the point of this meeting. But nonetheless, we know from many experiences in history that the pure scientist has done research because of pure science. But
that pure science has resulted in splitting the atom or some other process which is completely beyond
the power of the scientists who did the research to control it. And what we have here is people who
have, for every best reason in the world, pursued a direction of research. But there is now the point at
which the research results have to be handled, and even if this committee decides that there is no
association and that information gets out, the work that has been done and through the freedom of
information that will be taken by others and will be used in ways beyond the control of this group. And I
am very concerned about that as I suspect it is already too late to do anything regardless of any
professional body and what they say ..."

b. A Congressman’s Published Views on the CDC Study

On October 31, 2003, after reviewing the CDC-sponsored article and the report from the 2000
closed-door meeting, Congressman Dave Weldon, a concerned legislator and physician, wrote a
letter to Julie Gerberding136, Director of the CDC, stating:

“I have reviewed the article and have serious reservations about the four-year evolution and
conclusions of this study. . . ."

The Congressman then continued:

“I am a strong supporter of childhood vaccinations and know that they have saved us from
considerable death suffering. A key part of our vaccination program is to ensure that we do
everything possible to ensure that these vaccines, which are mandatory, are as safe as possible. We
must fully disclose adverse events. Anything less than this undermines public confidence.

I have read the upcoming *Pediatrics* study and several earlier versions of this study dating back to
February 2000. I have read various emails from Dr. Verstraeten and coauthors. I have reviewed
transcripts of a discussion at Simpsonwood, GA between the author, various CDC employees and
vaccine industry representatives. I have found a disturbing pattern which merits a thorough, open,
timely, and independent review by researchers outside of the CDC, HHS, the vaccine industry, and
others with a conflict of interest in vaccine related issues (including many in University settings who
may have conflicts).

A review of these documents leaves me very concerned that rather than seeking to understand
whether or not some children were exposed to harmful levels of mercury in childhood vaccines in the
1990s, there may have been a selective use of the data to make the associations in the earliest study
disappear. . . .

Furthermore, the lead author of the article, Dr. Thomas Verstraeten, worked for the CDC until he left
over two years ago to work for GlaxoSmithKline (GSK), a vaccine manufacturer facing liability over
TCVs. In violation of their own standards of conduct, *Pediatrics* failed to disclose that Dr.
Verstraeten is employed by GSK and incorrectly identifies him as an employee of the CDC. This
revelation undermines this study further.

The first version of the study, produced in February 2000, found a significant association between
exposure to thimerosal-containing vaccines (TCVs) and autism and neurological developmental
delays (NDDs). When comparing children exposed to 62.5 µg [micrograms] of mercury by 3 months
of age to those exposed to less than 37.5 µg, the study found a relative risk for autism of 2.48 for
those with the higher exposure levels. (While not significant in the 95% confidence interval for

136 Congressman Dr. Dave Weldon’s Official Letter to Julie Gerberding, Director of the CDC, dated October 31, 2003.
autism, this meets the legal standard of proof exceeding 2.0.) For NDDs, the study found a relative risk of 1.59 and a definite upward trend as exposure levels increased.

A June 2000 version of the study applied various data manipulations to reduce the autism association to 1.69 and the authors went outside of the VSD database to secure data from a Massachusetts HMO (Havard Pilgrim, HP) in order to counter the association found between TCVs and speech delay. At the time that HP's data was brought in, HP was in receivership by the state of Massachusetts, its computer records had been in shambles for years, it had multiple computer systems that could not communicate with one another, and it used a health care coding system totally different from the one used across the VSD. There are questions relating to a significant underreporting of Autism in Massachusetts. The HP dataset is only about 15% of the HMO dataset used in the February 2000 study. There may also be significant problems with the statistical power of the dataset.

In June 2000, a meeting was held in Simpsonwood, GA, involving the authors of the study, representatives of the CDC, and the vaccine industry. I have reviewed a transcript of this meeting that was obtained through FOIA. Comments from Simpsonwood meeting include: (summary form, not direct quotes):

- We found a statistically significant relationship between exposures and outcomes. There is certainly an under ascertainment of adverse outcomes because some children are just simply not old enough to be diagnosed, the current incidence rates are much lower than we would expect to see (Verstraeten);
- We could exclude the lower exposure children from our database. Also suggested with removing the children that got the highest exposure levels since they represented an unusually high percentage of outcomes (Rhodes);
- The significant association with language delay is quite large (Verstraeten);
- This information should be kept confidential and considered embargoed;
- We can push and pull this data anyway we want to get the results we want;
- We can alter the exclusion criteria any way we want, give reasonable justifications for doing so, and get any result we want;
- There was really no need to do this study. We could have predicted the outcomes;
- I will not give TCVs to my grandson until I find out what is going on here.

Another version of the study — after further manipulation — finds no association between TCVs and autism, and no consistency across HMOs between TCVs and NDDs and speech delay.

The final version of the study concludes that 'No consistent significant associations were found between TCVs and neurodevelopmental outcomes,' and that the lack of consistency argues against an association. In reviewing the study there are data points where children with higher exposures to the neurotoxin mercury had fewer developmental disorders. This demonstrates to me how excessive manipulation of data can lead to absurd results. Such a conclusion is not unexpected from an author with a serious, though undisclosed, conflict of interest. This study increases speculation of an association between TCVs and neurodevelopmental outcomes."

c. Epidemiological Studies from Other Developed Countries

Other epidemiological studies using the health records of groups of Danish, Swedish, English and Canadian children and purporting to show a negative correlation between the maximum level of
Thimerosal in their recommended vaccination program and autism have been published.\(^{137}\)

Sadly, for the most part, these studies have little applicability to the United States’ experience with Thimerosal-containing vaccine immunizations.

This is the case in Denmark, Sweden, England, and Canada because:

- Significantly lower maximum levels of Thimerosal were administered to their children as part of the childhood immunization schedule than to American children.

- *When compared to the vaccination schedules in these countries*, the CDC’s recommended vaccination schedules specified more Thimerosal-containing inoculations and, *in most cases*, a more compressed early childhood schedule.

Additionally, the studies in *Denmark* are flawed and have been criticized\(^{138}\) because:

- *Initially, only* inpatient diagnosed autistics were identified; later in these studies, *both* inpatient and outpatient diagnosed autistics were identified – leading to an increase in reporting being improperly twisted into an increase in incidence.

- Different diagnosis codes of neurodevelopmental maladies, i.e., psychosis infantilis posterior (ICD-8 299.01) versus atypical (i.e., regressive) autism (ICD-10 F84.1), were used before and during the periods of presumed increase in autism incidence, respectively.

- Data from additional clinics, with a significant portion of the autistic children in the entire country, were added as the studies progressed.


Further, the very Danish vaccine manufacturer who obtains a significant portion of its
profits from the manufacture and distribution of “Thimerosal-preserved” vaccines in
Denmark, Sweden and elsewhere, authored, financed, and/or resourced these studies.

Finally, much of the information needed to validly compare these results to those found in
the U.S. was simply not reported.

Additionally, the studies in England are flawed and have been criticized\textsuperscript{139} because:

- The study was compromised by undisclosed conflicts of interest from its inception.
- The study made a knowingly false claim about the equivalence of the mercury burden in the
  WHO and the UK routine-vaccination schedules.
- The database used in the study was, at best, weak, and
- The authors deliberately excluded confounding evidence that clearly established the autism
  rate rose when the schedule was changed in the UK in 1990.

Additionally, the study in Canada, which the FDA alluded to in the Agency’s “SEP 26 2006
letter (2004P-0349/PDN1), is flawed and it has been appropriately criticized\textsuperscript{140}

14. Studies Establishing Linkages Between Thimerosal Exposure And Adverse Outcomes, Including
"Neurodevelopmental Disorders" ("NDDs") in US Children

In stark contrast to the published epidemiological studies funded by pharmaceutical or
government monies, numerous published epidemiological studies by the Geiers\textsuperscript{141}, Holmes et al.\textsuperscript{142},

\textsuperscript{140} King PG (e-mail) to Fombonne E [27 August 2006];
\textsuperscript{141} a. Geier DA, Geier MR. A case series of children with apparent mercury toxic encephalopathies manifesting with
b. Geier DA, Geier MR. A meta-analysis epidemiological assessment of neurodevelopmental disorders following
c. Geier DA, Geier MR. An evaluation of the effects of thimerosal on neurodevelopmental disorders reported
  following DTP and Hib vaccines in comparison to DTPH vaccine in the United States. J Toxicol Environ
  Health A 2006; 69: 1481-1495.
d. Geier DA, Geier MR. An assessment of downward trends in neurodevelopmental disorders in the United States
and the Environmental Working Group\textsuperscript{143} clearly establish a causal association between increasing mercury exposure from Thimerosal-containing childhood vaccines/biological preparations and neurodevelopmental disorders.

In the studies by Geier and Geier and by Holmes et al., the authors found a statistically significant, "2- to 6- fold overall" and "dose-response related," increased risk, in the United States, for neurodevelopmental disorders following the administration of additional doses of Thimerosal-containing vaccines/biological preparations in conformance to the applicable recommended schedules.

In addition, Geier and Geier reported children received doses of mercury from Thimerosal-containing childhood vaccines that were in some cases more than 100-fold in excess of the FDA's and/or the EPA's allowable safety guidelines for instantaneous exposure to orally ingested methylmercury.

The Environmental Working Group reported on the results of an ecological epidemiological study correlating increases in the number of cases of autism in the California Department of Developmental Services with increasing cumulative doses of mercury that children received from Thimerosal-containing childhood vaccines.


Further, a series of population epidemiological studies have shown that there are significant associations between environmental mercury exposure and autism.

For example, Counter et al. conducted an epidemiological study of mercury exposure on the prevalence of neuro-otological symptoms among 114 primarily school children from gold-mining areas of Ecuador.\textsuperscript{144}

In the study areas, the sources of mercury exposure included: inhalation of mercury vapors during the burning of mercury, a process used to separate gold particulates from alluvial sediment and rock soil from the mountain mines and rivers, and possibly consumption of methylmercury contaminated fish from local rivers, and of domestic chickens and pigs that ate from mercury-contaminated ground soil.

These researchers observed prevalent learning disabilities, attention deficits, and autism among the school children examined.

A series of epidemiological studies conducted in the US (in California, Louisiana, and Texas) have all also found significant associations between mercury exposure and autistic disorders.\textsuperscript{145}

In the most recent study published from California (supported by the US CDC), 283 children with autism spectrum disorders and 657 controls, born in 1994 in the San Francisco Bay area, were examined.

These researchers assigned exposure level by census tract of birth residence for 19 chemicals.

Among the 19 chemicals examined to which children were exposed, mercury was found to be the single largest risk factor associated with autistic disorders.


\textsuperscript{145} a. Rury J (Thesis). Links between environmental mercury special education and autism in Louisiana. Department of Environmental Studies, Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College, May 2006.


When comparing high mercury exposure relative to low mercury exposure, there was a statistically significant increase of the risk, which was about double, for having an autistic disorder.146

15. Clinical Evidence

Growing clinical evidence strongly suggests that many, if not most, of these damaged children are members of a genetically vulnerable, mercury-sensitive subpopulation that have been, and are being, injured by:

a. The mercury-based preservatives in vaccines with which they have been immunized and/or,

b. In utero, by the mercury-based preservatives in some of the drugs prescribed to and/or used by their mothers.

Bradstreet et al. have evaluated the concentration of heavy metals in the urine among 221 children with autistic spectrum disorders against 18 neurotypical controls based upon excretion levels following a three-day treatment with DMSA, an US FDA approved chelating agent.147

The authors observed that the urinary mercury difference was statistically significant and about 3-fold higher, on average, in the urine of children with autistic spectrum disorders than in the urine of the neurotypical controls.

In contrast, after the treatment, the children with autistic spectrum disorders and neurotypical controls had similar urinary cadmium and lead concentrations in their urine samples.

Similarly, in 2003, Holmes et al. reported that one possible factor underlying this rapid growth in the number of children with neurodevelopmental disorders is the increased exposure to mercury


in vaccines arising from an increasing number of immunizations of newborns and young children with Thimerosal-containing vaccines.\textsuperscript{148}

However, these researchers cautioned that vaccine exposures should be evaluated in the context of cumulative exposures during gestation and early infancy.

These researchers commented that differential rates of postnatal mercury elimination may explain why similar gestational and infant exposures produce variable neurological effects.

First baby haircut samples were obtained from 94 children diagnosed with autism and 45 age- and gender-matched controls.

Information on diet, dental amalgam fillings, vaccine history, RhoD immunoglobulin administration, and autism symptom severity was collected through a maternal survey questionnaire and clinical observation.

Resulting average mercury levels in hair samples from the autistic group of children were 0.47 parts-per-million versus 3.63 parts-per-million in the control group of children, a significant difference.

Furthermore, the mothers of the children in the autistic group had significantly higher levels of mercury exposure through RhoD immunoglobulin injections and amalgam fillings than the mothers of the children in the control groups.

Within the autistic group, the mercury levels in their hair samples varied significantly across the mildly, moderately, and severely autistic subgroups of children, with mean subgroup levels of 0.79, 0.46, and 0.21 parts-per-million, respectively.

Among the infants in the two control groups, the mercury levels in their hair samples matched the levels expected from their historical exposures to mercury-containing materials, including exposure to mercury through pediatric vaccinations.

By contrast, these correlations were absent in the group of autistic children.

[Note: Based on the hair results, it is apparent that the mercury detoxification and excretion patterns among autistic infants were significantly reduced relative to those of the matched control infants.]

After a thorough review of clinical studies to date, Dr. H. Vasken Aposhian, Ph. D., Professor of Molecular and Cellular Biology, University of Arizona, referring to the causal association between mercury exposure and the disorder we have misnamed “autism,” declared before the Institute of Medicine (IOM) at its February 9, 2004 Meeting, “We are moving toward causality.”

[Note: Appropriately, Dr. Aposhian described “autism” as a “Mercury Effluxor” [elimination] “Disorder.”]

Recently, Adams et al. evaluated baby teeth as a measure of cumulative exposure to toxic metals during fetal development and early infancy in autistic children relative to matched controls.

They observed that mean mercury levels in baby teeth from autistic children were over 2-fold (significantly) higher than controls, whereas lead and zinc levels were similar in both groups.

In 2007, these researchers concluded that autistic children had a higher body burden of mercury during fetal/infant development than neurotypical children.

These researchers also commented that it is interesting to note that the median mercury level in the control teeth was 50 parts-per-billion, which is similar to the level of mercury (40–50 parts-per-billion) found by Burbacher et al. (2005) in the brains of infant monkeys following dosing of the monkeys with Thimerosal in a manner that mimicked the U.S. childhood vaccination schedule.

If baby teeth levels correlate with brain levels, then this suggests that the children with autism in this small study could have had median brain levels of mercury of 140 parts-per-billion, which is

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149 Institute of Medicine (IOM) meeting held at the National Academy of Sciences in Washington, DC on February 9, 2004.

approaching the level of what had previously been estimated as necessary to result in mercury-induced neurological disorders.

Other researchers have also recently analyzed the results from urinary porphyrin profile tests for two autistic-spectrum disorder (ASD) cohorts and compared their findings to the results found for sibling and unrelated matched controls.\(^{151}\)

Significantly, they observed that there were 2- to 3-fold increased concentrations of the urinary porphyrins specifically known to be associated with mercury poisoning (i.e., precoproporphyrin, pentacarboxyporphyrin, and coproporphyrin) among autistic individuals in comparison with controls with greater than 50% of children with an ASD diagnosis having urinary coproporphyrin levels more than 2 standard deviations above the control mean level for urinary coproporphyrin.

Furthermore, they observed that: a) the increasing clinical severity of autistic disorders correlated with increasing levels of those urinary porphyrins associated with mercury poisoning relative to the level of each sample’s uroporphyrin, and b) chelation significantly reduced the levels of the mercury-poisoning-related urinary porphyrins observed among individuals with an Autism Spectrum Disorder (ASD) diagnosis.

Vojdani et al. have reported that genetic and environmental factors including xenobiotics play a critical role in the development of autism.\(^{152}\)

In this study, the researchers postulated that ethyl mercury (xenobiotic) binds to different lymphocyte receptors and tissue enzymes (DPP IV or CD26).

They assessed this hypothesis first by measuring IgG, IgM and IgA antibodies against CD26, CD69, and against ethyl mercury bound to human serum albumin in patients with autism.


A significant percentage of children with autism developed anti-ethyl mercury antibodies, concomitant with the appearance of anti-CD26 and anti-CD69 autoantibodies.

These antibodies are synthesized as a result of 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 ethyl mercury binding to CD26 or CD69, microtiter wells were coated with CD26 or CD69 alone or in combination with 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.

These researchers, then, proposed that 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 demonstrates that ethyl mercury binds to lymphocyte receptors and/or tissue enzymes, resulting in autoimmune reaction in children with autism.

Deth and Waly have reported that methylation events play a critical role in the ability of growth factors to promote normal development.

They observed folate-dependent, phospholipid methylation in the lymphoblasts of children with an ASD diagnosis were, in a dose-response manner, significantly more sensitive to Thimerosal exposure than their unaffected siblings.¹⁵³

Walker et al. postulated that Thimerosal may be a potential triggering mechanism contributing to autism in susceptible individuals, and that one potential risk factor in these individuals may be an

inability to adequately up-regulate metallothionein (MT) biosynthesis in response to heavy metals (MTs may help to modulate mercury neurotoxicity).

Cultured lymphocytes from autistics challenged with zinc responded with an impressive up-regulation of MT transcripts (at least nine different MTs were over-expressed), whereas these same cells, when challenged with Thimerosal responded by up-regulating numerous heat shock protein transcripts, but not the MT transcripts.\textsuperscript{154}

In considering heavy metal toxicity, mercury binds to the cysteine thiol (-SH) groups in intracellular proteins and inactivates their function.

The cysteine-SH group of glutathione binds mercury and protects essential proteins from functional inactivation.\textsuperscript{155}

The synthesis of glutathione has been directly linked to the rate of mercury excretion and the cellular protection from mercury-induced damage.\textsuperscript{156}

Thus, individuals with genetic deficiencies in glutathione synthesis will be less able to excrete mercury and will be more sensitive to its adverse effects.\textsuperscript{157}

Several recent studies have examined blood markers in the transsulfuration pathway in autistic disorders.

These studies have demonstrated that autistic patients had significant reductions in cysteine, sulfate, total glutathione, and reduced glutathione (i.e., active glutathione that can bind mercury)

and significant increases in oxidized glutathione (i.e., inactive glutathione that cannot bind mercury) in comparison to controls.  

In addition to biochemical susceptibilities to heavy metal toxicity in children diagnosed with an autism spectrum disorder (ASD), several recent studies assessed genomic susceptibilities to heavy metal toxicity in those with an ASD diagnosis.

The results demonstrated that there were significant correlations between genomic changes associated with reduced functioning in heavy-metal detoxification enzymes (i.e. gene deletions/polymorphisms) and autistic disorders, including: reduced folate carrier (RFC), catechol-O-methyltransferase (COMT), transcobalamin II (TCN2), glutathione S-transferase M1 (GSTM1), glutathione S-transferase P1 (GSTP1), 10-methylenetetrahydrofolate reductase (MTHFR), metal-regulatory transcription factor 1 (MTF1), and divalent metal ion transporter SLC11A3.

16. Review Studies

Regarding the effects of mercury exposure on neuronal development, in 2000, Faustman et al. reported, “...mercury exposure altered cell number and cell division; these impacts have been postulated as modes of action for the observed adverse effects in neuronal development.


The potential implications of such observations are evident when evaluated in context with research showing that altered cell proliferation and focal neuropathologic effects have been linked with specific neurobehavioral deficits (e.g., autism)."  

Additionally, researchers reported that exposure to mercury can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autistic disorders, and that these similarities extend to neuroanatomy, neurotransmitters, and biochemistry.

The following is a listing of some additional relevant studies:

2. State of California 2004 review of the literature and conclusions classifying Thimerosal as a developmental and reproductive toxin.

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**17. The FDA’s Review of Thimerosal as a Problematic Preservative**

[Note: Where appropriate, bolding has been added to the quoted passages for emphasis.]

Sadly, for seven decades, the FDA has not heeded the recommendations (made by recognized researchers from many scientific and medicinal disciplines) published in the peer-reviewed scientific and medical literature, the pharmaceutical companies public disclosure documents, or the results of its own evaluations of Thimerosal that have shown Thimerosal to be extremely poisonous.

The following are just a few examples of FDA’s own findings of concern about Thimerosal.

For example, in late 1977 the FDA made the following recommendations as proposed rules regarding the use of Thimerosal as a preservative:

“There is now evidence that thimerosal may (1) induce cell mediated hypersensitivity and (2) affect the size of the delayed skin test reaction in some subjects. Therefore, (1) when other preservatives have been demonstrated to be safe, effective, nonsensitizing (as well as not causing deterioration of the product), products containing thimerosal should be discontinued; and (2) a search for safe, effective and nonsensitizing preservatives as alternatives to thimerosal should be initiated.”161

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As another example, in early 1999, an email string was started involving Dr. Ball of the FDA discussing the number of reaction reports in the FDA’s possession that mentioned Thimerosal.162

The following texts were posted:

"From: Varricchio, Frederick  
Sent: Thursday, January 07, 1999 10:17 AM  
To: Ball, Leslie  
Subject:  
I HAVE SOME RESULTS FOR YOU. PROBLEM IS THAT THERE ARE 7000 REPORTS THAT MENTION THIMERASOL. WHAT TO DO NOW. OBVIOUSLY LOOKING AT ALL 7000 IS A BRUTE FORCE APPROACH  
frederick varricchio"

From: Ball, Leslie  
Sent: Thursday, January 07, 1999 11:10 AM  
To: Vamcchio, Frederick  
Cc: Pratt, Douglas R.; Ball, Robert  
Subject: RE:  
Fred: Are there 7000 reports just for immune globulins and other biologics? Drugs have been excluded? If there are really 7000 reports for biologics, perhaps you can get records on a subset of 50 or so we can look at them and get a general feel for what’s been reported before we go any further. I’ll be out of the office for Dr. Hardegrees party until 1:30 or 2 today, or I can discuss it with you tomorrow after 1 pm.  
Leslie

From: Varricchio, Frederick  
Sent: Tuesday, January 19, 1999 5:31 PM  
To: Ball, Leslie  
Subject: RE:  
Our plan is to get whatever is on the summary for every 100th report. We should have that in a couple of days. I’ll let you know when it is here and we can see what to do next.”

Furthermore, as another example, on 28 June 1999, Dr. Esber of the FDA wrote an email (importance: high) on the excessive amounts of mercury present in childhood vaccines.163

In that email, she reported:

"Issue: A conference call was convened today by the American Academy of Pediatrics' Committee on Infectious Diseases (COID), joined by the Committees on Environmental Sciences and Fetal and Neonatal Issues along with approximately 20 others including PHS agency representatives (FDA, CDC, NIH, NVP), academicians, toxicologists, mercury experts, etc. The issue was a draft ‘recommendation’ prepared by the COID/AAP to ‘use Thimerosal-free vaccines whenever possible and eliminate recommendations for routine Hepatitis B vaccination at birth’ citing accumulating information on the risks of mercury containing compounds. The ‘urgency’ of the issue was precipitated by the recent accumulation of information by CBER scientists stimulated by FDAMA which showed that, if all vaccines used contained Thimerosal, the current immunization schedule contains an amount of Thimerosal that exceeds that amount currently recommended by various groups, including the WHO, EPA, ATSDR, FDA and others.”

162 7 – 19 January 1999 (Emails) – between Ball and Varricchio – 7,000 Thimerosal Reaction Reports.  
163 28 June 1999 (Email) – Esber of the FDA – Summarizing that the Mercury from Thimerosal-containing Vaccines Exceeds All Safety Guidelines.
Subsequent emails on the issue of Thimerosal in vaccines revealed just how “asleep at switch” the FDA was on this issue.

On June 29, 1999, regarding the removal Thimerosal from vaccines, Peter Patriarca stated:

“Will raise questions about FDA being ‘asleep at the switch’ for decades, by allowing a potentially hazardous compound to remain in many childhood vaccines, and not forcing manufacturers to exclude it from new products. Will also raise questions about various advisory bodies about aggressive recommendations for use. [We must keep in mind that the dose of ethyl mercury was not generated by ‘rocket science’” conversion of the % thimerosal to actual ug of mercury involves 9th grade algebra. What took the FDA so long to do the calculations? Why didn’t CDC and the advisory bodies do these calculations while rapidly expanding the childhood immunization schedule?]”164

FDAer Ruth Etzel later stated:

“The Committee on Environmental Health and the Committee on Infectious Diseases may want to look at the way Johnson and Johnson handled the poisoned Tylenol affair in 1982. It followed the three basic rules: (1) act quickly to recall the affected product (2) be open with consumers about what went wrong (3) show contrition. Seventeen years ago, when an extortionist tried to wring money out of Johnson & Johnson by lacing capsules of Tylenol with cyanide, 7 people died. While the government was still considering what to do (sound familiar?), and before the media had time to put the company on the defensive, Johnson & Johnson recalled all Tylenol products. That cost about $100-million and it lost short-term sales. But emerged from the episode with consumer confidence at a higher level than ever, and quickly regained its leadership of the painkiller market. The AAP [American Academy of Pediatrics] should be dedicated to promptly providing truthful information about this situation to pediatricians. We must follow the three basic rules: (1) Act quickly to inform pediatrics that the products have more mercury than we realized (2) Be open with consumers about why we didn’t catch this earlier (3) show contrition. As you know, the Public Health Service informed us yesterday that they were planning to conduct business as usual, and would probably indicate no preference for either product. While the Public Health Service may think that their ‘product’ is immunizations, I think that their ‘product’ is their recommendations. If the public loses faith in the PHS recommendations, then the immunization battle will falter. To keep faith, we must be open and honest now and move forward to quickly replace these products.”165

On July 2, 1999, FDAer Peter Patriarca expressed his concern in a “confidential” email:

“Finally, in my own personal opinion – and as a heads-up because I believe it could come up – the greatest point of vulnerability on this issue is that the systematic review of thimerosal in vaccines by the FDA could have been done years ago and on an ongoing basis as the childhood immunization schedule became more complex. The calculations done by FDA are not complex. I’m not sure if there will be an easy way out of the potential perception that the FDA, the CDC and immunization policy bodies may have been ‘asleep at the switch’ re: thimerosal until now.”166

164 29 June 1999 (Email) – Patriarca of the FDA – Asleep at the Switch & Interim Plan Re: Thimerosal.
165 2 July 1999 (Email) – Ruth Etzel on Thimerosal.
166 2 July 1999 (Email – Confidential) – Peter Patriarca to Lawrence Bachorik on Thimerosal.
On 11-12 August 1999 significant concerns were raised in closed-door meeting between members of the FDA, CDC and vaccine manufacturer representatives concerning the use of Thimerosal in vaccines.167

On March 20, 2000, a “National Toxicology Program; National Institute of Environmental Health Sciences; Center for the Evaluation of Risks to Human Reproduction” notice, which listed Thimerosal (54-64-8) as one of the eleven (11) “Chemicals Recommended for Further Consideration,” appeared in the U.S. Federal Register.168

In 2001, the National Toxicology Program (NTP) of the National Institutes of Health prepared an informational material on Thimerosal.169

It reported as follows:

“TOXICITY EVALUATION:
Poison by ingestion, subcutaneous, intravenous and possibly other routes. An experimental neoplastigen and teratogen. Experimental reproductive effects.
*CARCINOGENICITY:
Tumorigenic Data:
TDLo: scu-rat 104 mg/kg (1Y-I)...* 
*OTHER TOXICITY DATA:
Skin and Eye Irritation Data: eye-rbt 8{ ag MLD Status: EPA Genetox Program 1988, Positive: S cerevisiae gene conversion EPA TSCA Chemical Inventory-1986...
*SYMPTOMS: Symptoms of exposure to this class of compounds includes aphthous stomatitis, catarrhal gingivitis, nausea, liquid stools, pain, liver disorder, injury to the cardiovascular system and hematopoietic system, deafness and ataxia. Exposure may be fatal. Headache, paresthesia of the tongue, lips, fingers and toes, other non-specific dysfunctions, metallic taste, slight gastrointestinal disturbances, excessive flatus and diarrhea may occur. Acute poisoning may cause gastrointestinal irritation and renal failure. Early signs of severe poisoning include fine tremors of extended hands, loss of side vision, slight loss of coordination in the eyes, speech, writing and gait, inability to stand or carry out voluntary movements, occasional muscle atrophy and flexure contractures, generalized myoclonic movements, difficulty understanding ordinary speech, irritability and bad temper progressing to mania, stupor, coma, mental retardation in children, skin irritation, blisters and dermatitis [173]. Other symptoms include chorea, athetosis, tremors, convulsions, pain and numbness in the extremities, nephritis, salivation, loosening of the teeth, blue line on the gums, anxiety, mental depression, insomnia,
hallucinations and central nervous system effects [30]. Exposure may also cause irritation of the eyes, mucous membranes and upper respiratory tract [26]."

In addition, the pharmaceutical companies themselves in their Material Safety Data Sheet (MSDSs) for Thimerosal have recognized the extreme toxicity of Thimerosal (this information is publicly available to the U.S. FDA).170

The listing on the following page summarizes that data.

An attempted search on the NIEH website (http://www.niehs.gov) on 27 May 2007 led to the discovery that:

a. A search on “thimerosal” returned no hits – forcing a search of the NIH web site:

http://www.nih.gov to find the articles of interest,
b. The “04/22/2007” update of the web page: http://cerhr.niehs.nih.gov/chemicals/ reported:

<table>
<thead>
<tr>
<th>Chemical [CAS No.]</th>
<th>Date Nominated</th>
<th>Phase</th>
<th>Status</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thimerosal [54-64-8]</td>
<td>11/99</td>
<td>Nomination</td>
<td>Deferred 7/00</td>
<td>Chemicals with higher priorities</td>
</tr>
</tbody>
</table>

and indicated that full responsibility for Thimerosal toxicity research apparently has been:

1. Transferred to the National Institute of Allergy and Infectious Diseases (NIAID), Division of Microbiology and Infectious Diseases (DMID) as of October 2006 (at the beginning of FYI 2007) and

2. Limited to studies where the long-term toxic effects of Thimerosal and its initial metabolites in aqueous saline matrices, ethylmercury chloride and ethylmercury hydroxide, on susceptible animals, were either not studied or, if studied, intentionally concealed from the public

**Summary of MSDS Toxicity Data for Thimerosal**

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b. 30-Sept-2001 – Gihon Laboratories Material Safety Datasheet on Thimerosal
c. 1-Sept-1993 – Lilly & Company Material Safety Datasheet on Thimerosal
d. 28-July-2003 – Merck Material Safety Datasheet on Thimerosal

Coalition for Mercury-free Drugs (CoMeD) P-94 August 2007
Label Precautionary Statements:

Highly Toxic (USA)
Very toxic by inhalation, in contact with skin and if swallowed.
Danger of cumulative effects.

Acute Effects:
May be fatal if absorbed through skin.
May be fatal if inhaled.

Target Organ Data:
Brain and coverings (other degenerative changes)
Nervous system effects (insomnia, tremor, anorexia, weakness, headache)
Behavioral (anorexia, human)
Behavioral (change in motor activity)
Behavioral (ataxia)
Behavioral (coma)
Lung effects (tissue changes)
Gastrointestinal (nausea or vomiting)
Digestive effects (hypermotility, diarrhea)
Liver effects (jaundice)
Kidney, ureter, bladder (changes in tubules)
Nutritional and gross metabolic (changes in metabolic acidosis)
Effects on fertility (post-implantation mortality)
Effects on fertility (abortion)
Effects on embryo or fetus (fetal death)
Tumorigenic effects (uterine tumors)
Tumorigenic (neoplastic by Registry for Toxic Effects of Chemical Substances criteria)
Tumorigenic (tumors at site of application)

Reproduction: Offspring nervous system effects including mild to severe mental retardation and motor coordination impairment.

Caution Statement: Thimerosal may enter the body through the skin, is toxic, alters genetic material, may be irritating to the eyes, and cause allergic reactions. Effects of exposure may include numbness of extremities, fetal changes, decreased offspring survival, and lung tissue changes.

Regulatory Information: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

Toxicological Information: Pregnant women should not be exposed to the product.

The transfer to the NIAID, DMID is especially problematic as the NIAID is also responsible for the development of vaccines and, given its conflicts and its mindset, the DMID is not well suited to studying the toxic effects of Thimerosal and its metabolites.

18. Actions To: Remove Drug Products Containing Added Mercury, Disclose Mercury-related Risks, And Comply With Applicable Laws?

a. Introduction
Generally, the federal laws governing the safety and effectiveness of drugs have been enacted in response to public health issues created by the manufacturers thereof.

Moreover, the first federal statute addressing drugs, the **Pure Food and Drugs Act of 1906**, only addressed the “purity” of foods and drugs by prohibiting the interstate commerce of mislabeled and adulterated drugs and food.

However, this law created **no** requirement to prove the drug was either “safe” or “effective.”

1. **The Mandate to Prove Safety**

Reacting to a national outcry over the numerous deaths of children caused by a sulfanilamide drug product distributed without “proof of safety,” in **1938**, Congress passed and President Franklin Delano Roosevelt signed the present-day basis law governing drugs, the Federal Food, Drug and Cosmetic Act (FFDC Act).

Among other things, the FFDC Act of 1938 required **new** drugs to be “proven safe” by the manufacturers who were to: a) appropriately test them for safety, b) submit their safety testing results as a critical part of a new drug application (NDA) to the FDA, who was to approve the drug when the manufacturer’s submitted NDA’s safety testing proved the drug was safe, and c) obtain FDA approval before marketing their new drugs.

The FFDC Act of 1938 also required that drugs have adequate labeling for safe use and made the approval of the labeling a part of the FDA’s drug approval process.

Unfortunately, this statute’s provisions did **not** apply to existing drugs.

In the 1940s, amendments were added to the FFDC Act to require the FDA to certify first the “purity, strength, quality, and identity” of each batch of insulin (1941) and then penicillin (1945).

Subsequently, the FDA’s “each batch” certification requirements were extended to other antibiotics.
In 1951, the Durham-Humphrey Amendment to the FFDC Act clarified the distinction between prescription and nonprescription drugs and, for prescription drugs, added a requirement that the drug's label state: “Caution: Federal law prohibits dispensing without prescription.”

2. The Mandate to Prove Safety and Effectiveness

On October 10, 1962 President Kennedy signed the Kefauver-Harris Amendments to the FFDC Act.

These Amendments required drug manufacturers to prove to the FDA that their products were safe and effective prior to marketing.

These amendments also required that all antibiotics be certified, and gave FDA control over prescription drug advertising.

For this citizen petition, the most important addition was the language codified in 21 U.S.C. § 351(a)(2)(B),171 which renders a drug adulterated (with underlining added for emphasis) “if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety …”

To further comply with the 1962 drug amendments, in 1966, the FDA contracted with the National Academy of Sciences/National Research Council to study drugs approved between 1938 and 1962 from the standpoint of efficacy.

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171 21 U.S.C. “Sec. 351. Adulterated drugs and devices
A drug or device shall be deemed to be adulterated -
(a) Poisonous, insanitary, etc., ingredients; adequate controls in manufacture
(1) ...; or
(2) (A) ... ; or
(B) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess;”
The Drug Efficacy Study Implementation (DESI) evaluated over 3000 separate products and over 16,000 therapeutic claims.

The last NAS/NRC report was submitted in 1969, but the contract was extended through 1973 to cover ongoing issues.

The initial agency review of the NAS/NRC reports by the task force was completed in November 1970.

One of the early effects of the DESI study was the development of the Abbreviated New Drug Application (ANDA).

ANDAs were accepted for reviewed products that required changes in existing labeling to be in compliance.

In September 1981, final regulatory action had been taken on 90% of all DESI products.

By 1984, final action had been completed on 3,443 products; of these, 2,225 were found to be effective, 1,051 were found not effective, and 167 were pending.

In addition, the FDA began to require manufacturers of some products marketed before 1938 to submit fill “NDA” documentation because the reality was that their manufacturing, processing, packing and holding practices and locations had changed since the products were first marketed.

In May 1972, the FDA started applying the principles of retrospective review to over-the-counter (OTC) drugs.

The structure for this OTC review was necessarily different than that of the prescription drug review, mainly because of the vast array of available OTC products.

The OTC review focused on active ingredients, around 1,000 different items, and convened panels of experts to evaluate these OTC drugs.
When the panels issued their reports, the agency then reviewed them and published the results as a series of monographs in the Code of Federal Regulations, specifying the active ingredients, restrictions on formulations, and labeling by therapeutic category.

To facilitate this task, FDA formed seventeen panels, consisting of seven voting members (medical, dental, and scientific experts) and non-voting representatives for industry and consumers.

Initially, these panels were responsible for arranging the drugs into three categories: 1) safe and effective, 2) unsafe and/or ineffective (which should no longer be marketed), and 3) probably safe and effective, but needing further testing to establish significant proof.

The Agency subsequently decided that drugs in the last category, like those in the second, should be taken off the market until sufficient proof dictated otherwise.

This review process is still being conducted.

3. The Enhanced Requirements and Mandates to Prove/Improve Drug Safety

In the late 1970s, a renewed push for changes in drug regulation began at the highest levels of the FDA.

Health, Education and Welfare (HEW) Secretary Joseph Califano felt that, for such changes to be effective, they had to be made through legislation rather than administrative policy.

The initial bill, introduced in Congress on March 17, 1978, was titled the Drug Regulation Reform Act.

It contained nine main provisions to: 1) increase consumer protection, 2) encourage drug innovation, 3) increase consumer information, 4) protect patient rights, 5) improve FDA enforcement, 6) promote competition and cost savings through generic drugs, 7) increase FDA's public accountability, 8) make additional drugs available, and 9) encourage research and training.

Though the bill, strongly opposed and lobbied against by the pharmaceutical industry, failed to be enacted, on September 28, 1978, the FDA issued final regulations, titled "HUMAN AND
VETERINARY DRUGS Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding,\(^{172}\) effective March 28, 1979, that, in its “Summary” stated (with underlining added for emphasis):

“This document amends the FDA regulations that set forth current good manufacturing practice (CGMP) for human and veterinary drug products. The amendments update present regulations in light of current technology for drug manufacturing and delineate requirements more specifically than do the present regulations. Although some of the provisions in these amendments represent requirements not specifically included in the existing CGMP regulations, in many instances the revisions are practices that have been considered implicit in the regulations or are at least considered by most manufacturers to be desirable requirements for their own operations.

Under the Federal Food, Drug, and Cosmetic Act, a drug is deemed to be adulterated unless the methods used in its manufacture, processing, packing, and holding, and the facilities and controls used therefore, conform to current good manufacturing practice so that the drug meets the safety requirements of the act and has the identity and strength and meets the quality and purity characteristics that it is represented to have. The regulations are being updated and made more explicit, and therefore less subject to varying interpretations, to assure that all members of the drug industry are made aware of the level of performance expected of them to be in compliance with the act.”

In addition, in a section titled, “VI. APPLICABILITY OF CGMP REGULATIONS; EXEMPTIONS,” the preamble of the 1978 “HUMAN AND VETERINARY DRUGS Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding” regulations went on to state in paragraph three of Comment “42” (with underlining added for emphasis):

“... After considering these plans and the comments regarding exemptions for specialized drug products or manufacturing activities, the Commissioner has reached the following conclusions:

a. Bulk drugs. It is first necessary to distinguish between (1) "drug products" (i.e., finished dosage forms) that may be held in bulk containers, and (2) bulk drug "components" (i.e., ingredients intended for use in the manufacture or processing of a drug product). The CGMP requirements set forth in Part 211 are intended to apply to the preparation of a finished dosage form, whether or not in packaged form. This is clearly set forth in the regulations (210.3(b)(4) and 211.1(a)). Although these CGMP regulations are not applied to the manufacture of bulk drug components, there are numerous instances where good manufacturing practices for bulk drug components would parallel the requirements set forth in Part 211. For this reason, FDA will utilize the standards of Part 211 as guidelines during inspections of manufacturers of bulk drug components under the jurisdiction of the act.

b. Veterinary drug products. Veterinary drug products shall continue to be subject to the general CGMP regulations for all drug products, with certain specific exceptions, namely 211.42(d), 211.46 (d), and 211.72. Comments regarding the appropriateness of individual provisions of these regulations to veterinary drug products have been considered and responded to under the sections involved. When the provisions of a section in the

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\(^{172}\) FR 434: 5014 and following (September 29, 1978).