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September 21, 2011

Introduction

Following this page is this reviewer's review of "**Scientific Information Regarding the Use of Thimerosal As a Preservative in Vaccines**" submitted by unidentified agencies of the United States of America (USA, US) to the UN Environmental Programme (UNEP), downloaded from http://www.unep.org/hazardoussubstances/Portals/9/Mercury/Documents/INC3/US_information.pdf on 17 August 2011

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This review, titled "A Review of '**Scientific Information Regarding the Use of Thimerosal As a Preservative in Vaccines**'", begins on the next page.

Introductory Remarks

First, to "simplify" this response, when portions of the article, which are quoted in a "Times New Roman" font, being evaluated are specifically addressed in this assessment, those portions will be quoted in an italicized "Times New Roman" font.

Second, this reviewer's assessment follows each quoted portion of the article and is indented to clearly separate it from the preceding portion of the document that is being addressed.

Third, when other sources are quoted, the text is in a "Verdana" font except that references to or quotations from a US statute, law or legally binding regulation are in a bolded "**Arial Narrow**" font.

Finally, should anyone find any significant factual error for which they have independent[a], scientifically sound, peer-reviewed published substantiating documents, please submit that information to this reviewer so that he can improve his understanding of factual reality and, where appropriate, revise his views and this draft.

Respectfully,

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Tel. 1-973-997-1321, after 21:00 Eastern Time
[To whom all responses should be directed]

[a] To qualify, the study should be published by researchers who have no conflicts of interest from their ties to either those commercial entities who profit from the sale of vaccines or those entities, academic, commercial or governmental, who actively promote inoculation programs using vaccines.

A Review of 'Scientific Information Regarding the Use of Thimerosal As a Preservative in Vaccines'

Overview of the Review

In general, the unidentified authors of this document, "***Scientific Information Regarding the Use of Thimerosal As a Preservative in Vaccines***", have: a) provided very little scientifically sound information and b) made clearly unfounded claims regarding Thimerosal's safety for use as a "preservative" in vaccines.

Furthermore, this review has addressed each of the authors' assertions with the reviewer's in-depth understanding of the pertinent scientifically sound and appropriate studies regarding mercury and its compounds as well as the reviewer's general understanding of the "National Vaccine Injury Compensation Program " (NVICP), the administrative petition process it created, and how today's NVICP actually operates.

Hopefully, after reading this review and the information in the articles cited by this reviewer, the delegates to the mercury treaty negotiations will clearly understand the need to rapidly phase out all use of Thimerosal or any other mercury compound in all medicines, starting with an immediate ban on all "Thimerosal preserved" vaccines that can be given to pregnant women and children.

"Scientific Information Regarding the Use of Thimerosal As a Preservative in Vaccines"

In the title, this reviewer finds that the unidentified authors of this document assert that they intend to provide information about "***the Use of Thimerosal As a Preservative in Vaccines***".

However, after reading the text, this reviewer found that its authors often provided inaccurate information about the use of Thimerosal in vaccines as well as extraneous information about issues that did not bear on the use of Thimerosal as a preservative in vaccines (e.g., the toxicity of alkylmercury compounds at levels that are lethal).

With these caveats in mind, this reviewer will now examine the statements made by these anonymous authors.

"***Introduction***

At the second meeting of the mercury intergovernmental negotiating committee, participants requested, among other things, preparation of 'information on health aspects of mercury issues and the use of mercury preservatives in medicine, including vaccines.' As a result of that request, the Secretariat circulated an open-ended invitation for those with relevant expertise or experience to contribute to the process. The United States is responding to this invitation and providing scientific background information regarding thimerosal, an ethylmercury-containing preservative, in some U.S. licensed vaccines."

With respect to the assertion that the "*United States is responding to this invitation and providing scientific background information regarding thimerosal*", this reviewer finds that much of the information provided about Thimerosal, one trade name for sodium ethylmercurithiosalicylate, is not scientifically sound information and/or not information pertinent to the use of Thimerosal as a preservative in vaccines.

Unfortunately, the authors' statement about Thimerosal now purports to provide "*scientific background information regarding thimerosal, an ethylmercury-containing preservative, in some U.S. licensed vaccines*" rather than, as the title states, information about "***the Use of Thimerosal As a Preservative in Vaccines***".

Factually, Thimerosal is a mercury-containing compound that is a known human carcinogen, mutagen, teratogen and immune-system disruptor at levels below 1 part-per-million, and a compound to which some humans can have an anaphylactic shock reaction.

It is also a recognized reproductive and fetal toxin with no established toxicologically safe level of exposure for humans[1].

Thimerosal, often incorrectly referred to as a "preservative", is 49.55% mercury by weight (56.73% "ethyl mercury" by weight) and "*preservative*" is only one of its uses.

As this review will show, published studies have shown that, even at the nominal 0.01% level, Thimerosal is a less-than-effective preservative in some instances[2,3].

To be clear, Thimerosal is not a preservative; Thimerosal is one trade name, of many, for a chemical compound and "*preservative*" is but one of Thimerosal's uses.

"Vaccines have contributed greatly to the health and well-being of children, adolescents, and adults and their widespread use has significantly reduced many serious childhood diseases such as diphtheria, polio, measles, meningitis, and whooping cough in the United States and worldwide. Vaccines licensed in the United States, including the constituent materials such as preservatives, diluents, and adjuvants that may be used in vaccine manufacturing and may be part of the final product, must be determined to be safe and effective by the U.S. Food and Drug Administration (FDA). We offer the following information relating to the science, regulations and policy decisions that the FDA has used to license vaccines with thimerosal preservative in the United States."

First, this reviewer does not disagree with much of what is said in the preceding paragraph concerning vaccines.

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1 In toxicology, the safety limit for the "nontoxicity" of a compound is an appropriately confirmed "no-observed-adverse-effect level" or NOAEL. For "humans", the critical NOAELs would be the NOAEL values for various stages of human development. [**Note:** Outside of an upper-limit estimate of less than (<) 0.0086 micrograms (µg) of Thimerosal per kilogram (kg) of subject body weight per day [< 0.0046 µg of mercury/kg/day] for the NOAEL $_{\text{developing human}}$ and < 0.046 µg of mercury/kg/day] for the NOAEL $_{\text{adult human}}$, which were: **a)** derived from a chronic toxicity study that injected Thimerosal into rats (Mason MM, Cate CC, Baker. Toxicology and Carcinogenesis of Various Chemicals Used in the Preparation of Vaccines. ***J. Clin Toxicol*** 1971; **4**(2): 185-204, a study recognized by the US FDA), and **b)** published in http://mercury-freedrugs.org/docs/090812_fnldrft_TheTruthAboutTheToxicityOfThimerosalr5b.pdf in 2009, this reviewer knows of no other published NOAEL value estimates for injected Thimerosal in humans.]

2 Stetler HC, Garbe PL, Dwyer DM, et al. Outbreaks of group A streptococcal abscesses following diphtheria-tetanus toxoid-pertussis vaccination. ***Pediatrics*** 1985; **75**: 299-303.

3 Khandke L, Yang C, Krylova K, Jansen KU, Rashidbaig A. Preservative of choice for Prev(e)nar 13™ in a multi-dose formulation. ***Vaccine*** 2011, in press.

However, most of the vaccines that truly "*have contributed greatly to the health and well-being of children, adolescents, and adults*" neither contain Thimerosal nor use Thimerosal as a preservative.

Further, this reviewer notes that even the FDA has admitted that the safety of Thimerosal, when used as a preservative, has not been established to the regulatory standard, "sufficiently nontoxic …"[4] as set forth in Title 21 of the United States Code of Federal Regulations (21 CFR) at paragraph 610.15(a) [21 CFR § 610.15(a)].

This fact was established in a three-year investigation by a United States House Committee and set forth in the "**A. Findings**" section of its published 2003 report[5].

To date, the FDA has not provided the public any appropriate, scientifically sound toxicological studies conducted by the manufacturers of "Thimerosal preserved" vaccines that would be necessary to refute those published Congressional findings, even though this reviewer's organization, CoMeD, Inc. (the Coalition for Mercury-free Drugs) has repeatedly sought, and is currently seeking, such information.

Moreover, the authors' "*Vaccines licensed in the United States, …, must be determined to be safe and effective by the U.S. Food and Drug Administration (FDA)*" is a knowing misrepresentation because the manufacturer of a vaccine, which is regulated as a drug[6], *and not the FDA*, has the absolute, non-dischargeable duty to prove that each vaccine and the components[7] in it are safe to all of the standards established for the vaccine and the components in it as well as the responsibility to show that its

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4 The relevant portion of 21 CFR § 610.15(a), an explicit binding requirement on all manufacturers of biological drug products, including vaccines, states (emphasis added), "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,"

5 "**Mercury in Medicine – Taking Unnecessary Risks**, A Report Prepared by the Staff of the Subcommittee on Human Rights and Wellness, Committee on Government Reform United States House of Representatives, Chairman Dan Burton, May 2003 (This Report Is the Result of a Three Year Investigation Initiated in the Committee on Government Reform)", which was also published in the Extended Congressional Record, *May 21, 2003* CONGRESSIONAL RECORD—Extensions of Remarks, pages E1011-E1030; the relevant finding is disclosed in column 3 of page E1012 (emphasis added): "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."

6 21 CFR § 211.1 Scope. [emphasis added]

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.

(b) The current good manufacturing practice regulations in this chapter as they pertain to drug products; in parts 600 through 680 of this chapter, as they pertain to drugs that are also biological products for human use; and in part 1271 of this chapter, as they are applicable to drugs that are also human cells, tissues, and cellular and tissue-based products (HCT/Ps) and that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); supplement and do not supersede the regulations in this part unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, or in parts 600 through 680 of this chapter, or in part 1271 of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.

7 Title 21 of the United States Code (21 U.S.C.) at Section 321(g)(1) (21 U.S.C. § 321(g)(1)) [emphasis added]:
"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). …"

vaccine meets certain predetermined "efficacy" criteria that are presumed to reflect the vaccine's in-use "effectiveness".

For vaccines, the current role of the FDA is to make a "determination" that: a) the manufacturer has proven that the vaccine and its components are safe to all of the applicable safety standards and b) the vaccine has an accepted efficacy, as measured by some antibody titer criteria *again established by the vaccine maker*, that purports to be a suitable surrogate for the vaccine's in-use effectiveness before: i) issuing a biologics license or ii), *for vaccines licensed before 1977*, continuing to license that vaccine[8].

Apparently, *since before 1973 (when vaccines were regulated by the National Institutes of Health [NIH] and not the FDA)*, the manufacturers of "Thimerosal preserved" vaccines have *knowingly* failed to prove that the level of the Thimerosal, used as a preservative in each of their "Thimerosal preserved" vaccines, has met the

explicit US current good manufacturing practice (CGMP) safety requirement for a "preservative" in a biological drug product as set forth in 21 CFR § 610.15(a)[9].

Further, since 1977, the FDA has apparently failed to comply with the regulation set forth in 21 CFR § 601.4(a) governing its legal conduct and has licensed, and continued to license, "Thimerosal preserved" vaccines which it knew that the manufacturer had not met the clear CGMP safety minimum set forth in 21 CFR § 610.15(a) for preservatives in biological drug products, including vaccines.

Additionally, as the lack of toxicity information provided by these unnamed authors clearly indicates, the manufacturers of "Thimerosal preserved" vaccines and the FDA have failed to prove that the level of Thimerosal in a "Thimerosal preserved" vaccine is "sufficiently nontoxic ..."

If either or both had established a "sufficiently nontoxic ..." level for Thimerosal, then the authors would, at a minimum, be providing the United Nations (UN) toxicologically established no-observed-adverse-effect levels (NOAELs) for the developing fetus, the developing child, the adult and the elderly ($NOAEL_{developing\ fetus}$, $NOAEL_{developing\ child}$, $NOAEL_{adult}$, and $NOAEL_{elderly}$) because these represent the level at which Thimerosal would be "nontoxic ..." to the various age groups of humans that the FDA permits to be injected with "Thimerosal preserved" vaccines.

Yet, nowhere in the information that these authors provide do they furnish any study by any vaccine manufacturer that addresses any of the applicable NOAELs for its "Thimerosal preserved" vaccine(s) or a scientifically sound and appropriate study conducted by the FDA that addresses the level in a vaccine at which Thimerosal is "nontoxic ..." much less the level at which it is "sufficiently nontoxic so that the amount

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[8] 21 CFR § 601.4 Issuance and denial of license. [emphasis added]:
"(a) A biologics license shall be issued upon a determination by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research that the establishment(s) and the product meet the applicable requirements established in this chapter. A biologics license shall be valid until suspended or revoked.

[9] 21 CFR § 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 ..."

present in the recommended dose of the product will not be toxic to the recipient", which is explicitly required by 21 CFR § 610.15(a).

"Thimerosal is an organic mercury compound that is metabolized to ethylmercury and thiosalicylate and has been widely used as a preservative in vaccines since the 1930s. Because serious illness and death in vaccine recipients have followed with the use of multi-dose vials that did not contain a preservative, FDA regulations require the use of preservatives in multi-dose vials of vaccines, excepting some live-virus vaccines, to prevent fungal and bacterial contamination in the event that the sterile vaccine is accidently contaminated after production, as might occur with repeated puncture of multi-dose vials. A vaccine containing 0.01% thimerosal as a preservative contains 50 ug [sic; µg] of thimerosal, or approximately 25 ug [sic; µg] of mercury, per 0.5 mL dose."

This reviewer agrees that "*Thimerosal is an organic mercury compound*" and that it "*has been widely used as a preservative in vaccines since the 1930s*".

However, this reviewer finds that the text is, at best, inaccurate when it states that Thimerosal "*is metabolized to ethylmercury and thiosalicylate*".

Factually, under the physiological conditions found in the human body, Thimerosal is first "*metabolized*"/converted into a mixture of ethylmercury hydroxide, ethylmercury chloride, and sodium thiosalicylate.

Then, the ethylmercury compounds formed are transported throughout the body and further metabolized into tissue-/organ-retained "inorganic mercury" by at least one pathway that apparently proceeds through a demethylation process to produce the corresponding methylmercury compounds, methylmercury hydroxide and methylmercury chloride, before these are again demethylated to the as-yet-unidentified forms of "inorganic mercury" that many studies have found to the "mercury" that is retained in, and accumulated by, the organs[10].

With respect to "*serious illness and death in vaccine recipients have followed with the use of multi-dose vials that did not contain a preservative*", this reviewer notes that this only occurred when: **a)** an improper (septic) technique was used to remove the vaccine doses from the multiple-dose vials or **b)** the vaccine manufacture failed to produce the vaccines under the required aseptic processing conditions.

In addition, after an outbreak of group A streptococcal abscesses following vaccination using a "Thimerosal preserved" multidose "DTP" vaccine in the mid-1980s, a microbial-challenge research study using multi-dose vials of a DPT vaccine preserved with Thimerosal was conducted and the study's researchers reported:

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10 The degradation/metabolic pathway was deduced from the recent findings that, after being given Thimerosal and having their blood and tissues analyzed by a procedure that converts all groups of mercury compounds in them to common ethyl-, methyl- and inorganic mercury reference compounds, the samples initially taken from the test rats several hours after dosing were found to be a mixture of the ethylmercury, methylmercury and inorganic mercury compounds. In addition, when the animals were sacrificed after 5 days, though the blood was found to only contain "inorganic mercury" species, the organs were found to contain ethylmercury, methylmercury and inorganic mercury components, or, in the case of the heart, only methylmercury and inorganic mercury components (see: Rodriques JL, Serpeloni JM, Batista BL, Souza S, Barbosa Jr F. Identification and distribution of mercury species in rat tissues following administration of Thimerosal or methyl mercury. ***Arch Toxicol*** 2010; **84**: 891-896).

> "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"[11].

Based on their findings, those researchers suggested (emphasis added):

> "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."

Furthermore, with respect to the authors' "*FDA regulations require the use of preservatives in multi-dose vials of vaccines, excepting …*":

1. Nowhere do these FDA regulations require that Thimerosal, or any other bioaccumulative systemically poisonous mercury compound that is known to induce anaphylaxis in some, be used as the preservative in vaccines.
2. Under 21 CFR § 610.15(a), the manufacturer must prove that the compound used as a preservative is "sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient" and, *as far as this reviewer can ascertain*, the vaccine makers have never done this for Thimerosal used as a preservative in US-FDA-approved vaccines.
3. Under Title 42 of the United States Code (42 U.S.C.) at paragraph 300aa-27, "Mandate for safer childhood vaccines", the Secretary of Health and Human Services (HHS) has, *since 1987*, been required to (emphasis added): "make or assure improvements in, …, the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, and …, in order to reduce the risks of adverse reactions to vaccines"[12].

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11 Stetler HC, Garbe PL, Dwyer DM, et al. Outbreaks of group A streptococcal abscesses following diphtheria-tetanus toxoid-pertussis vaccination. ***Pediatrics*** 1985; **75**: 299-303.

12 Sec. 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 fewer and less serious adverse reactions than those vaccines on the market on December 22, 1987, and promote the refinement of such vaccines, and

(2) make or assure improvements in, and otherwise use the authorities of the Secretary with respect to, the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, and recall of reactogenic lots or batches, of vaccines, and research on vaccines, in order to reduce the risks of adverse reactions to vaccines.

Moreover, the FDA is an agency that reports and answers to the Secretary of HHS.

Yet, the Secretary of HHS has, at a minimum, failed to comply with the law requiring the Secretary to reduce the risks of adverse reactions based on the Secretary's allowing the use of Thimerosal, a compound proven to cause acute hypersensitivity reactions that can be life threatening, to continue until there was a public outcry in the late 1990s.

At that point, other safer and, in some aspects, more effective compounds were available that could be and were being used as vaccine preservatives.

Further, since August of 2004, *if not before*, the Secretary of HHS has *knowingly*[13] failed to comply with this statutory requirement when it comes

to allowing Thimerosal, a mercury-based compound that is known to cause hypersensitivity reactions[14], including anaphylactic shock, in some of those who are allergic to it, to be used as a "preservative" in vaccines, when the Secretary has had the legal authority and the mandate to order its replacement with a safer preservative since 1987.

With respect to the statement, "*A vaccine containing 0.01% thimerosal as a preservative contains 50 µg of thimerosal, or approximately 25 µg of mercury, per 0.5 mL dose*", this reviewer notes that authors' statement is misleading because a vaccine that nominally contains 0.01% Thimerosal as a preservative may contain up to 62.5 µg of Thimerosal, or approximately 31 µg of mercury, in a 0.50-mL dose.

In addition, for doses manually withdrawn from a multi-dose vial, where the volume overage in the dose may vary, the maximum dose may easily be close to a 0.6-mL dose.

Together these realities raise the maximum amount of mercury in a nominally "0.5 mL" dose to about 37 µg of mercury.

Based on this reviewer's estimated NOAEL $_{\text{developing human}}$ of < 0.0042 µg of mercury/kg/day for Thimerosal, this maximum dose of 37 µg of mercury exceeds the safe level of exposure by a factor of more than 8810 kg divided by the weight of the subject in kg.

For a 10-kg (22 pound) developing child, for example, this translates into more than 881 times the safe level of exposure[15].

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13 In August of 2004, CoMeD, the Coalition for Mercury-free Drugs filed a citizen petition with the FDA and served the Secretary of HHS with a copy. In that filing, CoMeD asked that Thimerosal be ether: **a)** proven to be safe as required by law when it is used as a preservative or **b)** banned from all use as a preservative and noted that, *since Thimerosal can and does cause anaphylaxis and that this allergy is common*, the Secretary of HHS should order its replacement with a compound that can be used as a preservative in vaccines but does not carry the risk of causing anaphylaxis.

14 Cox NH, Forsyth A. Thimerosal allergy and vaccination reactions. ***Contact Dermatitis*** 1988; **18**: 229-233.

15 Because Thimerosal is a bioaccumulative compound and the estimated NOAEL is an upper limit value, which may be a factor of 5 to 10 or more higher than the true NOAEL, averaging this value over any number of days is not appropriate.

"Page 2

Background: Safety Assessment of Thimerosal

Thimerosal has a long record of safe and effective use in preventing bacterial and fungal contamination of vaccines, with no ill effects established other than hypersensitivity and minor local reactions at the site of injection. In 1999, in response to the Food and Drug Administration Modernization Act of 1997, Section 413(c), FDA conducted a comprehensive review of the use of thimerosal as a preservative in medical products, including childhood vaccines. Other than local hypersensitivity reactions, FDA's review confirmed the safety of thimerosal as a vaccine preservative. The review findings were subsequently published (Ball et al. 2001)."

Here, the authors are simply repeating their unsupported claims of Thimerosal's "safety" and "effectiveness".

Ironically, these statements indirectly confirm that the requisite toxicological studies proving the toxicological safety of Thimerosal have never been conducted because, if they had, there would have been no need for "*a comprehensive review of the use of thimerosal as a preservative in medical products, including childhood vaccines*".

Moreover, *as this reviewer has shown*, the results of the one FDA-recognized chronic toxicity study of injected-Thimerosal solutions in rats clearly indicates that the 0.003% to 0.01% level of Thimerosal used as a preservative in vaccines does not meet the "sufficiently nontoxic …" safety requirement set forth in 21 CFR § 610.15(a).

Further, *as this reviewer has reported*, published studies have shown that Thimerosal is not a completely effective bacterial preservative in certain vaccines[16,17].

With respect to the literature review that the FDA reports it conducted in 1999, this reviewer finds that it was anything but comprehensive as it does not even mention the decades of Russian chronic-mercury-toxicity research published as a monograph in 1969 and available in a 1974 translated 300-plus-page monograph[18] or the Japanese animal studies using radiolabeled mercury (^{203}Hg) that clearly show that, for simple ethylmercury compounds, like Thimerosal, less than 15% of the dose is excreted in the urine and feces during the initial redistribution and metabolism of the mercury-containing components[19], or, in monkeys, the dose of the alkyl mercury compounds that is not rapidly excreted is distributed into all of the monkey's organs and tissues — while, in the rat, much of the retained dose was in localized in the rat's organs other

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16 Stetler HC, Garbe PL, Dwyer DM, et al. Outbreaks of group A streptococcal abscesses following diphtheria-tetanus toxoid-pertussis vaccination. *Pediatrics* 1985; **75**: 299-303.

17 Khandke L, Yang C, Krylova K, Jansen KU, Rashidbaig A. Preservative of choice for Prev(e)nar 13TM in a multi-dose formulation. Vaccine 2011, in press.

18 **Chronic Effects of Mercury on Organisms** by I. M. TRAKHTENBERG. "Translated from the Russian Language and Reproduced in limited quantities by the Geographic Health Studies Program of the JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES 1974. U. S. Department of Health, Education, and Welfare, Public Health Service National Institutes of Health, DHEW Publication No. (NIH) 74-473".

19 Takeda YA, Kunugi T, Hoshino O, Ukita T. Distribution of Inorganic, Aryl, and Alkyl Mercury Compounds in Rats. *Toxicol Applied Pharmacol* 1968; **13**: 156-164.

than the brain[20].

With respect to the authors' last two statements:

> "*Other than local hypersensitivity reactions, FDA's review confirmed the safety of thimerosal as a vaccine preservative. The review findings were subsequently published (Ball et al. 2001)*",

this reviewer found that the FDA has misrepresented this review.

First, the published review clearly states (column 1, bottom of page 1147):

> "The views in this article are those of the authors and are not intended to represent those of the Food and Drug Administration or the US Public Health Service",

which indicates, *to this reviewer*, that the article was not the "*FDA's review*".

Further, the published article did not confirm the safety of the use of Thimerosal as a preservative but rather reported that this literature review did not find any clear evidence of harm, and its "**Research Needs**" section stated (emphasis added):

> "Data are lacking regarding the biotransformation and pharmacokinetics of thimerosal and its derivatives after intramuscular injection in humans and animal models. Moreover, insufficient information is available to adequately assess the potential for neurodevelopmental, renal, immunologic, and reproductive toxicity of thimerosal. Limited data exist on the mercury exposure of infants from vaccines, and no observational studies have been done in humans to assess the effect of thimerosal exposure on neurodevelopment, renal, and immunologic function. Thimerosal is unlikely to be eliminated from all vaccines in the near future, and studies are needed to address these gaps to provide a more precise characterization of the potential risk from thimerosal in vaccines".

which plainly indicates that this literature review was, and is, insufficient to establish that the level of Thimerosal, when used as a preservative in vaccines, is safe.

Moreover, the paper's "**CONCLUSION**" section (emphasis added):

> "Our review revealed no evidence of harm caused by doses of thimerosal found in vaccines, except for local hypersensitivity reactions. At the time of our review, vaccines containing thimerosal as a preservative could expose infants to cumulative mercury at levels that exceed EPA recommendations during the first 6 months of life. The clinical significance of this conclusion is not currently known; …"

unambiguously states that this literature review "revealed no evidence of harm" and not that it confirmed "*the safety of thimerosal as a vaccine preservative*", as the

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20 Takkahashi T, Kimura T, Sato Y, Shiraki H, Ukita T. Time-Dependent Distribution of ^{203}Hg-Mercury Compounds in Rat and Monkey as studied by Whole Body Autoradiography. **The J Hygienic Chem** 1971; **17**(2): 93-107.

authors who cite it have asserted.

In addition, *as far as this reviewer can ascertain*, the FDA has neither funded the toxicity studies required to fill the gaps that were found nor required the manufacturers of "Thimerosal preserved" vaccines, as they are obligated to do by drug law, to conduct the requisite toxicity studies.

"As part of the review, FDA evaluated the amount of mercury an infant might receive in the form of ethylmercury, the metabolite of thimerosal, from vaccines under the U.S. recommended childhood immunization schedule and compared these levels with existing guidelines for exposure to methylmercury, as there are no existing guidelines for ethylmercury. At the time of this review, the maximum cumulative exposure to mercury from vaccines in the recommended childhood immunization schedule was within acceptable limits for methylmercury according to exposure guidelines set by FDA, the U.S. Agency for Toxic Substances and Disease Registry (ATSDR), and the World Health Organization (WHO). Depending on the vaccine formulations used and the weight of the infant, however, some infants could have been exposed during the first six months of life to cumulative levels of ethylmercury that exceeded the U.S. Environmental Protection Agency's (EPA) recommended guidelines for safe intake of methylmercury. At that time, FDA stated that there was uncertainty in applying guidelines for methylmercury to thimerosal, but that the use of a safety assessment for a related alkylmercurial was justified because guidelines for ethylmercury were not available. Since then, newer information suggests that the risk that occurs from long-term dietary exposures to methlymercury is not comparable with that from the transient ethylmercury exposure from vaccinations and indicates that the EPA reference dose for methylmercury may have been an overly restrictive limit to use for ethylmercury."

First, the authors' assertion, "*there are no existing guidelines for ethylmercury*" is a knowing misrepresentation of the facts.

In 1969, an international committee issued a report that was titled "Maximum Allowable Concentrations of Mercury Compounds"[21], which stated (emphasis added):

> "On the basis of existing knowledge, though with the limitations cited above, the group recommends the following MAC [maximum allowable concentration] values. These are to be used solely as guides, and not as exact indications of limits between safe and unsafe working conditions.
>
> 1. Methyl and ethyl mercury salts. No air concentration is recommended. The mercury level in whole blood should not exceed 10 µg of Hg/100 ml (as total mercury) [0.1 µg of Hg/mL]. This blood concentration is a ceiling value and it should not usually be exceeded with continuous eight-hour exposure to 0.01 mg/cu m of alkyl mercury in air.
> 2. Mercury vapor, 0.05 mg/cu m.

[21] Report of an International Committee: Maximum Allowable Concentrations of Mercury Compounds. ***Arch Environ Health*** 1969 Dec; **19**(6); 891-905.

3. Inorganic mercury salts, and phenyl and methoxyethyl mercury salts, 0.1 mg of Hg/cu m

Any other mercury compounds not in this list should have separate toxicological evaluation before an MAC value is adopted. Whenever exposure is to a mixture of mercury compounds falling into different groups and with different +MAC values, the standard rules for evaluating toxicity of mixtures should apply. When doubt exists about the character of the mixture, the lowest MAC level should be used.

The group did not discuss analytical methods for quantitative determination of mercury compounds, either in air or in biological materials, but it is obvious that the methods must be adequate, especially under conditions of mixed exposure."

Obviously, though these standards were occupational exposure limits set for adults, they clearly are "*existing guidelines for ethylmercury*" exposures.

To convert these occupational exposure limits for adults to limits appropriate for developing children, one would need to divide these by at least a factor of 10, which would, *for this 1969 guideline*, result in a maximum blood mercury concentration of 10 ng/mL (0.000001 %).

Moreover, in 2005, the Danish Environmental Agency reported on another set of guidelines, prepared with input from the Russian Federal Service for Environmental, Technological and Atomic Supervision[22], for mercury in air and water that addressed certain ethylmercury compounds as shown in the following tables (emphasis added).

"***Table 1.2 MAC of mercury and its compounds in the atmospheric air of the inhabited localities****

Substance**	**MAC, *mg/m3***	
	Maximum single	**Average daily**
Metallic mercury	-	0.0003
Diethyl mercury***	0.0003	-
Mercury***	-	0.0003
(II) dinitrate	-	0.0003
(I) nitrate	-	0.0003
(II) amidochloride *MAC of mercury and its compounds in the atmospheric air of the inhabited lo*	-	0.0003
(II) iodide	-	0.0003
(II) oxide	-	0.0003
(II) acetate	-	0.0003
(I) chloride	-	0.0003
(II) dichloride	-	0.0003

* Hygienic norms ĺH 2.1.6.695.98. Maximum allowable concentrations (MAC) in the atmospheric air of the inhabited localities. -Moscow: The Ministry of Health of RF, 1998.
** all regulated substances are related to the hazard class 1.
*** MAC for Hg compounds are presented in conversion to Hg.

22 Arctic Council Action Plan to Eliminate Pollution of the Arctic (ACAP), Reduction of Atmospheric Mercury Releases from Arctic States, Assessment of Mercury Releases from the Russian Federation. Prepared for the Arctic Council by: Russian Federal Service for Environmental, Technological and Atomic Supervision, Danish Environmental Protection Agency, 2005.

Table 1.3 MAC of mercury and its compounds in the indoor occupational air*

Substance **	MAC, *mg/m*^{3}		Prevailing aggregative state in occupational conditions
	Maximum	Average per shift	
Metallic	0.01	0.005	Vapours
Diethyl mercury	-	0.005	Vapours
Inorganic compounds of mercury ***	0.2	0.050	Aerosol
Ethyl mercury phosphate ***....	-	0.005	Mixture of vapours and aerosol
Ethyl mercury chloride ***	-	0.005	Mixture of vapours and aerosol

* Hygienic norms 2.1.6.686-98. Maximum allowable concentrations (MAC) in the occupational air. -Moscow: The Ministry of Health of RF, 1998. Mercury. Regulations and methodologicel guidelines. Reference Book. T. 1.Saint-Petersburg, 2001.

** All regulated substances are related to the hazard class 1.

*** MAC for Hg compounds are presented in conversion to Hg (influence of inorganic compounds requires special protection of eyes and skin)

Table 1.4* MAC *of mercury and its compounds in potable water sources and cultural and recreational water bodies *

Substance **	MAC, mg/l ***
Diethyl mercury	0.0001
Mercury (for inorganic compounds, given the gross content of all forms)	0.0005
Ethyl mercury chloride	0.0001

* Hygienic norms ĹH 2.1.5.690-98. Maximum allowable concentrations (MAC) of chemical substances in potable water sources and cultural and recreational water bodies. -Moscow: The Ministry of Health of RF, 1998.

** All regulated substances are related to the hazard class 1.

*** Releases of inorganic mercury (Hg2+) and mercuric chloride into water bodies used for fishery are prohibited."

Moreover, the Russian-derived limit of 0.0001 mg/liter, 0.1 µg/liter, or 0.1 nanogram (ng)/milliliter (0.1 ng/mL) for ethylmercury chloride in potable and recreational water is 20 times lower than the current United States (US) limit of 2 parts-per-billion (2 ng/mL) for the sum of all mercury species in potable water.

Perhaps, the authors meant to say that there were "no existing safe levels for exposure to Thimerosal in vaccines", which is, *of course*, an admission that the manufacturers of "Thimerosal preserved" vaccines have intentionally failed to comply with the applicable "sufficiently nontoxic ..." safety requirement set forth in 21 CFR § 610.15(a) since 1973 and that, *since that time*, the FDA has *knowingly* failed to enforce compliance with this current good manufacturing practice (CGMP) safety requirement.

Next, the authors conveniently ignore the reality that, since 1997, the US Centers for Disease Control and Prevention (CDC) had been recommending that women who were in their second and third trimester of pregnancy should get a flu shot, and that "at risk" pregnant women get the flu shot regardless of their stage in pregnancy[23].

Since all FDA-approved lots of flu shots were "Thimerosal preserved" with a nominal 0.01% level of Thimerosal until late in 2002, *at a minimum*, these authors should have started with an appropriate weight of the developing fetus at the beginning of the second trimester when the brain really starts to develop.

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23 Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). ***Morbidity and Mortality Weekly Report*** (***MMWR***) 1997 Apr 25; **46**(RR-9):1-25 (emphasis added):

"Summary

These recommendations update information concerning the vaccine and antiviral agents available for controlling influenza during the 1997-98 influenza season (superseding MMWR 1996;45{No. RR-5}:1-24). The principal changes include information about a) the influenza virus strains included in the trivalent vaccine for 1997-98, b) the vaccination of pregnant and breastfeeding women, and c) side effects and adverse reactions.

To facilitate this exercise, this reviewer is providing a suitable table that computes the relative level of exposure to the fetus for a flu shot given to the pregnant mother at various weeks during pregnancy (see **Table I** on the next page).

Here, *at every stage in pregnancy*, even if one allows for exposure to no more than 75% of the nominal dose of mercury in a flu shot (about 50% of the maximum dose), the fetus is exposed to mercury at levels ranging from > 50 to > 3,000,000 times the EPA Reference Dose (RfD) for ingested "methylmercury" from fish (probably methylmercury cysteine).

Moreover, since CDC's current guidelines allow the vaccination of a pregnant woman with a "Thimerosal preserved" flu shot at any time during her pregnancy, clearly "Thimerosal preserved" flu shots are not safe to inject into pregnant women.

With respect to the authors' statement:

> *"At that time, FDA stated that there was uncertainty in applying guidelines for methylmercury to thimerosal, but that the use of a safety assessment for a related alkylmercurial was justified because guidelines for ethylmercury were not available"*,

this reviewer notes that this assumption was also not justified in 1999 because "*guidelines for ethyl mercury*" were available; and data reported in Japanese studies, using radiolabeled alkyl mercury compounds, from the late 1960s[24] clearly showed that ethylmercury compounds bioaccumulate.

In addition, a more recent 2005 study (Burbacher TM, et al. 2005[25]) clearly showed that, *on average*, 2 to 3 times more "inorganic mercury" from Thimerosal had bioaccumulated in the monkeys' brains than "inorganic mercury" from methylmercury at the time the animals were sacrificed (up to 49 days after the start of the dosing regimen) to assess the levels of mercury in their organs.

Further, for two reasons (overestimation of fish consumption[26] and an unfounded assumption of a constant factor between the level of mercury in the hair and the body's burden of mercury[27]), the EPA RfD is an estimated value with no safety margin and is not, what is needed: valid toxicologically derived NOAEL values for: **a)** the fetus, **b)** the developing child, **c)** the adult, and **d)** the elderly.

Moreover, there are differences between the mercury exposure level and the rate of distribution when a person eats fish (less methylmercury compounds are absorbed into the body, the distribution into the body is slower, and the metallothionens in the gut bind up some percentage of the mercury in the dose so that that percentage is not

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24 Takeda YA, Kunugi T, Hoshino O, Ukita T. Distribution of Inorganic, Aryl, and Alkyl Mercury Compounds in Rats. ***Toxicol Applied Pharmacol*** 1968; **13**: 156-164.

25 Burbacher TM, et al. Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing Thimerosal. ***Environ Health Persp*** 2005; **113**(8): 1015-1021.

26 Gosselin NH, Brunet RC, Carrier GT, LeBouchard M, Feeley M. Reconstruction of methylmercury intakes in indigenous populations from biomarker data. ***J Exposure Anal Environ Epidemiol*** 2006, **16**(1): 19-29.

27 Canuel R, Boucher de Grosbois S, Atikessé L, Marc Lucotte M, Arp P, Ritchie C, Mergler D, Chan HM, Amyot M, Anderson R. New Evidence on Variations of Human Body Burden of Methylmercury from Fish Consumption. ***Environ Health Perspect*** 2006 Feb; **114**(2): 302-306.

Table I: Fetal Information Chart with Mercury (Hg) "Non-safety" Exposure Factors from Hg-Containing Flu Shots Based on EPA's RfD (0.1 µg Hg/kg/day)

Gestational Age #	Length (US)	Weight (US)	Length (cm)	Mass (g) %	Mass (kg) *	"18.6 mcg"[A] of Hg-preserved shot's multiple of the EPA's RfD *
	(crown to rump) ▼		(crown to rump) ▼			—
< 5 weeks				< 0.06 gram	< 0.00006 kg	>3,100,000
5 weeks				~ 0.125 gram	~ 0.000125 kg	~ 1,488,000
6 weeks*				~ 0.25 gram	~ 0.00025 kg	~ 744,000
7 weeks*				~ 0.5 gram	~ 0.0005 kg	~ 372,000
8 weeks	0.63 inch	0.04 ounce	1.6 cm	1 gram	0.001 kg	186,000
9 weeks	0.90 inch	0.07 ounce	2.3 cm	2 grams	0.002 kg	93,000
10 weeks	1.22 inch	0.14 ounce	3.1 cm	4 grams	0.004 kg	46,500
11 weeks	1.61 inch	0.25 ounce	4.1 cm	7 grams	0.007 kg	26,568
12 weeks	2.13 inches	0.49 ounce	5.4 cm	14 grams	0.014 kg	13,286
13 weeks	2.91 inches	0.81 ounce	7.4 cm	23 grams	0.023 kg	8,087
14 weeks	3.42 inches	1.52 ounce	8.7 cm	43 grams	0.043 kg	4,326
15 weeks	3.98 inches	2.47 ounces	10.1 cm	70 grams	0.070 kg	2,657
16 weeks	4.57 inches	3.53 ounces	11.6 cm	100 grams	0.100 kg	1,860
17 weeks	5.12 inches	4.94 ounces	13 cm	140 grams	0.140 kg	1,329
18 weeks	5.59 inches	6.70 ounces	14.2 cm	190 grams	0.190 kg	979
19 weeks	6.02 inches	8.47 ounces	15.3 cm	240 grams	0. 240 kg	775
20 weeks	6.46 inches	10.58 ounces	16.4 cm	300 grams	0.300 kg	620
	(crown to heel) ▼		(crown to heel) ▼			
20 weeks	10.08 inches	10.58 ounces	25.6 cm	300 grams	0.300 kg	620
21 weeks	10.51 inches	12.70 ounces	26.7 cm	360 grams	0.360 kg	516
22 weeks	10.94 inches	15.17 ounces	27.8 cm	430 grams	0.430 kg	432
23 weeks	11.38 inches	1.10 pound	28.9 cm	501 grams	0.501 kg	371
24 weeks	11.81 inches	1.32 pound	30 cm	600 grams	0.600 kg	310
25 weeks	13.62 inches	1.46 pound	34.6 cm	660 grams	0.660 kg	282
26 weeks	14.02 inches	1.68 pound	35.6 cm	760 grams	0.760 kg	245
27 weeks	14.41 inches	1.93 pound	36.6 cm	875 grams	0.875 kg	213
28 weeks	14.80 inches	2.22 pounds	37.6 cm	1005 grams	1.005 kg	185
29 weeks	15.2 inches	2.54 pounds	38.6 cm	1153 grams	1.053 kg	176
30 weeks	15.71 inches	2.91 pounds	39.9 cm	1319 grams	1.319 kg	141
31 weeks	16.18 inches	3.31 pounds	41.1 cm	1502 grams	1.502 kg	124
32 weeks	16.69 inches	3.75 pounds	42.4 cm	1702 grams	1.702 kg	109
33 weeks	17.20 inches	4.23 pounds	43.7 cm	1918 grams	1.918 kg	96.7
34 weeks	17.72 inches	4.73 pounds	45 cm	2146 grams	2.146 kg	86.3
35 weeks	18.19 inches	5.25 pounds	46.2 cm	2383 grams	2.383 kg	78.1
36 weeks	18.66 inches	5.78 pounds	47.4 cm	2622 grams	2.622 kg	70.9
37 weeks	19.13 inches	6.30 pounds	48.6 cm	2859 grams	2.859 kg	65.0
38 weeks	19.61 inches	6.80 pounds	49.8 cm	3083 grams	3.083 kg	60.3
39 weeks	19.96 inches	7.25 pounds	50.7 cm	3288 grams	3.288 kg	56.5
40 weeks	20.16 inches	7.63 pounds	51.2 cm	3462 grams	3.462 kg	53.7
41 weeks	20.35 inches	7.93 pounds	51.7 cm	3597 grams	3.597 kg	51.7
42 weeks	20.28 inches	8.12 pounds	51.5 cm	3685 grams	3.685 kg	50.4

[A] The 18.6 mcg of mercury is based on a presumption that 75% of the nominal dose given to the mother ends up in the fetus. This approximation is used because the data from animal (rabbit) studies clearly indicates that most of the mercury from injected Thimerosal ends up in the fetus.

Sources for "Weigh in" ounces and grams (weight values in "red' are this reviewer's estimates)**, and "Length" information:**

1. Doublet PM, Benson CB, Nadel AS, et al: Improved birth weight table for neonates developed from gestations dated by early ultrasonography. ***J Ultrasound Med*** 1997; **16**: 241.
2. Hadlock FP, Shah YP, Kanon DJ, et al. Fetal crown rump length: Reevaluation of relation to menstrual age with high resolution real-time US. ***Radiology*** 1992; 182: 501.
3. Usher R, McLean F. Intrauterine growth of live-born Caucasian infants at sea level: Standards obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation. ***Pediatrics*** 1969; **74**(6), 901-910.

absorbed) as opposed to someone's being injected with a "Thimerosal preserved" vaccine (where the mercury exposure is rapid and complete).

Finally, in comparative studies using developing cultured human cells (astrocytes, neurons and fetal "skin cells"), the results obtained indicated that Thimerosal is on the order of 2 to 10 times more toxic than methylmercury hydroxide to human cells at mercury exposure levels below 1 parts-per-million (ppm) [< 0.0001 %][28].

"Although other than hypersensitivity in some individuals, there was no known health risk from thimerosal-preservative at the concentration used in vaccines, in 1999, the Public Health Service,

Page 3

along with the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) concluded that because of scientific uncertainty at the time, as a precautionary measure, it was prudent to reduce childhood exposure to mercury from all sources, including vaccines, as feasible. On July 1, 1999, the Office of Vaccines Research and Review at FDA sent a letter to all licensed manufacturers of vaccines requesting their plans to remove thimerosal from U.S.-licensed vaccines. This step was taken because the elimination or reduction of mercury in vaccines was a feasible means of reducing an infant's total exposure to mercury in a world where other environmental sources of mercury are challenging to eliminate."

This reviewer finds the authors' initial statement here to be, at best, misleading because they ignore the reality that the Russians, in 1983, and the Scandinavian countries (Denmark, Norway, and Sweden), in the 1990s, had already stopped the use of "Thimerosal preserved" childhood vaccines — essentially on the grounds that they were an unnecessary and easily avoidable health risk.

The Russians made their decision after multigenerational rat studies unequivocally showed that Thimerosal at vaccine levels disrupted reproduction — taking more mating attempts for the Thimerosal-treated females to become pregnant, where these treated females then produced fewer, smaller, less healthy pups per litter than the control females who were dosed with sterile, pH-buffered, isotonic saline[29].

In addition, when the first generation female offspring of the Thimerosal-treated females matured and were mated without being dosed with Thimerosal, the first-generation female offspring borne by the Thimerosal-treated mothers also had trouble conceiving and produced fewer, smaller pups per litter than the first-generation control group's offspring's litters.

Clearly, the Russian studies established that the Thimerosal given to the female rats before mating not only negatively affected the reproductive health of the treated female rats but also adversely affected: **a)** the health of the litter of rat pups these treated females subsequently bore, **b)** the reproductive health of the female pups in

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28 Geier DA, King PG, Geier MR. Mitochondrial dysfunction, impaired oxidative-reduction activity, degeneration, and death in human neuronal and fetal cells induced by low-level exposure to Thimerosal and other metal compounds. ***Toxicol Environ Chem*** 2009; **91**: 735-749.

29 Goncharuk GA. Experimental investigation of the effect of organomercury pesticides on generative functions and on progeny. ***Hyg Sanit.*** 1971; **36**: 40-43.

that litter, and **c)** the health of the second-generation rat pups borne by the first-generation female pups delivered by the Thimerosal-treated female rats.

Yet, the US CDC and the FDA ignore the detrimental outcomes from Thimerosal exposure in this Russian multigenerational reproductive toxicity study and other animal studies like it, and continue to claim that there is: **a)** no "proof of harm" from the injected Thimerosal in "Thimerosal preserved" vaccines and **b)** no need to ban the administration of "Thimerosal preserved" flu shots to pregnant women, when the Russian studies clearly indicate that practice is detrimental to the reproductive health of the mother and the development of the child that she is carrying.

The Scandinavian and other countries also had health concerns about the ongoing use of "Thimerosal preserved" vaccines.

Their health concerns were articulated by Dr. Maurice Hilleman of Merck in a 1991 memo, written when he was on the Merck Vaccine Task Force[30] (emphasis added):

> "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."

Thus, based on the assessment of a world-recognized leader in the development of vaccines, Dr. Maurice Hilleman, the mercury exposure from vaccines in 1991 greatly exceeded a "Swedish daily allowance", which was 23 times the EPA's RfD, by a factor of 87[31] (or, *in other words*, exceeded the EPA's RfD by a factor of 2000)!

With respect to the authors' claim that (emphasis added):

> "*in 1999, the Public Health Service, along with the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) concluded that because of scientific uncertainty at the time, as a precautionary measure, it was prudent to reduce childhood exposure to mercury from all sources, including vaccines, as feasible*",

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30 Merck Vaccine Task Force Memo 1991.

31 Shortly after the 1991 Merck Vaccine Task Force Memo was written, the Scandinavian countries stopped using the one "Thimerosal preserved" vaccine that they had been using.

the 1999 published call[32] was for the removal of Thimerosal from vaccines – not for the reduction of: **a)** the level of Thimerosal in vaccines or **b)** the number of "Thimerosal preserved" vaccines (emphasis 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".

Further, this reviewer notes that, *unlike the US FDA and manufacturers of US-FDA-licensed vaccines*, many of the Western European agencies, who committed to stopping the use of "Thimerosal preserved" vaccines, have kept that commitment.

Finally, the authors' next two statements:

> *"On July 1, 1999, the Office of Vaccines Research and Review at FDA sent a letter to all licensed manufacturers of vaccines requesting their plans to remove thimerosal from U.S.-licensed vaccines. This step was taken because the elimination or reduction of mercury in vaccines was a feasible means of reducing an infant's total exposure to mercury in a world where other environmental sources of mercury are challenging to eliminate",*

are, respectively:

1. An attempt to let the reader know that the FDA chose to send a letter asking the vaccine makers for their plans to remove mercury from vaccines rather than, *as the FDA should have done under the authorities it has under 42 U.S.C. § 300aa-27(a), 42 U.S.C. § 262, 21 U.S.C. § 351(a)(2)(B) and 21 U.S.C. § 331*, ordering the vaccine makers to phase out "Thimerosal preserved" vaccines by some date certain and, *most importantly*, revoking the US licenses of all "Thimerosal preserved" vaccines on the date certain set for the removal of Thimerosal from vaccines to prevent US-licensed "Thimerosal preserved" vaccine formulations from being manufactured and distributed in the USA and other nations beyond that future established date, and
2. An attempt to portray the FDA as a US agency that was trying to protect our children and ourselves from the unnecessary and unjustifiable risk to being injected with "Thimerosal preserved" vaccines that, *in a worst single-dose case*, can inject up to 37 µg of mercury (a dose that exceeds the US EPA's RfD for mercury that is consumed in food unless the person being inoculated weighs more than 370 kg [816 pounds]) when, *as history has shown*, the FDA's actions have not protected us from this risk because: **a)**

[32] ***MMWR*** 1999; **48**(26): 563-565 (July 09, 1999 [original press release issued on July 7, 1999]) can be found by searching the MMWR sub site (http://www.cdc.gov/mmwr/).

the FDA is continuing to approve and license "Thimerosal preserved" vaccine formulations, and **b)** the CDC is continuing to make recommendations that vaccines be given to: **i)** pregnant women and **ii)** developing children without regard to the vaccines' mercury content.

"***Current Status***

With the exception of influenza vaccines, all vaccines manufactured since 2001 that are routinely recommended in the United States for children 6 years of age and under (diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP), hepatitis B vaccine, Haemophilus influenzae b conjugate (Hib) vaccine, pneumococcal conjugate vaccine, inactivated polio virus (IPV) vaccine, measles, mumps and rubella vaccine, rotavirus vaccine, and varicella vaccine) are presented in single-dose formulations and do not contain thimerosal as a preservative. Some may contain trace amounts of thimerosal used as part of the manufacturing process. As with pediatric vaccines, exposure to thimerosal in vaccines for adolescents and adults has also been reduced or eliminated (e.g., hepatitis B, Td, and TdaP vaccines, meningococcal conjugate vaccine, zoster vaccine, and human papillomavirus vaccine). Thus, as a result of the efforts described, the use of thimerosal preservative in FDA-licensed vaccines has significantly declined over the last decade."

This reviewer first notes that this paragraph is an attempt to obscure the FDA's failure to protect the American public from an increasing risk of exposure to "Thimerosal preserved" vaccine doses.

The authors accomplished this by focusing the reader's attention on the removal of a preservative level of Thimerosal from:

a. Three previously "Thimerosal preserved" childhood vaccines ("*diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP), hepatitis B vaccine, Haemophilus influenzae b conjugate (Hib) vaccine*"),
b. Vaccines that, *for whatever reasons*, never contained a preservative level of Thimerosal ("*pneumococcal conjugate vaccine" and "inactivated polio virus (IPV) vaccine*") and, *unbelievably*,
c. Live-virus vaccines that cannot contain any Thimerosal because Thimerosal denatures ("kills") those vaccines' live viruses ("*measles, mumps and rubella vaccine, rotavirus vaccine, and varicella vaccine*").

What the authors also avoid is the reality that, *for a person having a life expectancy of 78 years or more and vaccinated according to the CDC's recommended vaccination schedule*, the ***maximum*** number of nominally 25-µg dose equivalents of mercury from the recommended vaccination programs where the recommended vaccine is a "Thimerosal preserved" vaccine has increased:

FROM: A nominal level of "7 to 8" such childhood doses and "19 or more" adult doses (tetanus toxoid boosters every ten years and annual flu shots from 65 to 78) or "27 or more", 25-µg doses of mercury **in 1999** (when the commitment to remove the "Thimerosal preserved" vaccines was made),

TO: A nominal level of "more than 15 to 16" such childhood doses and "60

or more" such adult doses (all from the "Thimerosal preserved" flu shot) or "75 or more", 25-µg doses of mercury from the "Thimerosal preserved" flu shots alone **in 2010** where "all" of the other vaccines that are routinely recommended for children, pregnant women, and other adults either contain no added Thimerosal or, in a few instances, may contain a reduced level of Thimerosal (delivering *not more than* [≤] 1 µg of mercury per dose).

Thus, those following the CDC's recommendations and getting only "Thimerosal preserved" flu shots are now scheduled to receive over a 78-year lifetime about 2.8 times the mercury from vaccines that they were scheduled to receive in 1999.

Therefore, rather than reducing the ***maximum*** Thimerosal exposure, the FDA's and the CDC's actions have greatly increased the ***maximum*** mercury dose.

Obviously, by the FDA's refusing to ban "Thimerosal preserved" flu shots and the CDC's adding the flu shot to the recommended vaccination schedule for all children and pregnant women, and increasing the flu vaccine mandate until the flu vaccine is an annual recommendation for everyone, the government and the industry, by not removing Thimerosal from all flu shots, have acted to significantly increase the ***maximum*** mercury exposure from "Thimerosal preserved" flu vaccines.

Therefore, the authors of this document are focusing on the removal of Thimerosal from a few of the routinely recommended childhood and adult vaccines as if that removal means that the ***maximum*** exposure to Thimerosal has been reduced, when they know that the ***maximum*** lifetime exposure to Thimerosal from "Thimerosal preserved" flu shots has actually been increased more than 2.5 times for those who: **a)** faithfully follow the CDC's influenza vaccination recommendations and **b)** get a "Thimerosal preserved" flu shot each year.

"The exception is inactivated influenza virus vaccines that continue to be marketed in the United States in both thimerosal-free single dose and thimerosal preservative-containing multi-dose formulations. The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices does not preferentially recommend thimerosal-free vaccines for any populations. Notably, of the 160 million doses of FDA-licensed seasonal influenza vaccine distributed during the 2010/2011 season for administration to the U.S. population, approximately 90 million doses were made available in multi-dose vials containing thimerosal preservative. In the United States, the availability of influenza vaccines formulated in multi-dose vials is critical in situations of an influenza pandemic. Moreover, vaccines formulated in multi-dose vials

Page 4

containing thimerosal preservative remain an important component of immunization programs in developing countries because of their reduced cost and storage requirements."

Here, this reviewer is not surprised that the authors apparently did not know that the inactivated-influenza-virus vaccines are marketed with three levels of Thimerosal:

1. Single-dose, no-Thimerosal influenza vaccines [both inactivated and genetically engineered live-virus],

2. A single-dose reduced-Thimerosal influenza vaccine [not greater than 2 µg of Thimerosal per 0.5-ml dose], and
3. Multi-dose "Thimerosal preserved" influenza vaccines [containing nominally 50 µg of Thimerosal per 0.5-ml dose])

and not two levels as the authors state here: "*in both thimerosal-free single dose and thimerosal preservative-containing multi-dose …*"

While this reviewer agrees with the authors that

> "*[t]he Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices does not preferentially recommend thimerosal-free vaccines for any populations*",

this reviewer finds the CDC's policy decision, which permits "Thimerosal preserved" vaccines to be given to pregnant women and children, is a breach of medical ethics given the unrefuted evidence of reproductive and fetal harm that has been proven in animal studies[33,34,35,36,37].

With respect to the authors' next statement:

> "*Notably, of the 160 million doses of FDA-licensed seasonal influenza vaccine distributed during the 2010/2011 season for administration to the U.S. population, approximately 90 million doses were made available in multi-dose vials containing thimerosal preservative*",

this reviewer notes that the "90 million doses" translates into about 61 % of the about 146-to 148-million inactivated-influenza-virus vaccine doses

With respect to the authors' assertion:

> "*In the United States, the availability of influenza vaccines formulated in multi-dose vials is critical in situations of an influenza pandemic*",

this reviewer simply notes that: **a)** *while this statement may be true*, there is no need, or requirement, for the preservative in a multi-dose flu vaccine formulation to be Thimerosal, **b)** other compounds and compound mixtures have been used as a preservative for multi-dose inactivated-virus vaccines since the 1960s, and **c)**, for some recent vaccines (e.g., Pfizer's Prevnar 13®/Prevenar 13®, pneumococcal pneumonia vaccine), 2-phenoxyethanol [2-PE] has been shown to be a less toxic and more effective preservative than Thimerosal in that vaccine's formulation[38,39].

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33 Goncharuk GA. Experimental investigation of the effect of organomercury pesticides on generative functions and on progeny. ***Hyg Sanit.*** 1971; **36**: 40-43.

34 Digar A, Sensharma GC, Samal SN. Lethality and teratogenicity of organic mercury (Thimerosal) on the chick embryo. ***J Anat Soc India*** 1987; **36**: 153-159.

35 Spann JW, Health RG, Kreitzer JF. Ethyl mercury p-toluene sulfonanilide: lethal and reproductive effects on pheasants. ***Science*** 1972; **175**: 328-331.

36 Clarkson TW, Nordberg GF, Sager PR. Reproductive and developmental toxicity of metals. ***Scand J Work Environ Health*** 1985; **11**: 145-154.

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

38 "Development of a Multi-Dose Formulation of Prevenar 13" Lakshmi Khandke, et al., supported by the World Health Organization, GAVI Alliance, UNICEF, the Bill & Melinda Gates Foundation, and Pfizer (emphasis added):

Finally, with respect to the authors' assertion:

> "*Moreover, vaccines formulated in multi-dose vials containing thimerosal preservative remain an important component of immunization programs in developing countries because of their reduced cost and storage requirements*"

this reviewer notes that this is a false statement because 2-PE, a non-bioaccumulative compound that is much less toxic than Thimerosal to human cells[40], has not only been shown to be an effective preservative in many vaccine formulations, including some approved by the FDA, but also a cost-effective replacement that should raise the manufacturing costs for a preserved vaccine by much less than a penny a dose[41].

Surely, none should object to a significantly safer non-bioaccumulatively toxic preservative in their flu vaccines if it cost much less than a penny more per dose than the current bioaccumulatively toxic, teratogenic, mutagenic, carcinogenic, reproductively toxic, and immunologically toxic Thimerosal, which is currently used as the "preservative" in "Thimerosal preserved" vaccines.

"The FDA has not identified any preservative as effective as thimerosal preservative. Some have suggested the use of 2-phenoxyethanol as an alternative; however, this component has not been widely used as a preservative in U.S.-licensed vaccines and, for some vaccines, it was shown not to be effective when used alone as a preservative."

First and foremost, this reviewer notes that it is the nondischargeable, legal duty of the manufacturer of a preserved biological product, *and not the FDA*, to:

a. Find and qualify an appropriate preservative system for its preserved drug products and
b. Establish that that preservative system they choose to use meets the "sufficiently nontoxic …" safety minimum set forth in 21 CFR § 620.15(a).

Second, contrary to the authors' assertions, the manufacturers of several vaccines licensed by the US FDA have successfully used 2-phenoxyethanol or a mixture of 2-phenoxyethanol and phenol as a preservative in US-FDA-approved vaccine formulations as well as in vaccine formulations approved by regulatory authorities around the world (see footnotes 38 and 39).

Third, that a component or a mixture of components "*has not been widely used as a preservative in*" US-licensed vaccines has no bearing on the issue of a preservative system's usability or safety.

"Conclusions…Thimerosal is not an effective preservative compared to 2-PE [i.e., 2-phenoxyethanol] … The data support the use of 2-PE as a more effective preservative with the potential to replace thimerosal, the most commonly used preservative in multi-dose vaccine formulations".

39 Khandke L, Yang C, Krylova K, Jansen KU, Rashidbaig A. Preservative of choice for Prev(e)nar 13™ in a multi-dose formulation. *Vaccine* 2011, in press.

40 Geier DA, Jordan SK, Geier MR. The relative toxicity of compounds used as preservatives in vaccines and biologics. *Med Sci Monit*. 2010 Apr 28; 16(5): SR21-SR27.

41 "**The Viability of Using Non-mercury Preservatives in Vaccines**" available for download and printing: at: http://mercury-freedrugs.org/docs/20110105_CoMeD_onepager_Preservatives_rb.pdf

The safety standard for the preservative, "sufficiently nontoxic …", is a US issue that the pharmaceutical manufacturer has been required to properly address by law *since 1968* – from before the responsibility for compliance enforcement was transferred from the NIH to the FDA in 1973.

The preceding facts again bring this reviewer to the reality: The manufacturers that use Thimerosal have never proven that the level of Thimerosal used as a preservative in their vaccines meets the toxicological safety standard, "sufficiently nontoxic …", as required by law (21 CFR § 610.15(a)) nor has the FDA apparently required them to prove the toxicological safety of Thimerosal used as a preservative to this current good manufacturing practice (CGMP) standard minimum set forth in 21 CFR § 610.15(a) as the FDA is required by law to do since 1977 (see 21 CFR 601.4(a)) before approving any "Thimerosal preserved" vaccine.

Fourth, because there is no requirement that the "*preservative*" in a US-FDA-licensed vaccine be a single component, the authors' assertion: "*for some vaccines, it was shown not to be effective when used alone as a preservative*" is an obvious admission that 2-phenoxyethanol has been used with other chemicals as an effective vaccine preservative.

Based on the preceding, it is clear that all of the authors' comments in this paragraph are unfounded.

"***Notable Studies and Assessments of the Use of Thimerosal in Vaccines***

In the past decade, U.S. Public Health Service agencies collaborated with a number of academic and scientific investigators to initiate further studies to better understand any possible health effects from exposure to thimerosal in vaccines and to further assess the comparative toxicity of ethyl-and methylmercury (Burbacher et al 2005, Pichichero ME, et al, 2002 & 2008). Results identified differences in the way that thimerosal and methylmercury are distributed, metabolized, and excreted. In particular, studies by Pichichero showed that in all infants studied, blood levels of ethylmercury did not exceed safe levels for methylmercury. Further, ethylmercury was cleared from the blood in infants who received thimerosal-containing vaccines faster than would be predicted for methylmercury and infants excreted significant amounts of mercury in stool after receiving thimerosal-containing vaccines, thus highlighting an important mechanism by which mercury was cleared from their bodies."

Review of the Studies Cited

Here, this reviewer must first note that the authors rely on studies that: **a)** seem designed to obscure the differences between the specific toxicities of Thimerosal and some reference methylmercury compound (usually, methylmercury chloride or, less commonly, methylmercury hydroxide) or **b)** do not adequately address the differences.

This reviewer can make this assertion for the following reasons:

1. In "*Burbacher et al 2005*", the researchers did not administer the "Thimerosal preserved"-vaccine-equivalent doses to the monkeys in the same manner as they administered the "methylmercury" solution — rather, they injected the vaccine doses but force-fed the "methylmercury" solution.

Thus, the data for the effective dose administered, the dose uptake and the distribution was confounded by this difference in administration mode.

Therefore, the half-life estimates for the clearance of the methylmercury dosed from the blood are biased by an unassessed absorption retarded uptake of the force-fed methylmercury solution.

2. In "*Burbacher et al 2005*", the comparison was further obscured by the failure of the researchers to collect, analyze and/or report the levels of mercury in the hair, urine and feces of the animals exposed to either mercury compound.

   When you force feed rather than inject a substance, you may need to correct the amount administered for the amount that is bound up by the gut and incorporated into the feces without being absorbed into the animal.

   Without the data for the level of mercury in: **a)** the feces before dosing and **b)** the bowel movements after dosing, there is no way to estimate the percentage of the administered dose that was not absorbed.

   This is especially important because there are metallothioneins in the gut whose job it is to complex mercury and other heavy metals in order to prevent them from being fully absorbed into the body.

3. Had these researchers wanted to make an unbiased comparison, they would have injected the "Thimerosal preserved" vaccine solutions and an isotonic, pH-buffered sterile solution of the methylmercury compound they used in this study.

4. In "*Pichichero ME, et al, 2002 …*", the flaws are both more pervasive and more insidious.

   Again, if the goal were to actually measure the clearance of Thimerosal from the body, *as the researchers statements imply*, then one would need to take blood, fecal and urine samples from each child just before they were given a vaccine dose and then at 1 hour, 8 hours, 1 day, 2 days, 3 days, 4days, 5 days, 6 days, 7 days, 10 days, 15 days, and so on until the total amount of mercury that exited the body was at least 95% of the mercury that was dosed — the researchers did not do this.

   Moreover, from the narrative, all that the first study did was take 1 set of samples from each of the small non-random sample of children so that there was no way to correlate the differences in levels observed with changes in the children.

   Given the small size of the study and its failure to adequately establish mercury clearance from the body, all that this study provided are inaccurate estimates of the half-life for mercury clearance from the infants' blood.

   Moreover, since there were no comparative studies using a vaccine with methylmercury thiosalicylate as the preservative, there is no valid way to obtain the valid comparative distribution values required to make a valid differential blood clearance assessment.

5. In "*Pichichero ME, et al, …2008*", though the number of subjects is significantly larger ("200"), the study design still has the same flaws.

   Again, from the narrative, all the study did is take one set of samples from each child at some predefined random time point.

   All that is truly better in the second study is that the time points include some data:

   a. From before the randomly chosen subject's last dosing and
   b. Closer to the time that the last dose was administered.

   However, again all that this study allows one to validly do is generate a somewhat better estimate of the initial half-life for the clearance of the organic mercury species from the blood.

   The data collected and reported do not allow one to make any valid estimate of the clearance from the bodies of the children of the mercury species derived from the "Thimerosal preserved" vaccines administered.

   As before, the fairly wide range of mercury levels in the vaccines administered as well as, for the 2-month-old and the 6-month-old children, the variability in the level of mercury exposure in the current and prior vaccinations, precludes any exact estimate of the effect of dose, if any, on half-life for mercury clearance from the blood in each of the children — for this you would need more than one set of samples from each child.

   Interestingly, when the researchers found both methylmercury and ethylmercury species in the blood but found only ethylmercury species in the vaccine, the researchers reported (emphasis added):

> "Fish is not a commonly consumed food in Argentina, and in preliminary studies, we did not detect any mercury in a sample of 10 randomly selected umbilical cord blood samples from the R. Gutierrez hospital (data not shown); however, blood mercury levels ranging from 0.3 to 5.0 ng/mL were detected in prevaccination samples from all 3 age groups in this study, including newborns, in which we detected blood mercury levels as high as 2.6 ng/mL before vaccination. Therefore, speciation of organic mercury into ethyl and methyl mercury by gas chromatography atomic fluorescence was performed on 23 blood samples that had sufficient remaining volume for testing. These included 5 postvaccination samples from newborns (1 collected at 48 hours and 4 collected at day 5), 9 post-vaccination samples from 2-month-olds (3 collected at 24 hours, 4 collected on day 3, and 2 collected on day 5), and 9 postvaccination samples from 6-month-olds (5 collected at 24 hours and 4 collected at day 3). No prevaccination samples were available for speciation.
>
> Some methyl mercury was detected in all of the samples tes

ted, ranging from 1% to 50% of the total organic mercury in samples with both methyl and ethyl mercury, and in 2 samples (a newborn 48 hours after vaccination and a 2-month-old 5 days after vaccination), only methyl mercury was detected. The mean concentration of methyl mercury in the postvaccination blood of newborns was 0.39 ± 0.44 ng/mL (minimum: 0.067 ng/mL; maximum: 1.06 ng/mL). In the 2-month-old group, the mean concentration of methyl mercury in the blood was 0.26 ± 0.30 ng/mL (minimum: 0.37 ng/mL" [sic; the data values reported here are inconsistent: the mean cannot be less than the minimum]"; maximum: 0.79 ng/mL). In the 6-month-old group, the mean concentration of methyl mercury in the blood was 0.10 ± 0.07 ng/mL (minimum: 0.02 µg/mL; maximum: 0.23 ng/mL).

We also measured mercury levels in the administered vaccines and found that the stated amounts from the manufacturers were accurate and that the mercury in the vaccines was exclusively ethyl mercury. The presence of methyl mercury in the blood samples therefore suggests that sources of mercury other than thimerosal contributed to the total mercury measurements".

Instead of understanding that, after each vaccination with a "Thimerosal preserved" vaccine, they were seeing the sequential demethylation of the ethylmercury species formed from Thimerosal into first the corresponding "methylmercury species" and then into the fully demethylated "inorganic mercury species", the researchers looked for another source for the methylmercury species even though they found "in 2 samples (a newborn 48 hours after vaccination and a 2-month-old 5 days after vaccination), only methyl mercury was detected"

These results indicate that, *in these vaccinated children*, the conversion of all of the ethylmercury species remaining in the blood into methylmercury and "inorganic" mercury had been effected within 2 to 5 days after vaccination in these two individuals.

A similar "no ethylmercury species – only methylmercury and inorganic mercury species" phenomenon was noted in the heart tissue in a rat study where the rats were sacrificed "5" days after a "vaccine level" exposure[42].

6. Thus, at best, "*Pichichero ME, et al, 2002 & 2008*" only sheds some light on the apparent average half-life of Thimerosal-derived mercury in the blood but provides no valid estimates for the half-life of the clearance of the mercury from the infants' body.

[42] Rodriques JL, Serpeloni JM, Batista BL, Souza S, Barbosa Jr F. Identification and distribution of mercury species in rat tissues following administration of Thimerosal or methyl mercury. ***Arch Toxicol*** 2010; **84**: 891-896.

In addition, *though the researchers did not realize it*, the 2008 study helped to established that the degradation of Thimerosal in the blood (and in the tissues and organs, as other animal studies have shown) proceeds via a set of demethylation steps to the residual "inorganic mercury" species in blood.

Other studies in animals (rats) have found these specie at low levels compared to the overall tissue levels of the ethylmercury, methylmercury and "inorganic mercury" species in the organs at the comparison point – indicating that, although rapidly cleared from the blood, the breakdown mercury-containing products from the metabolism of Thimerosal are retained for significant periods of time in the tissues and organs.

Using a different approach, Japanese researchers found that the half-life for the "inorganic mercury" species retained in the human brain was about 18 to 20 years[43].

Moreover, the authors' last assertions:

> *"Further, ethylmercury was cleared from the blood in infants who received thimerosal-containing vaccines faster than would be predicted for methylmercury and infants excreted significant amounts of mercury in stool after receiving thimerosal-containing vaccines, thus highlighting an important mechanism by which mercury was cleared from their bodies*",

are not supported by the results reported.

This is the case because:

a. No repeated, 24-hour stool samples were collected and analyzed to determine the percent of the dose found in them,
b. The children were tested only once and not tested repeatedly as would be required to show the individual loss of mercury from the blood and
c. No mass balance studies were conducted to show where all of the mercury in the doses of vaccines was deposited.

Thus, there is insufficient data to support the authors' assertion that the mercury from the injected Thimerosal was "*cleared from their* [the babies inoculated with "Thimerosal preserved" vaccines] *bodies*" — only data supporting the fairly rapid clearance of most of the mercury in the variable vaccine doses from the infants' blood.

Factually, rat studies using radiolabeled alkyl and aryl mercury compounds have shown that, *for simple ethylmercury compounds like Thimerosal*, no more than 15 % of the ethylmercury compound dosed was rapidly cleared from the treated rats — with the remaining "85 %" only being slowly cleared from the treated rats' bodies[44].

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43 Sugita M. The biological half-time of heavy metals. The existence of a third, "slowest" component. ***Int Arch Occup Environ Health*** 1978; **41**(1): 25-40.

44 Takeda YA, Kunugi T, Hoshino O, Ukita T. Distribution of Inorganic, Aryl, and Alkyl Mercury Compounds in Rats. ***Toxicol Applied Pharmacol*** 1968; **13**: 156-164.

Review of Important Neonatal Studies Not Addressed

First, the authors did not address the study of the mercury levels in premature and low-birth-weight newborns given Thimerosal-containing vaccines[45].

In that study's abstract, the researchers stated (emphasis added):

> "**Objective** We conducted a population-based pharmacokinetic study to assess blood levels and elimination of mercury after vaccination of premature infants born at 2::32 and <37 weeks of gestation and with birth weight 2::2000 but <3000 g.
> **Study design** Blood, stool, and urine samples were obtained before vaccination and 12 hours to 30 days after vaccination from 72 premature newborn infants. Total mercury levels were measured by atomic absorption.
> **Results** The mean ± standard deviation (SD) birth weight was 2.4 ± 0.3 kg for the study population. Maximal mean ± SD blood mercury level was 3.6 ± 2.1 ng/mL, occurring at 1 day after vaccination; maximal mean ± SD stool mercury level was 35.4 ± 38.0 ng/g, occurring on day 5 after vaccination; and urine mercury levels were mostly nondetectable. The blood mercury half-life was calculated to be 6.3 (95% el, 3.85 to 8.77) days, and mercury levels returned to prevaccination levels by day 30.
> **Conclusions** The blood half-life of intramuscular ethyl mercury from thimerosal in vaccines given to premature infants is substantially shorter than that of oral methyl mercury in adults. Because of the differing pharmacokinetics, exposure guidelines based on oral methyl mercury in adults may not be accurate for children who receive thimerosal-containing vaccines."

Though the study design suffers from the same deficiencies as the two studies the authors cited (only measures of the mercury levels in blood, stool and urine from single-point sampling from each infant, no measure of mercury body burden and no mass balance for the mercury), the single-point mercury levels seen in some of the infants studies clearly were concerning (>5 ng of mercury/mL of blood.

Further, the blood levels observed at 30 days were, on average, lower than those at day zero, indicating that the data values were biased by the particular infants whose single-point blood sample were used for each time-point assessment.

Moreover, the "**Results**" in the abstract inaccurately states that the "mercury levels returned to prevaccination levels …" when it should have stated "[blood] mercury levels [apparently] returned to prevaccination levels …"

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45 Pichichero ME, Gentile A, Giglio N, Alonso MM, Fernandez Mentaberri MV, Zareba G, Clarkson T, Gotelli C, Gotelli M, Van L, Treanor J. Mercury Levels in Premature and Low Birth Weight Newborn Infants after Receipt of Thimerosal-Containing Vaccines. *J Pediatrics* 2009 Oct; **155**(4): 495-499.

To be clear, this observation was only applicable to the mercury level in the infants' blood and, because the infants tested at day "0" and day "30" were different infants, the return to "prevaccination levels" was not supported by testing the same infants at day "0" and day "30".

In addition, the authors chose not to even cite, much less discuss, a study by Stajich GV, et al. (2000) in which the blood mercury levels for the same infants in two cohorts, pre-term and term, were studied from blood samples taken:

a. Just before their "at birth" hepatitis B vaccination and
b. At 48 to 72 hours after vaccination[46].

In this study, though no samples were taken at 12, 24, or 36 hours after vaccination, where the study by Pichichero ME, et al (2008) found the highest mercury levels, the mercury levels in some of the preterm infants exceeded 10 mcg (µg)/L or 10 ng/mL and it is clear that the blood mercury level was in the range that should be considered toxic for these infants based on the results from the studies conducted by Pichichero ME, et al. (2002, 2008, 2009)[47,48,49].

In the abstract for this "iatrogenic exposure to mercury", these researchers stated:

> "Thimerosal, a derivative of mercury, is used as a preservative in hepatitis B vaccines. We measured total mercury levels before and after the administration of this vaccine in 15 preterm and 5 term infants. Comparison of pre- and post-vaccination mercury levels showed a significant increase in both preterm and term infants after vaccination. Additionally, post-vaccination mercury levels were significantly higher in preterm infants as compared with term infants. Because mercury is known to be a potential neurotoxin to infants, further study of its pharmacodynamics is warranted."

For the preterm infants, the day zero, blood levels of mercury were reported in the "***Table***" as "**.54, ± .79**" µg/L [0.54 ± 0.79 ng/mL], while the level in the term infants was "**.04, ± .09**" µg/L [0.04 ± 0.09 ng/mL].

For the preterm infants, the post-vaccination levels for mercury were reported as "**7.36, ± 4.99**" µg/L [7.36 ± 4.99 ng/mL], while the level in the term infants was "**2.24, ± 0.58**" µg/L [2.24 ± 0.58 ng/mL].

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46 Stajich GV, Lopez GP, Harry SW, Sexson, WR. Iatrogenic exposure to mercury after hepatitis B vaccination in preterm infants. ***J Pediatrics*** 2000 May; **136**(5): 679-681.

47 Pichichero, ME, E Cernichari, J Lopreiato, and J Treanor. (2002) Mercury Concentrations and Metabolism in Infants Receiving Vaccines Containing Thiomersal: A Descriptive Study. ***The Lancet*** 2002; **360**: 1737-1741.

48 Pichichero ME, Gentile A, Giglio N, Umido V, Clarkson T, Cernichiari E, Zareba G, Gotelli C, Gotelli M, Yan L, and Treanor J. (2008) Mercury Levels in Newborns and Infants After Receipt of Thimerosal-Containing Vaccines. ***Pediatrics*** 2008; **121**(2): e208-e214.

49 Pichichero ME, Gentile A, Giglio N, Martin Alonso M, Fernandez Mentaberri MV, Zareba G, Clarkson T, Gotelli C, Gotelli M, Van L, Treanor J. Mercury Levels in Premature and Low Birth Weight Newborn Infants after Receipt of Thimerosal-Containing Vaccines. ***J Pediatrics*** 2009 Oct; **155**(4): 495-499.e2.

Moreover, the post-vaccination average difference observed was statistically significant (P<0.01).

Unfortunately, the individual mercury values for each of the infants tested were not reported nor was there an attempt to discover the source of the prenatal exposure to mercury for the high values of blood mercury in some of the preterm infants before they were vaccinated or to study the correlation between the degree of prematurity and the blood mercury level in the preterm infants.

However, this study again established that some neonates, in this case preterm babies, had a toxic level of mercury exposure (a blood mercury level of ≥ 10 ng/mL) for some period of time after a single dose of a hepatitis B vaccine that nominally delivered a 125 µg (12,500 ng) dose of mercury to the vaccinated neonate.

"In 2004, the independent U.S. Institute of Medicine's Immunization Safety Review Committee issued a report examining the hypothesis that vaccines, specifically the MMR vaccines and thimerosal-containing vaccines, may be causally associated with autism. This report was based on the committee's review of biology, physiology, and the available epidemiological studies and concluded that the body of epidemiological evidence favors rejection of a causal relationship between either MMR vaccine or thimerosal-containing vaccines and autism."

Here, the authors start by stating a truth,

> "*In 2004, the independent U.S. Institute of Medicine's Immunization Safety Review Committee issued a report examining the hypothesis that vaccines, specifically the MMR vaccines and thimerosal-containing vaccines, may be causally associated with autism*",

but then, misrepresent the basis that the 2004 IOM "*Immunization Safety Review Committee*" used for its report as "*the committee's review of biology, physiology, and the available epidemiological studies*", when that report was actually based on a selective review of ***only*** those epidemiological studies that did not report a statistically significant link between the level of exposure to Thimerosal and only the risk of neurodevelopmental damage that was diagnosed as "autism".

Those epidemiological papers that found evidence of a statistically significant linkage to "autism" were simply labeled as "unintelligible" or "poorly defined" studies even though: **a)** the dismissed studies had used the same methodology that the CDC statisticians had developed and used for similar studies and **b)** the dismissed studies had been published in recognized peer-reviewed journals where the peer reviewers included recognized biostatisticians.

Moreover, in mid-2006, the National Institute for Environmental Health Sciences (NIEHS) issued a report that stated[50] (emphasis added):

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50 REPORT OF THE EXPERT PANEL TO THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES: Thimerosal Exposure in Pediatric Vaccines: Feasibility of Studies Using the Vaccine Safety Datalink August 24, 2006, page 2.

> "The panel identified several serious problems that were judged to reduce the usefulness of an ecologic study design using the VSD to address the potential association between thimerosal and the risk of AD/ASD. These included uncertainties in case ascertainment, heterogeneity of business practices within and across MCOs and their systematic changes over time, misclassification of exposure status using comparisons of before vs. after removal of thimerosal from most childhood vaccines, and the inability to control for temporal changes in awareness, diagnostic practices and potential confounding factors. In light of the cumulative effect of these limitations, the panel reached consensus that an analysis comparing the rates of AD/ASD in the VSD over the time period before, during and after the removal of thimerosal from most childhood vaccines would be uninformative and potentially misleading",

which logically also invalidated the CDC's 2003 study (Verstraeten T et al. 2003).

This "Verstraeten" study was likely the "key study"[51] that the 2004 IOM "*Immunization Safety Review Committee*" used to assert that there no evidence of a link between Thimerosal and autism) because the "Verstraeten" study was subject to: **a)** the VSD flaws to which the NIEHS report was alluding and **b)** in violation of the fundamental precepts of epidemiological study execution, the authors repeatedly modified the study design with the "undisguised" intent to minimize the associations found between the level of mercury (Thimerosal) exposure and the risk of "autism".

In 2007, in a report to Congress[52], in response to the 2006 NIEHS report, Dr. Julie Louise Gerberding, then Director of the CDC, essentially testified that the CDC concurred with the 2006 NIEHS report's findings.

However, though all of the epidemiological studies on which the 2004 report by the "*Immunization Safety Review Committee*" was based had some or all of the flaws that the 2006 NIEHS report identified and a 2007 report issued by then CDC Director, Dr. Gerberding, supported the NIEHS report, the IOM has, *to date*, elected not to withdraw the 2004 report of the "*Immunization Safety Review Committee*".

Finally, in spite of repeated requests for all of the raw data that was available to the researchers in each study for all of the epidemiological studies that the 2004 IOM committee used as its basis for its report (so that the validity of the findings reported by the researchers could be confirmed), *to date*, the requestors have been unable to obtain that raw data even though, *by law*, because the US government helped fund all

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51 Because: **a)** the 2004 IOM committee only used the epidemiological studies as the basis for its findings and **b)** the CDC's "Verstraeten T et al. 2003" study was the only US study, this study was obviously the "key study". Had it found a statistically significant link between the level of Thimerosal exposure and the risk of "autism", the findings of the equally or more problematic studies in the UK, Denmark, and Sweden would not have mattered because the level of Thimerosal exposure in those studies was lower and, in the case of the UK study, the CDC's own e-mails revealed the UK database to be error ridden.

52 DEPARTMENT OF HEALTH AND HUMAN SERVICES, CENTERS FOR DISEASE CONTROL AND PREVENTION, REPORT TO CONGRESS ON VACCINE SAFETY DATALINK. Report delivered to the House Appropriations Committee by Julie Louise Gerberding, M.D., M.P.H., on July 13, 2007.

of the studies or, for the US "Verstraeten" study, the researchers were employed by the US government, qualified independent researchers are entitled to a personal-patient-information-redacted copy of all of the raw data they requested.

In the case of the US "Verstraeten" studies conducted by the CDC, the CDC has even claimed that it has "lost" all of the raw data requested.

In science, any study that, *for whatever reason (including "lost data")*, cannot be replicated by qualified independent researchers is an irreproducible study and the journals who published such irreproducible studies are supposed to withdraw such papers.

However, to date, the editors of the journals that published the original studies have elected to neither remove these "irreproducible" studies from their journals nor repudiate the articles because their results have not been/cannot be independently confirmed.

"More recent studies performed both in Canada and in the United States did not demonstrate a causal association between thimerosal exposure from childhood vaccines and autism or neuropsychological functioning in children when they reached 7 to10 years of age (Fombonne et al 2006, Thompson et al 2007)."

Here, this reviewer notes that this convoluted sentence states a compound negative:

> "*more recent studies … did not demonstrate a causal association between thimerosal exposure from childhood vaccines and* [a)] *autism or* [b)] *neuropsychological functioning in children when they reached 7 to10 years of age*",

but ignores the reality that "*Fombonne et al 2006*" has been shown to contain false or misleading information about: a) the Canadian vaccination uptake rates for measles in province of Quebec, b) the number of children in the "Montreal English-speaking School System" with a diagnosis of any pervasive developmental disorder (PDD), including "autism", and c) the actual vaccination programs to which the children were subject.

In addition, the study inappropriately equated the school's grades with the "age" of the students, when a significant percentage of the students were at least one "year" older[53].

Moreover, though this reviewer and at least one other recognized independent vaccine epidemiologist have requested Dr. Fombonne to provide the identification-redacted raw data available to him for use in this paper, to date, Dr. Fombonne has not provided the data requested by either requestor.

Further, attempts by a Canadian citizen living Montreal to lawfully obtain that raw data from the school system used in the study through the "Canadian Freedom of

[53] Because the school year starts in the August/September timeframe, children born late in the year, typically after September are generally not allowed to start school until the following year.

Information" laws were answered with a coincidental claim that it had been "lost", like the CDC's answer to those who sought the "Verstraeten" study's raw data.

In spite of not being given the raw data requested, this reviewer was able to show that, if you removed: **a)** the data for Grade "11"[54] and **b)** the data for "Kindergarten" (grade "K")[55], the data for grades "1" through "10" indicated a rise in PDD cases from grade "10" through "3" and a decrease in PDD cases from grade "3" through grade "1"[56].

Though this reviewer e-mailed Dr. Fombonne a copy of this reviewer's assessment of "Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations" by Eric Fombonne, Rita Zakarian, Andrew Bennett, Linyan Meng, and Diane McLean-Heywood, as published in ***Pediatrics***, Vol. 118, No. 1, July 2006, pp. e139-e150 (doi:10.1542/peds.2005-2993), neither he nor any of the other authors of the paper have provided the requested raw data nor have any of them even attempted to refute this reviewer's assessment, which found that there was an obvious link between the number of students with a diagnosis of a PDD and the change in the level of Thimerosal exposure.

Further, *contrary to the authors' assertions*, for mercury exposure, the "*Fombonne et al 2006*" study does show a decline in the incidence of PDDs after the level of mercury exposure from vaccines was significantly reduced in the late 1990s.

Finally, were the reported incidence for grade "K" to be corrected for the general under enrollment of normal students in this optional grade, then, instead of a clearly biased rate of "107.6", the under-enrollment-corrected rate would have been "about 54" for "1998" – clearly a rate significantly lower than the paper's "66.8" rate for "1996" and "76.8" for "1997".

Obviously, for the data from 1994 through 1998 in the paper, when the level of mercury exposure from vaccines was reduced, the rate of PDD declined.

In the "*Thompson et al 2007*" instance, this reviewer notes that the children assessed in this study were a group of "neurotypical" children who were assessed for their "autistic behaviors/tendencies".

In spite of all the exclusions and manipulations of the composition of the test group, the study still found evidence of a statistically significant link between the level of Thimerosal exposure and **a)** "tics" and **b)** a "speech/language delay".

Obviously, though these papers are "newer", they seem to be as scientifically unsound as the epidemiological studies used by the IOM "*Immunization Safety Review Committee*" as the basis for its 2004 report.

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54 The data for this grade was properly removed because there was no way to determine an accurate number of cases or an appropriate denominator since children with a PDD diagnosis were retained in that grade for several years.

55 The data for this grade was properly removed because attendance is optional but, since support services are provided to children with a diagnosis of a PDD, most of the children with a diagnosis are enrolled, while, as far as this reviewer could ascertain, only about half of the children who were eligible to be enrolled in this optional grade were actually enrolled in grade "K")

56 http://mercury-freedrugs.org/docs/060827_PGKsCmmnts_CanadianEpidemioStudy_Pediatrics-Full-b.pdf.

"Page 5

In July 2006, the WHO issued a statement on Thiomersal (Thimerosal) through the Global Advisory Committee on Vaccine Safety. It concluded that there is no evidence of toxicity in infants, children, or adults exposed to Thiomersal (Thimerosal) in vaccines (WHO 2006). This statement applies to the full suite of recommended infant and childhood vaccines with preservatives, which are used extensively outside the United States, and not just to influenza vaccines with preservatives to which U.S. children may be exposed."

First of all, this reviewer must thank the authors for bringing up the World Health Organization (WHO) and its Global Advisory Committee on Vaccine Safety (GACVS), which apparently more than doubled the level of mercury exposure from Thimerosal in "Thimerosal preserved", inactivated-"A-H1N1"-influenza vaccines as part of a pandemic response.

This avoidable exposure directly affected pregnant women and their unborn children.

It assured that many of them would get an extra dose of mercury from the "Thimerosal preserved" A-H1N1 vaccines that most who allowed themselves to be given this flu shot in the 2009-2010 flu season would receive.

Many of them were given a Thimerosal-containing pandemic flu shot with, or in addition to, the now "seasonal" "Thimerosal preserved" trivalent flu shots or, in some instances, two Thimerosal-containing pandemic flu shots.

Based on the reports to the VAERS (Vaccine Adverse-Events Reporting System) database, the extra dose of mercury increased their risk of miscarriage or stillbirth in the 2009-2010 flu season by more than an order of magnitude[57] (by about 11.2 times) over the previous flu season's risk as well as by slightly less than a 20-fold magnitude[58] (about 18.1 times) over the 2010-2011 flu season's level.

Thus, on average, it appears that giving pregnant women a second dose of a "Thimerosal preserved" flu shot in the 2009-2010 flu season caused an 11- to 18-fold increase in the reports of miscarriages and stillbirths to VAERS.

Unfortunately, *unlike the rat pups in the controlled study*, there is no way to assess the relative level of the increase in adverse effects on the children who "survived" the two-fold increase in their level of mercury exposure when they were in the womb.

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57 The US reports of inactivated-influenza-vaccine-related miscarriage and stillbirth to VAERS (the Vaccine Adverse-Events Reporting System) data base increased from "4" reports when the vaccination uptake level was about "25%" for 1 dose of vaccine in the 2008-2009 flu season to "174" US inactivated-influenza-vaccine-related reports of miscarriage and stillbirth to the VAERS database in the 2009-2010 flu season when the vaccination uptake rate for the inactivated-virus seasonal and A-H1N1flu shots (2 doses of flu vaccine) was at an average vaccination level of about 49% for both flu vaccines – or (the equivalent of about 174/4 x about 25 % for a single dose of vaccine in the 2008-2009 flu season/the equivalent of about 97% uptake for a single dose of vaccine in the 2009-2010 flu season) or a 11.2-fold increase.

58 The increase in the level of reports of stillbirths and miscarriages to VAERS in the 2009-2010 flu season was apparently about (174/19 x 97 % equivalent/49%) the level of reports of stillbirths and miscarriages to VAERS in the 2010-2011 flu season or a normalized 18.1-fold increase.

Turning to the authors' next statement, "*It concluded that there is no evidence of toxicity in infants, children, or adults exposed to Thiomersal (Thimerosal) in vaccines (WHO 2006)*", this reviewer notes that the WHO's "Statement on thiomersal" states (emphasis added):

"**Statement on thiomersal**

The Global Advisory Committee on Vaccine Safety concludes that there is no evidence of toxicity in infants, children or adults exposed to thiomersal (containing ethyl mercury) in vaccines.

July 2006

In 1999, concerns were raised in the United States of America about exposure to mercury in vaccines. This was based on the realization that the cumulative amount of mercury in the infant immunization schedule potentially exceeded the recommended threshold set by the United States government for methyl mercury. However, thiomersal, the preservative in some vaccines, contains ethyl mercury not methyl mercury. The Global Advisory Committee on Vaccine Safety (GACVS) first assessed this issue at a special meeting in August 2000. The Committee review has been ongoing since then.

Expert consultation and data presented to the GACVS indicate that the pharmacokinetic profile of ethyl mercury is substantially different from that of methyl mercury. The half-life of ethyl mercury is short (less than one week) compared to methyl mercury (1.5 months) making exposure to ethyl mercury in blood comparatively brief. Further, ethyl mercury is actively excreted via the gut unlike methyl mercury that accumulates in the body.

Four independently conducted epidemiological studies investigating associations and frequency of neurobehavioural disorders in relation to vaccination with thiomersal-containing vaccines have been completed in the United Kingdom of Great Britain and Northern Ireland and Denmark. The findings from these studies do not challenge the safety of existing thiomersal-containing vaccines in infants. Recently two studies were published alleging reduction of neurodevelopmental disorders in the United States of America following discontinuation of thiomersal-containing vaccines in the national immunization programme. The Committee found the conclusions made by the authors unconvincing due to the study design, and the data source.

The GACVS reviewed available information on an ongoing thiomersal pharmacokinetic study in macaque monkeys and assessed the validity of animal models in studying associations between thiomersal and neurobehavioural disorders in humans. The Committee was informed of ongoing human neurobehavioural studies and thiomersal exposure in the United States of America and Italy and of a study on the suitability of thiomersal-free vaccines in multidose vial presentations, assessed by retained sterility for up to 30 days.

On the basis of the foregoing, the GACVS concluded that the most recent pharmacokinetic and developmental studies do not support concerns over

> the safety of thiomersal (ethyl mercury) in vaccines. The Committee concluded, and advises accordingly, that there is no reason on grounds of safety to change current immunization practices with thiomersal-containing vaccines, as the risks are unproven. However, data for well-nourished neonates born at term cannot necessarily be extrapolated to preterm or malnourished infants. Studies on the latter group would be difficult to conduct, but the GACVS encourages further research.
>
> The GACVS will continue to review the evidence, including any epidemiological data, that might emerge from on-going studies.
>
> *The GACVS is a scientific advisory body established by WHO to provide a reliable and independent scientific assessment of vaccine safety issues in order to respond promptly, efficiently and with scientific rigour to such issues. Membership includes experts from around the world in the fields of epidemiology, paediatrics, internal medicine, pharmacology and toxicology, infectious diseases, public health, immunology and autoimmunity, drug regulation, and safety."*

contains a collection of statements that deflect liability from the government and the pharmaceutical manufacturers.

Unfortunately, for the most part, many of these statements are misleading.

For example, most glaringly, the fact that the 2006 GACVS' "**Statement on thiomersal**" has not been updated since 2006 clearly indicates that GACVS is not responding "*promptly, efficiently and with scientific rigour*" to vaccine safety issues.

Evidently, the members of GACVS are unresponsive to the ever-increasing number of toxicity studies that have proven that weight– and developmental–stage–appropriate vaccine doses of "Thimerosal preserved" vaccines or preservative levels of Thimerosal are clearly toxic to developing animals, including Macaque monkeys[59] and humans[60].

In addition, these authors rely on epidemiological studies that cannot validly be used to determine whether or not Thimerosal is "sufficiently nontoxic …"

Only scientifically sound and appropriate toxicity studies can establish the level below which an injected dose of Thimerosal is ***nontoxic***, i.e., the set of Thimerosal's age-, sex-, and function- appropriate NOAEL (no observed adverse-effect-level) values below which low-level exposures to Thimerosal have no clinically observable chronic adverse health effects for a single or multiple low-dose exposures,

Based on the only FDA-recognized chronic toxicity study for injected Thimerosal[61], a study done in developing and adult rats, and its reported findings, the upper limit for the NOAEL for mercury from injected "Thimerosal preserved" vaccines in developing

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59 Hewitson L, Houser LA, Stott C, Sackett G, Tomko JL, Atwood D, Blue L, White ER. Delayed Acquisition of Neonatal Reflexes in Newborn Primates Receiving a Thimerosal-containing Hepatitis B Vaccine: Influence of Gestational Age and Birth Weight. ***J Toxicol Environmental Health, A***, 2010; **73**: 1298–1313.

60 Gallagher CM, Melody S. Goodman MS. Hepatitis B Vaccination of Male Neonates and Autism Diagnosis, NHIS 1997–2002. ***J Toxicol Environmental Health, A***, 2010; **73**: 1665–1677, 2010.

61 Mason MM, Cate CC, Baker. Toxicology and Carcinogenesis of Various Chemicals Used in the Preparation of Vaccines. ***J. CLIN TOXICOL***, 1971; **4**(2): 185-204.

humans given multiple doses is *less than* (<) 0.0042 µg/kg/day[62].

Moreover, even if that upper-limit estimate were the NOAEL for the developing children (NOAEL $_{\text{developing children}}$), to meet the "sufficiently nontoxic …" requirement for a preservative in a vaccine set forth in 21 CFR § 610.15(a), the level of Thimerosal would have to be *no more than* (≤) 0.00042 µg of mercury from injected Thimerosal/kg of body weight/day or ≤ 0.42 ng of mercury from injected Thimerosal/kg/ day.

Based on the preceding values, presuming that a 2 kg weight should be the least weight for a healthy baby to be vaccinated and that the injected Thimerosal were uniformly distributed in the body, the maximum "**sufficiently nontoxic …**" dose would be no more than (≤) 0.84 ng of mercury from Thimerosal or ≤ 1.7 ng of Thimerosal.

Since the least nominal level of Thimerosal in a US vaccine that is claimed to be preserved is about 33,000 ng of Thimerosal per mL of vaccine or 8,250 ng of Thimerosal per 0.25-mL dose and the most common nominal level off Thimerosal in a "Thimerosal preserved" vaccine is 100,000 ng/mL or 25,000 ng of Thimerosal/ 0.25-mL of multi-dose influenza vaccine given to children under three years of age in the USA and most young children weight less than 20 kg, it is obvious that the nominal level of Thimerosal in the current FDA-approved "Thimerosal preserved" vaccines is *much greater than* (>>) 248 to 735 times the putative "sufficiently nontoxic …" level.

Further, the assertion that "*The GACVS will continue to review the evidence, including any epidemiological data, that might emerge from on-going studies*" clearly shows that the GACVS is not focused on the disputed safety of the use of Thimerosal since only relevant, scientifically sound and appropriate toxicity data can be used to determine when the level of Thimerosal is "sufficiently nontoxic …" (safe).

In addition, the GACVS statement:

> "Expert consultation and data presented to the GACVS indicate that the pharmacokinetic profile of ethyl mercury is substantially different from that of methyl mercury. The half-life of ethyl mercury is short (less than one week) compared to methyl mercury (1.5 months) making exposure to ethyl mercury in blood comparatively brief. Further, ethyl mercury is actively excreted via the gut unlike methyl mercury that accumulates in the body",

begins with an initial assertion with which this reviewer generally agrees: "[T]he pharmacokinetic profile of ethyl mercury is substantially different from that of methyl mercury".

As a chemist, this reviewer knows that, in a homologous series of alkyl compounds, the chemical properties of the methyl member significantly differ from the ethyl (and propyl, butyl, …) members of the series[63].

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62 http://mercury-freedrugs.org/docs/090812_fnldrft_TheTruthAboutTheToxicityOfThimerosalr5b.pdf.

63 For example, methyl alcohol rapidly alkylates (methylates) proteins in human systems rendering people who drink a significant amount of methyl alcohol blind, However, ethyl alcohol does not rapidly alkylate (ethylate) proteins in human systems and people are generally not blinded by drinking several ounces of it.

Furthermore, this reviewer accepts that the blood half-lives of the ethyl mercury compounds, e.g., Thimerosal and its initial "metabolites" (ethylmercury hydroxide and ethylmercury chloride), may be "less than one week" and accepts that the blood half-lives of methylmercury compounds may be on the order of "1.5 months".

However, as speciation studies of the mercury species present in "blood" samples[64] and blood and tissue samples[65] have shown, though the researchers who published them did not articulate (or recognize) this biochemical process: In the body, a major degradation pathway for ethylmercury compounds in blood and tissues apparently proceeds by a sequential demethylation mechanism.

Thus, simple ethylmercury compounds, like ethylmercury hydroxide and ethylmercury chloride (the initial mercury-containing breakdown products of Thimerosal in the body), are first rapidly demethylated (with half-lives of "*less than a week*" in human blood) to form the corresponding methylmercury compounds and then these methylmercury compounds are more slowly demethylated (with half-lives on the order of "*1.5 months*" in human blood) to the tissue-retained "inorganic mercury" species that have tissue and organ half-lives in humans that are on the order of *one to two decades* depending on the tissue or organ[66].

Therefore, even though: **a)** there are initial immunological differences between Thimerosal and methylmercury (hydroxide or chloride) and **b)** there may be significant differences in the initial redistribution of the particular mercury compound injected throughout the body, the longer-term neurological effects of both compounds appear to be similar because, after a few weeks, the neurotoxicity of the mercury in the body is being controlled by the more persistent methylmercury compounds and the "inorganic mercury species" whether the material injected was Thimerosal (effectively, shortly after injection, a mixture of ethylmercury hydroxide and ethylmercury chloride) or similar mixture of methylmercury hydroxide and methylmercury chloride.

Except that the timeframes in the organs are longer than the timeframes in the blood, similar realities apply to the levels of the poisonous organic mercury species in the tissues and the organs.

The preceding realities are consistent with Pichichero ME, et al. (2008)[67] who studied the distribution of mercury species in the blood of young humans and the findings reported by Rodriques JL, et al. (2010) in a study using rats[68].

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64 Pichichero ME, Gentile A, Giglio N, Umido V, Clarkson T, Cernichiari E, Zareba G, Gotelli C, Gotelli M, Yan L, and Treanor J. Mercury Levels in Newborns and Infants After Receipt of Thimerosal-Containing Vaccines. ***Pediatrics*** 2008; **121**(2): e208-e214.

65 Rodriques JL, Serpeloni JM, Batista BL, Souza S, Barbosa Jr F. Identification and distribution of mercury species in rat tissues following administration of Thimerosal or methyl mercury. ***Arch Toxicol*** 2010; **84**: 891-896.

66 Sugita M. The biological half-time of heavy metals. The existence of a third, "slowest" component. ***Int Arch Occup Environ Health*** 1978; **41**(1): 25-40.

67 Pichichero ME, Gentile A, Giglio N, Umido V, Clarkson T, Cernichiari E, Zareba G, Gotelli C, Gotelli M, Yan L, and Treanor J. Mercury Levels in Newborns and Infants After Receipt of Thimerosal-Containing Vaccines. ***Pediatrics*** 2008; **121**(2): e208-e214.

68 Rodriques JL, Serpeloni JM, Batista BL, Souza S, Barbosa Jr F. Identification and distribution of mercury species in rat tissues following administration of Thimerosal or methyl mercury. ***Arch Toxicol*** 2010; **84**: 891-896.

Both groups observed that, even though the administered Thimerosal (sodium ethylmercurithiosalicylate) contained no methylmercury contaminant, after some time, the mercury species identified in some samples consisted of only methylmercury and "inorganic" mercury species and, in other samples, a mixture of ethyl-, methyl-, and "inorganic"- mercury species.

Hopefully, after reading this reviewer's hypothesis and studying the ever-growing body of speciated-sample analyses that supports it, an appropriate animal study using injected sodium $^{13}CH_3$-$^{14}CH_2$-^{203}Hg-thiosalicylate and/or a 50:50 mixture of $^{14}CH_3$-$^{13}CH_2$-^{203}Hg-OH and $^{13}CH_3$-$^{14}CH_2$-^{203}Hg-Cl in a simulated vaccine solution will be conducted and high-performance liquid chromatographic separation of the mercury-containing moieties in blood samples collected at appropriate intervals coupled with mass spectral analysis of the separated components to determine the exact nature and level of each separated mercury-containing component will be carried out.

The samples should be collected from just before the animals are inoculated with a vaccine-level dose until there is no more evidence of any ethylmercury species in the test animals' blood; the collected samples appropriately worked up and analyzed; and the results of the analyses published that confirm this reviewer's results-based hypothesis (or unequivocally establish an alternate degradation pathway for Thimerosal and its ethylmercury-containing metabolites in blood).

In addition, the last statement in this paragraph, "Further, ethyl mercury is actively excreted via the gut unlike methyl mercury that accumulates in the body", is totally at odds with the results from studies in rats or rats and monkeys using radiolabeled ethylmercury (^{203}Hg) compounds[69,70], which indicate that most (> 75%) of the radiolabeled (^{203}Hg) dose of the administered ethylmercury-containing compound is retained in the body for some significant period of time.

Finally, this reviewer notes that the GACVS' view of itself as a body that can "provide reliable and independent scientific assessment of vaccine safety issues" is not supported by the statements it has made — statements that are, in many instances, clearly at odds with the relevant, scientifically sound and appropriate toxicological data for Thimerosal and its mercury-poisoning effects at levels below 1 ppm[71].

"***Studies Evaluating the Kinetics and Toxicity of Ethylmercury Compared to Methylmercury***

Pharmacokinetics

Long-term, low-level steady-state exposure to methylmercury (e.g., through consumption of fish) contrasts with the short-term intermittent exposure to ethylmercury that individuals receive through

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69 Takeda YA, Kunugi T, Hoshino O, Ukita T. Distribution of Inorganic, Aryl, and Alkyl Mercury Compounds in Rats. *Toxicol Applied Pharmacol* 1968; **13**: 156-164.

70 Takkahashi T, Kimura T, Sato Y, Shiraki H, Ukita T. Time-Dependent Distribution of ^{203}Hg-Mercury Compounds in Rat and Monkey as studied by Whole Body Autoradiography. **The J Hygienic Chem** [Japan] 1971; **17**(2): 93-107.

71 Geier DA, Sykes LK, Geier MR. A review of Thimerosal (Merthiolate) and its ethylmercury breakdown product: specific historical considerations regarding safety and effectiveness. *J Toxicol Environ Health B Crit Rev* 2007; **10**: 575-596.

vaccinations. The half-life of ethylmercury in blood is between 4 and 7 days and complete washout of mercury from the blood of both pre- and full-term infants has been shown to occur 30 days after immunization (Pichichero 2002; 2008; 2009; Barregard et al 2011). The half-life of ethylmercury in human infants has been shown to be similar to that in infant macaques (monkeys) (Burbacher et al 2005), which indicates that infant monkeys are a good animal model for human infant exposures to ethylmercury in vaccines. In addition, very recent results from a clinical trial in Sweden show that adult patients who received a thimerosal-containing staphylococcus toxoid vaccine once per month for several years for the treatment of chronic fatigue syndrome had similar levels of total blood mercury as non-treated controls by the end of the study (Barregard et al 2011), which indicates that ethylmercury is rapidly cleared from the blood of adults as well as infants. By way of contrast, the half-life of methylmercury in humans is approximately 50 days (ATSDR 1999), approximately 10 times longer than that for ethylmercury."

The authors' narrative here is typical of what those who are mistaken about the "*Pharmacokinetics*" of mercury compounds write.

Moreover, the preceding narrative fails to address one of the fundamental precepts of the science-based study of the pharmacokinetics of the distribution of any compound administered to an animal or human: the study must establish a mass balance between the dose of chemical administered and the end products of the metabolism that accounts for nearly all of the dose that was administered.

To date, this reviewer is <u>not</u> aware of any published or presented study that has ***completely*** elucidated the fate of even a single dose of Thimerosal, or of any ethylmercury model compound, at vaccine levels in any primate species.

Though the allowable tolerance for mass loss is related to the level of the dose (the lower the dose, the higher the allowable mass deficit), for the vaccine-level dose of tens of microgram amounts of Thimerosal or a related ethylmercury compound or a methylmercury analog typically administered to humans and animals in pharmacoki

netic studies, a 90%-105% recovery level is usually considered to be acceptable.

At the low level of dosing needed for Thimerosal, the only way to validly assess this mass balance for the ethylmercury moiety in Thimerosal is to use appropriately elementally labeled analogs of Thimerosal or a model compound like ethylmercury hydroxide[72].

For example, to completely study the pharmacokinetics of the metabolism of the ethylmercury moiety of a model compound like ethylmercury hydroxide, one could use an isotopically substituted analog of ethylmercury hydroxide, like $^{13}CH_3$-$^{14*}CH_2$-^{203*}Hg-OH ["R-Hg labeled" ethylmercury hydroxide], where the asterisks indicate that the isotope is radioactive.

Accepting that, as the authors assert, the Macaque monkey is a good model, all one would need to do is house a few subjects, half male and half female (typically a minimum of three each), of the appropriate starting age in cages designed to provide

[72] Since Thimerosal is highly soluble in water, the initial choice of a model compound should be an ethylmercury compound that is highly soluble in water. Ethylmercury hydroxide is the simplest model compound containing the ethylmercury moiety that is highly soluble in water. If one wanted to use a model system that mimics the actual behavior of Thimerosal in mammalian systems, then, the simplest model should be a 1:1 mixture of ethylmercury hydroxide and ethylmercury chloride at the 100-ppm level (50-ppm of each) in an isotonic pH-buffered solution.

ready access to mercury-free food and water and to collect the animals feces and urine.

Then, after taking baseline samples of their blood, urine, feces and hair, inject the test animals with the appropriate amount of a pH and ionic-strength-balanced solution of the "R-Hg labeled" ethylmercury hydroxide and then periodically collect the requisite samples to track the disposition of the injected "R-Hg labeled" ethylmercury hydroxide.

As the samples are collected, each set should be appropriately worked up and the level of the species containing any of the marker elements should be quantitated, the nature of each label-containing species should be determined, and the results of these evaluations used to monitor the overall level of the labeled atoms remaining in each test subject until the shorter of: **a)** more than 90% of all the labeled mercury atoms have been excreted or **b)** the test subject has been studied for more than half of its nominal lifetime.

When all of the required data has been collected, then the test subjects should be sacrificed and the residual levels of all of the elemental labels in the tissues should be assessed and, to the extent possible, the nature of the compounds in the tissues that contain any of the labels should be identified.

Then, and only then, would the results obtained permit a researcher to establish the pharmacokinetics of the "metabolism" of "R-Hg labeled" ethylmercury hydroxide and the pathways by which the "R-Hg labeled" ethylmercury hydroxide was metabolized.

If, as this reviewer has hypothesized, the metabolism of the ethyl group proceeds by a successive demethylation mechanism, then, focusing on the ethyl group and the mercury, one should see that the blood samples go from containing $^{13}CH_3$-$^{14*}CH_2$-$^{203*}Hg$-- to containing a mixture of $^{13}CH_3$-$^{14*}CH_2$-$^{203*}Hg$-- , $^{14*}CH_3$-$^{203*}Hg$— and $^{203*}Hg$-- to, *after some time*, containing a mixture of $^{14*}CH_3$-$^{203*}Hg$--, and $^{203*}Hg$-- to, finally, containing only $^{203*}Hg$--.

In addition, from the weight of the urine and feces excreted and the concentration of mercury in them, the percentage loss in the mercury dose administered could be tracked.

From the timeframes for the progression of the metabolism and the distribution of the components in the body of the test subjects and in their excretions and the weight of the test subjects and their excretions, one should then be able to determine the true half-lives for the transport of the various species out of and/or into the blood and either into or out of the tissues and organs, and into the test subject's excretions including the test subjects' urine, feces, hair and nails as well as find the ultimate fate of at least 90% of each of the labeled elements.

Unfortunately, from the studies discussed by the authors of this document, all that one can estimate is the apparent half-lives for all of the mercury-containing components in the test subjects' blood.

If the authors really do think that there is a need to ascertain the accurate "*Pharmacokinetics*" of Thimerosal or of Thimerosal and its methyl mercury analog so

that there can be a valid comparison of the pharmacokinetics of these two compounds, then, this reviewer looks forward to seeing results from appropriately designed studies such as those just described.

However, all that the current types of studies cited by these authors can accurately do is follow the level and nature of the alkylmercury moieties in blood and the level of the inorganic mercury moieties in the blood of the test subjects as well as, at sacrifice, make a single-point assessment of the moieties in the organs and tissues of the test subjects.

Moreover, the mercury-clearance studies using radiolabeled mercury (^{203}Hg) that the Japanese conducted in the 1960s and 1970s with various ethylmercury compounds have clearly established that: **a)** *no more than* about 15% of the labeled mercury (^{203}Hg) in the labeled ethylmercury compounds studied was excreted "rapidly"[73]; and **b)** the radiomicrographs of whole body sections of monkeys eight days after being treated with ^{203}Hg-labeled ethylmercury chloride (EtMC) showed distribution of the label throughout the body.

Further, the researchers[74] reported:

> "In the case of the monkey, the ratio of the concentration in the brain (1.27*μg/g* on average) to the liver (3.04 *μg/g*) was 0.42 and this value was much larger than the corresponding ratio of 0.094 for rat indicating the higher distribution of mercury into the brain in money than in rat after intravenous injection of EtMC. There was no remarkable difference between the concentrations of mercury in the liver for these two species of animals, however …"

Thus, this study seems to confirm that the rat's biochemistry protects the rat brain from exposure to "ethylmercury" species about 4.5 times better than the monkey's biochemistry protects the monkey's brain.

Further, these authors implicitly admit that the monkey's biochemistry appears to be much more like humans' biochemistry[75] than the rat's biochemistry.

Moreover, these radiolabeled mercury studies of ethylmercury compounds clearly show that, while the radiolabeled mercury may clear the blood rapidly, it does <u>not</u> rapidly clear the body.

Therefore, the preceding facts show that the authors of the document being reviewed do <u>not</u> understand the basics of pharmacokinetics as it applies to ethylmercury compounds.

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73 Takeda YA, Kunugi T, Hoshino O, Ukita T. Distribution of Inorganic, Aryl, and Alkyl Mercury Compounds in Rats. ***Toxicol Applied Pharmacol*** 1968; **13**: 156-164.

74 Takkahashi T, Kimura T, Sato Y, Shiraki H, Ukita T. Time-Dependent Distribution of ^{203}Hg-Mercury Compounds in Rat and Monkey as studied by Whole Body Autoradiography. ***The J Hygienic Chem*** [Japan] 1971; **17**(2): 93-107.

75 Specifically, the authors of the submission being reviewed stated, "*The half-life of ethylmercury in human infants has been shown to be similar to that in infant macaques (monkeys) (Burbacher et al 2005), which indicates that infant monkeys are a good animal model for human infant exposures to ethylmercury in vaccines.*" [See: The middle of page 5 of the authors' submission.]

"*Toxicity*

Since 1999, the toxicity of ethylmercury has been studied extensively in animals. These studies indicate that while the nervous system and kidneys are primary targets of ethylmercury exposure at high doses, there is a clear dose threshold between adverse and non-adverse effects. In studies in rats, rabbits, and dogs, doses up to 45 mg/kg bw/day have been reported to cause death, slight

Page 6

decreases in body weight gain, neurotoxicity (motor incoordination), or toxicity to the kidney (cited in Ball et al 2001). However, chronic daily doses approximately 4 orders of magnitude lower (1 or 6 µg/kg bw/day), which is within the range of doses that human infants are exposed to from a yearly influenza vaccine, have yielded no evidence of toxicity either to the kidney or the brain, the two major target organs of mercurials in adult squirrel monkeys (Blair 1975). Recently, Olczak et al (2010) reported that pathological changes were observed in the brains of neonatal Wistar rat pups treated with ethylmercury at doses at least 3-fold higher than what human infants could receive in a yearly influenza vaccine. Most notably, the sequence of injections in this animal model study (4 injections administered only 2-4 days apart) was quite different from influenza vaccination, where a child would typically receive a single annual dose or, at most, two doses separated by at least one month when children younger than 9 years of age are receiving influenza vaccine for the first time."

Here, the authors begin with an intentional distortion of reality when they state:

"Since 1999, the toxicity of ethylmercury has been studied extensively in animals."

Factually, the toxicity of ethylmercury compounds has been extensively studied in plants and animals since the "1930s", although the authors have failed to include much of that body of evidence.

Moreover, because of their toxicity, the use of "ethylmercury compounds" in the US has been banned in agriculture since the late 1950s and, in the manufacture of US over-the-counter drugs that are "antiseptics" and "spermicides" since 1998, where Thimerosal/Thiomersal/Merthiolate (sodium ethylmercurithiosalicylate) was nominally formulated at a 0.1% level, a level which is only "10" times higher than the nominal level of the Thimerosal in most of today's US-FDA-approved "Thimerosal preserved" vaccines.

Yet, though: **a)** the US nominal maximum level for Thimerosal is 0.01% when used as a preservative, **b)** Russia banned its use as a preservative in medicines on the grounds of its toxicity in 1983, and **c)** other countries, citing their own safety concerns, have subsequently banned its use as a preservative in vaccines, the authors of this document fail to acknowledge that:

1. No toxicologically safe level has been established for injected Thimerosal and
2. As researchers have looked at increasingly lower levels of Thimerosal exposure, the *upper limit* of on the safe level, the "nontoxic ..." level, for exposure of developing humans to ***injected*** Thimerosal has continually fallen until today it may be:

   Not greater than (≤) 0.0042 µg (42 ng) of mercury (Hg)/kg of body weight

per day[76].

In addition, the authors' statements concerning the effects of Thimerosal or other mercury compounds at exposure levels significantly higher than vaccine exposures:

> *"These studies indicate that while the nervous system and kidneys are primary targets of ethylmercury exposure at high doses, there is a clear dose threshold between adverse and non-adverse effects. In studies in rats, rabbits, and dogs, doses up to 45 mg/kg bw/day have been reported to cause death, slight*
>
> *Page 6*
>
> *decreases in body weight gain, neurotoxicity (motor incoordination), or toxicity to the kidney (cited in Ball et al 2001).",*

are <u>not</u> relevant to the issue of toxicity at vaccine levels of Thimerosal.

Returning to issues that are relevant to vaccine levels of Thimerosal, this reviewer again notices that these authors are apparently confused about the facts concerning the animal studies they have chosen to cite.

For example, in citing "*Olczak et al (2010)*", the authors focus on the dose ("*at least 3-fold higher than what human infants could receive in a yearly influenza vaccine*") but neglect to mention that, in general, rats are considered to be 10-fold more resistant to neurological brain damage than humans.

Moreover, the cited radiolabeled study clearly shows at least an approximately 4.5-fold protective effect in the rat brain as compared to the monkey brain.

Thus, after correcting for the ***recognized*** 10-fold interspecies differences between rats and humans for mercury toxicity to the brain, the 12 and 240 µg Hg/kg doses given to the rats are equivalent to 1.2 or 24 µg Hg/kg doses given to human infants.

Even if the lower "4.5-fold" higher mercury level in the monkey as compared to the rat[77] were directly applicable to humans, the rat doses would have been the equivalent to 2.66 or 53 µg Hg/kg doses given to developing humans.

Considering the reality that nominally 12.5 µg doses of mercury from a hepatitis B vaccine were routinely given at birth to American babies weighing less than 2 kg (4.4 pounds) [> 6.25 µg Hg/kg], and then 37.5, 25, and 37.5 µg doses of mercury from "Thimerosal preserved" vaccines were routinely given to American babies at 2, 4 and 6 months in the 1990s that weighed[78] < 4 kg (< 8.8 pounds) [> 9.3 µg Hg/kg], < 5 kg (< 11 pounds) [> 5 µg Hg/kg] and < 6.2 kg (<13.7 pounds) [> 6 µg Hg/kg], respectively – for a cumulative dose of on the order of nominally 112.5 µg of Hg from injected Thimerosal, it would appear that the lowest specific doses (dose/kg) used in the animal studies were significantly lower than the ***species-equivalent*** specific doses that humans received in the USA in the 1990s or that Polish infants were receiving in the Polish vaccination program on which the cited study was modeled.

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76 http://mercury-freedrugs.org/docs/090812_fnldrft_TheTruthAboutTheToxicityOfThimerosalr5b.pdf.

77 Takkahashi T, Kimura T, Sato Y, Shiraki H, Ukita T. Time-Dependent Distribution of ^{203}Hg-Mercury Compounds in Rat and Monkey as studied by Whole Body Autoradiography. ***The J Hygienic Chem*** [Japan] 1971; **17**(2): 93-107.

78 Weights from: Geier MR, Geier DA. Thimerosal in childhood vaccines, neurodevelopmental disorders, and heart disease in the United States. ***J Am Phys Surg*** 2003; **8**(1): 6-11.

Moreover, because the rat pup's brain matures so much faster than the developing human brain, the dosing sequence cited "*(4 injections administered only 2-4 days apart*)" was chosen to ***developmentally*** mimic an initial early childhood dosing sequence that was given to developing humans.

Thus, the adverse effects seen occurred at ***species-equivalent*** doses that were lower than human infants received and the dosing intervals were modeled on the Polish, early childhood, "Thimerosal preserved"-vaccine inoculation program that was, and may still be, in use in Poland in spite of this study's findings and not the childhood influenza program currently in use in the USA[79].

Thus, some of the toxicity observed was at lower than "species-equivalent doses" given at "developmentally equivalent" times and, *as such*, the results obtained clearly indicate that the damage to the developing infants in Poland may be significantly greater than observed for the low-dosed Wistar rat pups.

Further, this reviewer must note that, in 2009, American children 3 through 9 years of age were recommended to get as many as four 0.5-mL flu inoculations if they were being vaccinated for the first time — two (2) "seasonal" inoculations and two (2) "2009-A-H1N1" inoculations — and not "*a single annual dose or, at most, two doses separated by at least one month when children younger than 9 years of age*".

If all of the four inoculations used a "Thimerosal preserved" inactivated-influenza vaccine, these American children received four 0.5-mL doses of a vaccine that nominally delivered 50 µg of Thimerosal per dose or 200 µg of Thimerosal (nominally, 99.1 µg of Hg) in a period as short as 30 days since the "seasonal" and the "2009-A-H1N1" influenza vaccines were allowed to be given at the same time and, *because the dose given to children 6 to 35 months of age is 0.25-mL*, American children younger than three could have been given half this amount (or nominally 49.55 µg of Hg).

However, if the authors wished to cite relevant toxicological studies, *given that American women are advised to get a flu shot that may be "Thimerosal preserved" at any stage during pregnancy*, this reviewer is surprised that they did not cite the fetal rat study by Ida-Eto M, et al. (2011)[80].

In this study, pregnant female rats were injected with 1 µg of Thimerosal/kg at day 9 of gestation (*roughly corresponding to 20 to 35 days post-conception in humans*).

The study's abstract reported (emphasis added):

> "Even though neuronal toxicity due to organomercury compounds is well known, thimerosal, an organomercury compound, is widely used in pediatric vaccine preservation. In the present study, we examined whether embryonic exposure to thimerosal affects early

[79] After all, the researchers who conducted this study (Mieszko Olczak, Michalina Duszczyk, Pawel Mierzejewski, Teresa Wierzba-Bobrowicz, and Maria Dorota Majewska) conducted this research in Warsaw, Poland and, as Polish residents, were more concerned about the toxicity of the "Thimerosal preserved" Polish vaccines given to very young Polish children than they are about the influenza vaccines being recommended in the USA.

[80] Ida-Eto M, Oyabu A, Ohkawara T, Tashiro Y, Narita N, Narita M. Embryonic exposure to thimerosal, an organomercury compound, causes abnormal early development of serotonergic neurons. ***Neuroscience Letters*** 2011, in press, doi:10.1016/j.neulet.2011.05.053.

development of serotonergic neurons. Thimerosal (1 mg Hg/kg) was intramuscularly administered to pregnant rats on gestational day 9 (susceptible time window for development of fetal serotonergic system), and fetal serotonergic neurons were assessed at embryonic day 15 using anti-serotonin antibodies. A dramatic increase in the number of serotonergic neurons localized to the lateral portion of the caudal raphe was observed in thimerosal group (1.9-fold increase, $p < 0.01$ compared to control). These results indicate that embryonic exposure to thimerosal affects early development of serotonergic neurons."

Ignoring the reality that the rats are significantly more resistant to the effects of mercury exposure than humans, the 1 µg of Thimerosal/kg dose is in the range of doses given to pregnant Americans (nominally 50 µg of Thimerosal in a pregnant American women who, on average, weigh about 70 kg or an "average" dose of 0.71 µg of Thimerosal/kg).

If the species-specific susceptibility to mercury poisoning is included, the human-equivalent doses of Thimerosal, 0.1 to 0.22 µg of Thimerosal/kg, are the equivalent of between 14 % and 31 % of the dose given to the average 70-kg pregnant American.

Obviously, given these findings, it does not appear to be "safe" to give a pregnant woman a "Thimerosal preserved" flu shot.

Still more puzzling is the authors' failure to cite Olczak M, et al. (2011)[81] that was published earlier this year.

Using the same dosing pattern as they did in their previous study (cited by these authors), the abstract of this study reported (emphasis added):

"The neurotoxic organomercurial thimerosal (THIM), used for decades as vaccine preservative, is a suspected factor in the pathogenesis of some neurodevelopmental disorders. Previously we showed that neonatal administration of THIM at doses equivalent to those used in infant vaccines or higher, causes lasting alterations in the brain opioid system in rats. Here we investigated neonatal treatment with THIM (at doses 12, 240, 1440 and 3000 µg Hg/kg) on behaviors, which are characteristically altered in autism, such as locomotor activity, anxiety, social interactions, spatial learning, and on the brain dopaminergic system in Wistar rats of both sexes. Adult male and female rats, which were exposed to the entire range of THIM doses during the early postnatal life, manifested impairments of locomotor activity and increased anxiety/neophobia in the open field test. In animals of both sexes treated with the highest THIM dose, the frequency of prosocial interactions was reduced, while the

[81] Olczak M, Duszczyk M, Mierzejewski P, Meyza K, Majewska MD. Persistent behavioral impairments and alterations of brain dopamine system after early postnatal administration of thimerosal in rats. *Behavioural Brain Res* 2011; **223**: 107-118.

> frequency of asocial/antisocial interactions was increased in males, but decreased in females. Neonatal THIM treatment did not significantly affect spatial learning and memory. THIM-exposed rats also manifested reduced haloperidol-induced catalepsy, accompanied by a marked decline in the density of striatal D2 receptors, measured by immunohistochemical staining, suggesting alterations to the brain dopaminergic system. Males were more sensitive than females to some neurodisruptive/ neurotoxic actions of THIM. These data document that early postnatal THIM administration causes lasting neurobehavioral impairments and neurochemical alterations in the brain, dependent on dose and sex. If similar changes occur in THIM/mercurial-exposed children, they could contribute do [sic; to] neurodevelopmental disorders."

Thus, where the first paper only established that low-dose injected-Thimerosal-solution exposure caused alterations in "the brain opioid system in Wistar rats", this follow-on paper establishes that those alterations in the brain of the Thimerosal-treated rats translate into "lasting neurobehavioral impairments and neuro-chemical alterations in the brain".

Finally, since these authors have recognized that the Macaque monkey is a good model for the effects of mercury poisoning in humans ("*The half-life of ethylmercury in human infants has been shown to be similar to that in infant macaques (monkeys) (Burbacher et al 2005), which indicates that infant monkeys are a good animal model for human infant exposures to ethylmercury in vaccines*", [on the authors' page 5]), this reviewer finds the authors' omission of Hewitson L, et al. (2010)[82] to be of concern.

Here, that paper's abstract states (emphasis added):

> "This study examined whether acquisition of neonatal reflexes in newborn rhesus macaques was influenced by receipt of a single neonatal dose of hepatitis B vaccine containing the preservative thimerosal (Th). Hepatitis B vaccine containing a weight-adjusted Th dose was administered to male macaques within 24 h of birth (n = 13). Unexposed animals received saline placebo (n = 4) or no injection (n = 3). Infants were tested daily for acquisition of nine survival, motor, and sensorimotor reflexes. In exposed animals there was a significant delay in the acquisition of *root*, *snout*, and *suck* reflexes, compared with unexposed animals. No neonatal responses were significantly delayed in unexposed animals. Gestational age (GA) and birth weight (BW) were not significantly correlated. Cox regression models were used to evaluate main effects and interactions of exposure with BW and GA

[82] Hewitson L, Houser LA, Stott C, Sackett G, Tomko JL, Atwood D, Blue L, White ER. Delayed Acquisition of Neonatal Reflexes in Newborn Primates Receiving a Thimerosal-containing Hepatitis B Vaccine: Influence of Gestational Age and Birth Weight. ***J Toxicol Environmental Health, A***, 2010; **73**: 1298–1313.

> as independent predictors and time-invariant covariates. Significant main effects remained for exposure on *root* and *suck* when controlling for GA and BW, such that exposed animals were relatively delayed in time-to-criterion. Interaction models indicated there were various interactions between exposure, GA, and BW and that inclusion of the relevant interaction terms significantly improved model fit. This, in turn, indicated that lower BW and/or lower GA exacerbated the adverse effects following vaccine exposure. This primate model provides a possible means of assessing adverse neurodevelopmental outcomes from neonatal Th-containing hepatitis B vaccine exposure, particularly in infants of lower GA or BW. The mechanisms underlying these effects and the requirements for Th requires further study."

Essentially, this paper established that a single weight-adjusted "12.5 µg of mercury equivalent" hepatitis B vaccine dose (equivalent to 25 µg of Thimerosal injected into a human neonate) in Macaque monkeys was sufficient to induce significant neurodevelopmental delays that, in nature, could have been fatal to the male infants who were given the hepatitis B vaccine, because they must nurse to survive.

Given the preceding realities, the "third" of the infants whose sucking reflex was still absent on day 3 would not be expected to survive in their natural habitat.

To verify that the effects observed in this monkey study have applicability to humans, this reviewer suggests that everyone should read Gallager CM and Goodman MS (2010)[83], which studies the effects on males of the birth-dose of a "Thimerosal preserved" hepatitis B vaccine.

Here, the paper's abstract reads (emphasis added):

> "Universal hepatitis B vaccination was recommended for U.S. newborns in 1991; however, safety findings are mixed. The association between hepatitis B vaccination of male neonates and parental report of autism diagnosis was determined. This cross-sectional study used weighted probability samples obtained from National Health Interview Survey 1997–2002 data sets. Vaccination status was determined from the vaccination record. Logistic regression was used to estimate the odds for autism diagnosis associated with neonatal hepatitis B vaccination among boys age 3–17 years, born before 1999, adjusted for race, maternal education, and two-parent household. Boys vaccinated as neonates had threefold greater odds for autism diagnosis compared to boys never vaccinated or vaccinated after the first month of life. Non-Hispanic white boys were 64% less likely to have autism diagnosis relative to

[83] Gallager CM, Goodman MS. Hepatitis B Vaccination of Male Neonates and Autism Diagnosis, NHIS 1997–2002. *J Toxicol Environmental Health A* 2010; **73**: 1665–1677.

> nonwhite boys. Findings suggest that U.S. male neonates vaccinated with the hepatitis B vaccine prior to 1999 (from vaccination record) had a threefold higher risk for parental report of autism diagnosis compared to boys not vaccinated as neonates during that same time period. Nonwhite boys bore a greater risk."

The researchers did not emphasize the likelihood that the effect observed may be related to the Thimerosal (49.55% by weight mercury) content of the "Thimerosal preserved" hepatitis B vaccines administered.

However, in light of the adverse neonatal findings by Hewitson L, et al. (2010) for a weight-adjusted birth dose of a "Thimerosal preserved" hepatitis B vaccine given at birth to Macaque monkeys, it is clear that the birth-dose of organic mercury delivered by the hepatitis B dose was either: **a)** a direct causal factor, or **b)** a causal indicator factor, for the risk of an autism diagnosis as Gallager CM and Goodman MS (2010) implies (emphasis added):

> "Because the current study's sample represents infants born prior to the manufacture of thimerosal-free vaccines, questions are raised regarding the possible adverse affects of the vaccine preservative thimerosal. Of note, the relationship between neonatal hepatitis B vaccination and autism diagnosis among boys was also examined without restricting birth year to before 1999, and it was found that the association became marginally significant, and attenuated. There was one observation with autism diagnosis born in the later period, and this single observation was unvaccinated during the neonatal period. Thus, there is insufficient sample size to evaluate vaccination exposure before and after the availability of thimerosal-free vaccines."

Minimally, the results found by Gallager CM and Goodman MS (2010) reveal that the birth dose of Thimerosal in the hepatitis B vaccine is an indicator/factor for the risk for a subsequent autism diagnosis.

Based on the findings by Hewitson L, et al. (2010), these results indicate that Thimerosal at the "3" to "6" µg/kg level is sufficiently toxic to male human neonates to be considered a causal factor in their subsequent risk for being diagnosed with autism.

"A comparison of the toxicity of ethylmercury with methylmercury, for which "safe" levels in food have been established by the EPA from environmental exposures, indicates that methylmercury has a kinetic profile that is not relevant to ethylmercury, and that methylmercury is more toxic than ethylmercury. As mentioned earlier, methylmercury has a blood half-life in humans that is approximately 10-fold longer than ethylmercury. In addition, recent studies in infant monkeys indicate that the brains of infant monkeys receive approximately 3-fold higher doses of mercury following exposure to methylmercury than from an equivalent dose of ethylmercury, and that mercury remains in the brain 2-3 times longer following exposure to methylmercury as compared to an equivalent dose of ethylmercury (Burbacher et al 2005). "

First, the "reference dose" (RfD) established by the EPA is not a "safe" level for mercury ingestion (mercury that is eaten and that is bound up in a tissue-complexed form, probably as methylmercury cysteine) but rather a level that might be "safe".

This is the case because it is not based on any applicable study of the toxicity of ingested mercury (as some form of methylmercury, probably methylmercury cysteine that is found in fish), in an appropriate animal model population but rather on: **a)** uncertain (and currently recognized as inflated[84]) extrapolations of what the dietary intake of mercury may have been in certain studies and **b)** a presumption, *which was subsequently proven to be false*[85], that there was a single definitive relational factor between the level of mercury in human hair and the person's mercury body burden.

Second, as the previous discussions have established, with respect to the long-term harm caused by mercury poisoning, the critical values are the half-lives of the "tissue retained", "inorganic" mercury species and not the half-lives of the transient organic mercury species in the blood or, for that matter, the tissues and organs.

Third, the authors' remarks about "*Burbacher et al 2005*", are inaccurate because

the critical values are the levels of "inorganic" mercury in the monkeys' brains and not the levels of the "organic" mercury species.

This is true because the retained "inorganic" mercury species in the brains of the monkeys and humans are the species that cause the long-term harm – the injected-Thimerosal itself is responsible for short-term mercury effects, like local cell death, gene reregulation, immune system dysfunction and anaphylaxis.

The retained "inorganic" mercury species are the bioaccumulative toxins, which persist for very long times in various organs and, in the human brain, have half-lives of about 18-20 years[86].

On that basis, the average level of the "inorganic" mercury in the brains of the Thimerosal-injected monkeys was more than twice the average level of "inorganic" mercury in the brains of the methylmercury-chloride-force-fed monkeys[87].

Further, the methodology used by these researchers to measure the mercury as "organic" and "inorganic" was outdated.

This is the case because other robust biological-sample analytical methods that allow the work-up of blood and tissue samples into derivatized components that can be separated and each mercury-component type can be quantitated against known standards (as "ethylmercury", "methylmercury" or "inorganic mercury") have been available since the 1970s, using gas chromatography (GS) to separate the derivatized components, and the 1980s, using high-performance liquid chromatography to separate the derivatized components.

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84 Gosselin NH, Brunet RC, Carrier GT, LeBouchard M, Feeley M. Reconstruction of methylmercury intakes in indigenous populations from biomarker data. ***J Exposure Anal Environ Epidemiol*** 2006, **16**(1): 19-29.

85 Canuel R, Boucher de Grosbois S, Atikessé L, Marc Lucotte M, Arp P, Ritchie C, Mergler D, Chan HM, Amyot M, Anderson R. New Evidence on Variations of Human Body Burden of Methylmercury from Fish Consumption. ***Environ Health Perspect*** 2006 Feb; **114**(2): 302-306.

86 Sugita M. The biological half-time of heavy metals. The existence of a third, "slowest" component. ***Int Arch Occup Environ Health*** 1978; **41**(1): 25-40.

87 http://mercury-freedrugs.org/docs/UpdtdThimCausesHgPoisoninfl_RebutaltoDrNovellasViews.pdf, page 53.

Had "*Burbacher et al 2005*" used one of these methods, the study might have noticed that the "organic mercury" in the brains of the Thimerosal-treated monkeys at sacrifice included a "methylmercury" component.

More recent studies[88,89] have clearly indicated that the ethylmercury components are apparently converted into the corresponding "methylmercury" species, which, apparently in turn, are then converted into the "inorganic mercury" species that are long retained in the human organs, including the brain.

Finally, the authors assertion that "*mercury remains in the brain 2-3 times longer following exposure to methylmercury as compared to an equivalent dose of ethylmercury*", is inaccurate.

Perhaps these authors fail to understand that the differences in the levels of the "organic mercury" levels, about which they are writing, in the two treatment arms (Thimerosal and methylmercury chloride) of the cited study at a given point in time, cannot validly be translated into a difference in the retention times of two different "organic mercury" species in the brain unless there are no biochemical pathways by which the components may be further metabolized.

As other studies have shown, both the "ethylmercury" and the "methylmercury" species in the brain are further degraded into the "inorganic mercury" species that are retained for significant periods of time.

"With regard to toxicity, several studies support the conclusion that ethylmercury is less toxic to the brain than methylmercury. Magos et al (1985) found that when rats were given high (near lethal) oral doses of ethylmercury and methylmercury (11.2 mg/kg bw/day), ethylmercury and methylmercury each caused physical damage to the brain as well as kidney toxicity, but methylmercury caused more severe brain damage and decreased coordination compared to ethylmercury. Conversely, ethylmercury caused greater kidney toxicity than methylmercury when tested at an identical dose. Tryphonas and Nielsen (1973) compared intoxication of pigs with a range of identical doses of methylmercury and ethylmercury for 60 and 90 days

Page 7

respectively. They reported that the pigs receiving ethylmercury experienced significantly higher accumulations of mercury in the kidney compared to pigs receiving methylmercury, which is an observation that agrees with Magos, et al. (1985). However, that result may also have been due to the longer exposure period to ethylmercury. In addition, although brain lesions were observed in pigs treated with both ethylmercury and methylmercury, pigs treated with methylmercury had the most advanced damage, despite a shorter length of exposure."

Since the levels of mercury dosed and the frequency of dosing were designed to study acute toxicity and chronic toxicity and not solely chronic toxicity in the studies cited by the authors, the authors' statements are less than relevant to the issue of the

88 Pichichero ME, Gentile A, Giglio N, Umido V, Clarkson T, Cernichiari E, Zareba G, Gotelli C, Gotelli M, Yan L, and Treanor J. Mercury Levels in Newborns and Infants After Receipt of Thimerosal-Containing Vaccines. ***Pediatrics*** 2008; **121**(2): e208-e214.

89 Rodriques JL, Serpeloni JM, Batista BL, Souza S, Barbosa Jr F. Identification and distribution of mercury species in rat tissues following administration of Thimerosal or methyl mercury. ***Arch Toxicol*** 2010; **84**: 891-896.

toxicity of Thimerosal at vaccine-level, or lower, species-equivalent doses – doses that are not cumulatively lethal but rather induce subtle mercury-poisoning effects.

Moreover, this reviewer notes that the one comparative chronic alkyl mercury study that these authors could have discussed at length, but did not, is Tryphonas L and Neilson NO (1973)[90], which reported:

> "… ethylmercuric chloride (EMC) w(as) 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 mescolon, 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".

Thus, the findings in Tryphonas L and Nielsen DO (1973) are clearly at odds with the "non-toxicity" for chronic "ethylmercury" dosing and clearly show that, at chronic levels, the delayed poisoning is the result of the bioaccumulation of mercury in the tissues and organs of the young pigs that were being dosed.

"Other recent studies that have exposed animals to doses of ethylmercury include those conducted in mice by Hornig et al (2004) and Berman et al (2008). Hornig et al (2004) found no effect on any of a host of clinical, behavioral, and histopathological endpoints in normal newborn mice exposed repeatedly to 5.6, 9.2, 10.8, or 14.2 μg ethylmercury/kg bw, although when tested in a strain of genetically modified autoimmune disease-susceptible mouse pups (SJL/J), these mice exhibited decreased body weight gain in addition to a number of behavioral and neuropathological effects that were not observed in the two strains without autoimmune sensitivity. Berman et al. (2008) attempted to replicate the study by Hornig et al (2004); however, in contrast to Hornig et al (2004), the study by Berman et al (2008) was more comprehensive because it added a dose-ranging component to the study design, used improved testing methodologies and expanded data collection by adding several measures, such as tests of social interaction, sensory gating and anxiety to assess behavioral domains considered relevant to core deficits in neurodevelopmental disorders. Notably, Berman et al (2008) found no effects in the same autoimmune disease-susceptible strain of mice (SJL/J), even at 10-fold higher doses of ethylmercury. In addition, and particularly relevant to human health concerns, Berman et al (2008) concluded that current data do not support the inference that neonatal thimerosal exposure related to neurodevelopmental disorders that alter

[90] Tryphonas L, Nielsen NO. Pathology of chronic alkylmercurial poisoning in swine. *Am J Vet Res*. 1973; **34**: 379-392.

social behaviors in humans, such as autism. This conclusion is identical to that reached previously by the Institute of Medicine (National Academy of Sciences) and based on human epidemiological studies (IOM 2004). Lastly, in a review of the toxicity of ethylmercury in humans, Clarkson (2002) concluded that ethylmercury is less potent (toxic) than methylmercury based on a lack of ethylmercury neurotoxicity in humans at measured mercury blood levels up to 0.65 μg/ml, an amount that is more than 3-fold higher than the blood concentration of 0.20 μg Hg/ml at which neurotoxic effects were observed following oral exposure to methylmercury (Magos 2001; Clarkson 2002)."

With respect to the authors' comment: "*Berman et al. (2008) attempted to replicate the study by Hornig et al (2004)*" acknowledges that "*Berman et al (2008)*" did not really replicate the study by "*Hornig et al (2004)*" because they deviated from the original sample work up and evaluation protocols.

Also, because there are sub-strains of the SJL/J mouse, the specific sub-strains that the two groups tested may not have been the same.

In addition, there may be other areas where a "subtle" difference may have had a large effect for which "*Berman et al (2008)*" may have made different choices than "*Hornig et al (2004)*".

For all of the preceding reasons, this reviewer basically recommends that both studies should be ignored as there are newer studies that have unequivocally shown injected-Thimerosal solutions are toxic to developing animals at dosing levels that are equal to or lower than the ***species-adjusted*** levels given to developing humans.

With respect to the authors' *"Lastly, in a review of the toxicity of ethylmercury in humans, Clarkson (2002) …"*, this reviewer first notes that the review is out of date and second notes that the statement about the level of mercury in the blood has little to do with the long-term toxicological effects observed.

If the authors had wished to be current in regard to the science vis-à-vis (with respect to) vaccine-level exposures to injected Thimerosal at vaccine levels, they would have cited the recent review by Dórea JG 2011[91] where the abstract states:

> "**Abstract** There is a need to interpret neurotoxic studies to help deal with uncertainties surrounding pregnant mothers, newborns and young children who must receive repeated doses of Thimerosal-containing vaccines (TCVs). This review integrates information derived from emerging experimental studies (in vitro and in vivo) of low-dose Thimerosal (sodium ethyl mercury thiosalicylate). Major databases (PubMed and Web-of-science) were searched for in vitro and in vivo experimental studies that addressed the effects of low-dose Thimerosal (or ethylmercury) on neural tissues and animal behaviour. Information extracted from studies indicates that: (a) activity of low doses of Thimerosal against isolated human and animal brain cells was found in all studies and is consistent with Hg

[91] Dórea JG. Integrating Experimental (In Vitro and In Vivo) Neurotoxicity Studies of Low-dose Thimerosal Relevant to Vaccines ***Neurochem Res*** 2011; **36**(6): 927-938. DOI: 10.1007/s11064-011-0427-0 available online in February of 2011.

neurotoxicity; (b) the neurotoxic effect of ethylmercury has not been studied with co-occurring adjuvant-Al in TCVs; (c) animal studies have shown that exposure to Thimerosal-Hg can lead to accumulation of inorganic Hg in brain, and that (d) doses relevant to TCV exposure possess the potential to affect human neuro-development. Thimerosal at concentrations relevant for infants' exposure (in vaccines) is toxic to cultured human-brain cells and to laboratory animals. The persisting use of TCV (in developing countries) is counterintuitive to global efforts to lower Hg exposure and to ban Hg in medical products; its continued use in TCV requires evaluation of a sufficiently nontoxic level of ethylmercury compatible with repeated exposure (co-occurring with adjuvant-Al) during early life."

In discussing the interpretation of the research, this paper states:

"Different outcomes of neural cell challenges with Thimerosal imply different hazards in terms of animal neurodevelopment; animal models did differentiate some of these complex outcomes which have implications for translating such results to risks (or risk severity for vulnerable subgroups) of suboptimal neurodevelopment of human infants. Indeed, Judson et al. [80] showed that a statistically significant inverse association exists between the number of pathways perturbed by a chemical at low in vitro concentrations and the lowest in vivo dose at which a chemical causes toxicity. Therefore, concurrent with the conventional thinking of neurodevelopmental toxicology, early exposure to Hg is detrimental to the CNS, and the increasing pattern of TCV-Hg exposure during pregnancy and infancy has the potential to contribute to an elevated risk of neurotoxicity.

[80]Judson RS, Houck KA, Kavlock RJ et al (2010) In vitro screening of environmental chemicals for targeted testing prioritization: the ToxCast project. ***Environ Health Perspect*** **118**:485–492"

Finally, this paper concludes with the following bulleted remarks concerning vaccination and the use of a "Thimerosal preserved" vaccine [which are described as a Thimerosal-containing vaccine (TCV)]:

"• Without vaccination it would be impossible to eradicate or control infectious disease that otherwise would be devastating to children, causing unnecessary suffering and waste of human and material resources. However, the use of thimerosal in vaccines should be reconsidered by public health authorities, especially in those vaccines intended for pregnant women and children.

• In vitro and animal studies have shown consistently that low dose of Thimerosal (or ethylmercury) is active against brain cells.

Animal studies with Thimerosal at concentrations used in vaccines have demonstrated toxicity compatible with low-dose Hg exposure. Thus, from observed changes in animal behaviour it is reasonable to expect biological consequences in terms of neurodevelopment in susceptible infants.

- Despite demonstrable toxicity of EtHg, TCV are still used in large scale in developing countries; however, because of global actions to reduce Hg exposure we need to extend such concerns to pregnant women, newborns, and young children still receiving TCV.
- We cannot compare the risk of tangible deadly diseases (preventable by immunization) with plausible neurodevelopment delays (clinically undefined) which can be transient and mostly unperceived in the majority of children (as a result of low-dose of Thimerosal). Nevertheless, we know for sure that Thimerosal-Hg (and Al as a binary mixture) in the child's brain is an issue of concern, and that an ever increasing pattern of exposure (from vaccine schedule) deserves special attention.
- We urgently need studies that address TCV-EtHg exposure in pregnant mothers, neonates, and young children of less developed nations where immunization programs are most needed and where confounding factors related to endemic undernutrition and coexposure to intestinal parasites and other toxic substances are more prevalent.
- The persisting use of TCV (in developing countries) is counterintuitive to global efforts to lower Hg exposure and to ban Hg in medical products; its continued use in TCV requires evaluation of a sufficiently nontoxic level of ethylmercury compatible with repeated exposure (co-occurring with adjuvant-Al) during early life."

Hopefully, all who read the preceding passages will understand that the use of Thimerosal as a preservative in vaccines is an ongoing problem that urgently needs to be addressed and that cost-effective, "sufficiently nontoxic ..." replacements are doable in all countries, developed and developing.

These safer alternative preservatives need to be "found" and used.

"Page 8

In summary, ethylmercury and methylmercury are very different molecules. Methylmercury can actively cross the blood-brain barrier (BBB), whereas a similar pathway has not been identified for ethylmercury. Ethylmercury is a larger molecule, thereby leading to slower diffusion across the BBB, and is cleared from the blood more quickly than methylmercury. Also, ethylmercury has a metal-alkyl bond that is more easily broken than methylmercury. Because of these chemical characteristics, less ethylmercury than

methylmercury will enter the brain for an equivalent dose. Therefore, ethylmercury may be considered less neurotoxic than methylmercury in both humans and experimental animals for acute exposures.

Here, this reviewer notes that most of these statements are not relevant to the issues associated with vaccine-level exposures to Thimerosal.

Factually, a given ethylmercury compound and its methylmercury analog are different molecules but not "*very different molecules*" as the authors assert because their nominal masses differ only by "14" atomic mass units.

Though simple ethylmercury compounds are somewhat larger than their methylmercury analogs and simple ethylmercury compounds do appear to clear the blood faster than their methylmercury analogs, this reviewer is aware of no study using an appropriate, multiply labeled, ethylmercury compound and its methylmercury analog have been studied to determine their diffusion/transport rates into the human brain or a suitable animal-model brain, like, perhaps, the macaque monkey's brain.

Factually, simple radiolabeled ethylmercury compounds, like ethylmercury chloride, have been found to fairly rapidly enter the brain when a solution containing it at the "0.8" mg of mercury per kg of animal weight is injected interperitoneally or intra-venously.

Since the degradation pathway for simple ethylmercury compounds has not been shown to proceed by the direct breaking of the "*metal-alkyl bond*" and there is some evidence that the degradation of simple ethylmercury compounds involves demethylation, the strength of the "*metal-alkyl bond*" may not be highly relevant.

In addition, there is no definitive study that has shown that "*less ethylmercury than methylmercury will enter the brain for an equivalent dose*".

Further, since: **a)** the critical mercury for the long-term toxicities observed is the "inorganic mercury" level and not the "organic mercury" level and **b)** the authors' cited study ("*Burbacher et al 2005*") clearly showed that when the monkeys were sacrificed, the Thimerosal-treated monkeys had, *on average*, 2-plus times higher "inorganic mercury" levels in their brain than the "methylmercury"-treated monkeys, clearly Thimerosal appeared to be more neurologically long-term toxic than the methyl-mercury compound against which it was compared.

Also in the chronic toxicity study in pigs[92], individuals in both sets of pigs in the two treatment groups ("ethylmercury" and "methylmercury") were treated with "comparable" low, medium and high levels of each test compound and the effects seen in the low and high dose treatments were comparable.

However, in the medium-dose animals, the "ethylmercury" compound was signifi-cantly more toxic than the "methylmercury" compound to the point that an animal died of neurological complications in the mid-level "ethylmercury" test group, while no animals in the "mid-level "methylmercury" test group died or had serious neurological impairments.

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92 Tryphonas L, Nielsen NO. Pathology of chronic alkylmercurial poisoning in swine. ***Am J Vet Res***. 1973; **34**: 379-392.

Therefore, *for what counts*, the effects of toxicity at low levels, it seems to be clear that Thimerosal and other simpler ethylmercury compounds are much more toxic than the similar methylmercury compounds when their chronic toxicities were compared.

Finally, the authors' "*ethylmercury may be considered less neurotoxic than methylmercury in both humans and experimental animals for acute exposures*" (emphasis added) is not relevant and may be inaccurate: "*acute exposures*" have no bearing on the issue of the toxicity of Thimerosal at the preserved-vaccine-dose levels (preservative levels that, by law [21 CFR 610.15(a)], are supposed to be below the level where ***any*** toxicity is observed).

"***Studies on the Association between Thimerosal and Autism***

To date, a number of epidemiological studies independently conducted by different investigators using various designs in different samples and countries (e.g., Sweden, Denmark, United States, United Kingdom, and Canada) all have consistently shown no association between exposure to thimerosal-containing vaccines and the development of autism. Importantly, investigators in different countries with different populations using different methods came to similar conclusions. With the exception of the study performed by Fombonne, et al., and reported in 2006, all of these studies were part of the 2004 report of the independent Institute of Medicine's Immunization Safety Review Committee which concluded that the studies 'consistently provided evidence of no association between thimerosal-containing vaccines and autism' (IOM, 2004). In addition, a more recent study by Schechter, et al., (2008) evaluated whether reduced exposure to thimerosal in vaccines in the United States has been associated with a decrease in reported autism. The researchers analyzed the California Department of Developmental Services (DDS) data to estimate time trends in the prevalence of autism in children reported in California. The authors 'found that the prevalence of autism in children reported to the DDS has increased consistently for children born from 1989 through 2003, inclusive of the period when exposure to [thimerosal containing vaccines] has declined. Moreover, since 2004, the absolute increase and the rate of increase in DDS clients aged 3 to 5 years with autism were higher than those in DDS clients of the same ages with any eligible condition, including autism.' (Schechter, et al. 2008). The authors concluded that '[t]hese time trends are inconsistent with the hypothesis that

Page 9

thimerosal exposure is a primary cause of autism in California.' These findings are consistent with other recent findings, e.g., Fombonne, et al. (2006).

With respect to the authors' statements about the epidemiological studies that the promoters of Thimerosal-preserved vaccines have selected to provide, numerous reviews of them have found that the studies selected are fundamentally unsound.

There were truly independent, peer-reviewed, published, epidemiological studies that had clearly established a link between the level of Thimerosal exposure and the risk of a neurodevelopmental disorder, including autism, which the 2004 Institute of Medicine's Immunization Safety Review Committee (ISRC) did not consider.

In 2004, the ISRC discarded the independent studies on the grounds that those studies which reported a link between Thimerosal and autism were "unintelligible" or "poorly designed".

Unfortunately, the studies the 2004 ISRC chose to use for their report were as, or

much more, poorly designed.

Further, in case of the ISRC-accepted US study, Verstraeten T et al (2003), statistically significant links were still found between the level of Thimerosal exposure from vaccine and the risk of "tics" (which includes Tourette's syndrome) and "language/speech delay".

Yet, the ISRC simply limited its consideration to the issue of the link between Thimerosal exposure level and timing and the risk of "autism".

Moreover, as this reviewer has established previously, "*Fombonne, et al. (2006)*" is a study with significant flaws.

With respect to the author's assertion:

> "*all of these studies were part of the 2004 report of the independent Institute of Medicine's Immunization Safety Review Committee which concluded that the studies 'consistently provided evidence of no association between thimerosal-containing vaccines and autism' (IOM, 2004)*"

this reviewer simply notes that, *since all of the studies that the IOM ISRC used as the basis for its report were conducted by, funded by and/or overseen by the CDC, who hired, paid,* ***and defined the operating limits for,*** *the "Institute of Medicine's Immunization Safety Review Committee"*, this committee and its report were <u>neither</u> independent <u>nor</u> unbiased.

With respect to the authors' extended narrative about Thimerosal exposure levels and autism rates:

> "*In addition, a more recent study by Schechter, et al., (2008) evaluated whether reduced exposure to thimerosal in vaccines in the United States has been associated with a decrease in reported autism. The researchers analyzed the California Department of Developmental Services (DDS) data to estimate time trends in the prevalence of autism in children reported in California. The authors 'found that the prevalence of autism in children reported to the DDS has increased consistently for children born from 1989 through 2003, inclusive of the period when exposure to [thimerosal containing vaccines] has declined. Moreover, since 2004, the absolute increase and the rate of increase in DDS clients aged 3 to 5 years with autism were higher than those in DDS clients of the same ages with any eligible condition, including autism.' (Schechter, et al. 2008). The authors concluded that '[t]hese time trends are inconsistent with the hypothesis that*
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> *Page 9*
>
> *thimerosal exposure is a primary cause of autism in California.'.*"

this reviewer simply notes that, <u>given</u>:

- The CDC's 2002 recommendation that all children 6 months to 23 months of age be given a flu shot and its reemphasis of its 1997 recommendation that

all pregnant women be given a flu shot if they would be pregnant during the 2nd and 3rd trimesters[93];

- The CDC's subsequent broadening of the age range until, in 2009. it became a recommendation for all children to get one or two flu shots initially followed by an annual flu vaccination and, of course, 1 or 2 "pandemic" flu inoculations,
- The reality that the last doses of the "Thimerosal preserved" routine childhood vaccines did not expire until some time in 2005 — not in 2003,
- The reality that the CDC's 2010[94] and 2011[95] recommendations are that everyone get a flu inoculation annually from essentially before birth until death,

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93 *Morbidity and Mortality Weekly Report* (*MMWR*) 2002 Apr 12; **51**(RR03):1-31. Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP), with added emphasis.

"**The 2002 recommendations include five principal changes or updates, as follows:**

1. The optimal time to receive influenza vaccine is during October and November. However, because of vaccine distribution delays during the past 2 years, **ACIP recommends that vaccination efforts in October focus on persons at greatest risk for influenza-related complications and health-care workers and that vaccination of other groups begin in November**.
2. Vaccination efforts for all groups should continue into December and later, for as long as vaccine is available.
3. **Because young, otherwise healthy children are at increased risk for influenza-related hospitalization, influenza vaccination of healthy children aged 6--23 months is encouraged when feasible**. Vaccination of children aged >6 months who have certain medical conditions continues to be strongly recommended.
4. The 2002--2003 trivalent vaccine virus strains are A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Hong Kong/330/2001-like strains.
5. A limited amount of influenza vaccine with reduced thimerosal content will be available for the 2002--2003 influenza season."

"**Target Groups for Vaccination**

Persons at Increased Risk for Complications

Vaccination is recommended for the following groups of persons who are at increased risk for complications from influenza:

- persons aged >65 years;
- residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;
- adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma;
- adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency [HIV] virus);
- children and adolescents (aged 6 months--18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for developing Reye syndrome after influenza infection; and
- **women who will be in the second or third trimester of pregnancy during the influenza season**."

94 *Morbidity and Mortality Weekly Report* (*MMWR*) 2010 Aug 6; **59**(RR08):1-62. Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP). "**Highlights of the 2010 recommendations include 1) a recommendation that annual vaccination be administered to all persons aged ≥6 months for the 2010 --11 influenza season**; 2) a recommendation that children aged 6 months--8 years whose vaccination status is unknown or who have never received seasonal influenza vaccine before (or who received seasonal vaccine for the first time in 2009--10 but received only 1 dose in their first year of vaccination) as well as children who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine regardless of previous influenza vaccine history should receive 2 doses of a 2010--11 seasonal influenza vaccine (minimum interval: 4 weeks) during the 2010--11 season; …"

- The reality that the childhood vaccines. which replaced the "Thimerosal preserved" childhood vaccines, were mostly "reduced-Thimerosal" vaccines that were only shipped out after all of the "Thimerosal preserved" doses had been shipped, and
- The reality that, *with respect to the* "Thimerosal preserved" *influenza vaccines*, the percentage of the "Thimerosal preserved" doses has ranged from nearly 100% of the doses in the 2002-2003 flu season to about 55% of the doses in the 2010-2011 flu season,

rather than declining, the ***maximum*** lifetime exposure to mercury from "Thimerosal preserved" vaccines has **increased** from 2002 onward to the point that, in 2009[96], with the "pandemic" flu vaccines, the ***maximum*** lifetime exposure was approaching twice the 1999 level.

Moreover, today, with the CDC's 2010 recommendation for 47-48 more flu-vaccine doses for adults from 18 to 65 years of age, it is more than 2.5 times the level that a person vaccinated under the 1999 vaccination schedule with the CDC-recommended vaccines, including a tetanus booster every 10 years, would have received.

Clearly, the effective ***maximum*** mercury-exposure level in the lifetime inoculation schedule has <u>not</u> declined as the authors, governmental agencies, the mainstream media, the manufacturers and others often claim.

Under the current CDC, FDA and vaccine-maker policies, the ***maximum*** level of Thimerosal exposure from vaccines in the USA will <u>not</u> ***significantly*** decline until: **a)** the FDA revokes the approvals for all "Thimerosal preserved" influenza vaccine formulations or the manufacturers "voluntarily" remove them from the market, or **b)** the CDC starts recommending that <u>no</u> one should be given a "Thimerosal preserved" flu shot.

Moreover, because the time for a diagnosis typically takes until the child is at least 3 years of age and most of the children who have developmental and/or behavioral problems that might lead to a diagnosis in the "autism spectrum" are <u>not</u> diagnosed until 8 years of age, if the FDA were to announce a ban on all "Thimerosal preserved" flu vaccines on October 1, 2011 with an effective date of October 1, 2012 and rigorously enforce that ban, the effect of this ban would <u>not</u> be clearly noticeable until some date in the 2015–2018 timeframe <u>provided</u> no other neurologically damaging substance (e.g., an oil-in-water adjuvant) is added to the inactivated-influenza vaccines' formulations to confound the change.

"Not only is there increasing and consistent compelling evidence for a lack of association between thimerosal-containing vaccines and autism, in addition, a study published by Thompson, et al. (2007), does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and/or immunoglobulins and neuropsychological functioning in children aged 7 to 10 years old.

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95 ***Morbidity and Mortality Weekly Report*** (***MMWR***) 2011 Aug 18; **60**(Early Release):1-6. Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP). "Vaccination of all persons aged ≥6 months continues to be recommended."

96 http://mercury-freedrugs.org/docs/090813_fnldrft_TheNoThimerosalPreservedVaccineLie_r6b.pdf

The study evaluated a total of 42 neuropsychological outcomes, including speech and language skills, executive functioning/attention, fine motor coordination, perceptual organization, motor tics, academic functioning, intellectual functioning, and ADHD (attention deficit hyperactivity disorder) symptomatology. The study was designed and interpreted with extensive input from independent outside consultants and the data set is publicly available. The study enrolled 1047 children between the age of 7 and 10 years (born 1993-1997) who had received thimerosal preservative-containing vaccines and evaluated a possible association between current neuropsychological performance and exposure to mercury during the prenatal period, the neonatal period, and the first 7 months of life. The investigators concluded that their 'study does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and immune globulins and deficits in neuropsychological functioning at the ages of 7 to 10 years.' In summary, the consistent findings in studies by Fombonne, et al. (2006), Thompson, et al. (2007), and Schechter, et al. (2008), provide further support that thimerosal exposure of children from vaccines is not associated with neurodevelopmental disorders, including autism. In addition, a recent study conducted by the CDC showed that prenatal and infant exposure to vaccines that contain thimerosal preservative does not increase risk for autism spectrum disorders (ASD). This study found that children with any ASD conditions and those without ASD had similar ethylmercury exposures at the end of each exposure period from pregnancy to 20 months of age. Exposure to ethylmercury from thimerosal-containing immunizations during pregnancy, or as a young child, was not associated with ASD outcomes Price et al. (2010)."

The fact is that there is an ever-increasing body of toxicological, case and case-control study evidence linking the level of Thimerosal exposure to adverse neuro-developmental outcomes in our children, including "autism".

As to the "*study published by Thompson, et al. (2007)*", the main reason that it "*does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and/or immunoglobulins and neuropsychological functioning in children aged 7 to 10 years old*" is that the study excluded all children who had any diagnosed neuropsychological malfunction from the children in the study, for example (emphasis added):

"**Methods**

We enrolled 1047 children between the ages of 7 and 10 years and administered standardized tests assessing 42 neuropsychological outcomes. (We did not assess autism-spectrum disorders.)"

More specifically, under "**STUDY POPULATION**", the article states (emphasis added):

"Children ere excluded if they had certain conditions recorded in their medical records that could bias neuropsychological testing (e.g., encephalitis, meningitis, or hydrocephalus) or if their birth weight was less than 2500 g (Table A of the Supplementary Appendix, available with the full text of this article at www.nejm.org)."

When a study excludes the children who have diagnosed "*neuropsychological functioning*" problems (children with autism-spectrum disorders and those who met the preceding exclusion criteria in this instance) from a study, then one would not expect to find any linkage in the included children between their level of "*early*

exposure to mercury from thimerosal-containing vaccines and/or immunoglobulins and neuropsychological functioning".

Thus, the study did not find any consistent linkages because it is very hard to find a linkage to any medical condition in children when all the children with that medical condition, or a risk for it, were excluded from the study.

Moreover, under the heading "**EXPOSURE TO MERCURY**", the assessment of mercury exposure was conflicted by a decision to not look at the variable mercury exposure from vaccines that a child received more than 214 days after birth:

> "We defined postnatal exposure as micrograms of mercury divided by the weight of the child in kilograms at the time of administration of each vaccine or immune globulin. Individual exposures were summed during the period of interest: birth to 1 month and birth to 7 months (1 to 214 days). We did not assess periods of thimerosal exposure after 214 days of age because we hypothesized that the potential effect of such exposure would be small. (Since most vaccines that are administered after 214 days would typically be given at 12 to 18 months of age, the dose per kilogram would be substantially lower."

This reviewer notes that, since the children assessed were 7 to 10 years of age, this decision could have included children with exposures to up to the equivalent of six, 25-µg doses of Thimerosal-derived mercury (150 µg of mercury) from annual flu shots plus up to another 50-plus µg of mercury from the other childhood "Thimerosal preserved" booster shots.

In 2006, when this study was conducted, 7- to 10- year-olds would have been born in 1995-1999 when the childhood DTP, Hib, and hepatitis B vaccines were Thimerosal preserved and, except for "at risk" children, they received no influenza vaccines until 2002.

Ironically, although the exclusion process was meant to exclude those with obvious neurodevelopmental disorders, there were two categories that, given the exclusion criteria used, did produce a signal that was relatively significant in some sub category or categories even though most of the children with a clinical level of the condition would have been excluded before the study evaluations were initiated.

Those categories were "**Tics**" and "**Speech and language**".

For "**Tics**", the general results reported can be found in reviewer's "**Table II"** (on the following page) that was taken from the paper.

In addition for both "**Tics**" and "**Speech and language**", when the evaluations were stratified "**According to Age Range**" and the "Birth to 7 Months" and "Birth to 1 Months" results were tabulated, the magnitude of the signal increased for those measures that had shown some significant signal previously, "Stuttering" under "**Speech and language**" and both categories of "**Tics**".

When discussing the study, the researchers included a paragraph on the weaknesses of their study that stated (emphasis added):

Table II. "Association between Prenatal Thimerosal Exposure and Neuropsychological Outcomes.*"

Evaluation Category and Instrument	Estimate (95% CI)		
	Full Model	Boys	Girls
Tics (lower = better)‡			
Rating by evaluator			
Motor tics	1.34 (0.94 to 1.89)	1.21 (0.80 to 1.84)	1.73 (0.89 to 3.36)
Phonic tics	0.84 (0.46 to 1.51)	0.89 (0.48 to 1.65)	0.62 (0.14 to 2.75)
Rating by parent			
Motor tics	1.04 (0.70 to 1.55)	1.14 (0.76 to 1.70)	0.42 (0.07 to 2.43)
Phonic tics	0.80 (0.47 to 1.36)	0.97 (0.58 to 1.64)	0.32 (0.06 to 1.71)

* Unless otherwise noted, all estimates are given as standardized coefficients, which represent the change in the outcome, expressed in standard-deviation units, given a change of 1 SD in exposure to thimerosal. Higher scores on scales indicate better outcomes, except where indicated. Independent variables in the full model were as follows: measures of cumulative exposure prenatally, from birth to 1 month, and from 1 to 7 months; age; sex; HMO; maternal IQ; family income (expressed as a percentage of the poverty line); maternal education level; single-parent status; score on the Home Observation for Measurement of the Environment scale; and other covariates if they met criteria for inclusion in the full model. Effects of sex were estimated from a full model with sex-by-exposure interaction terms. Postnatal exposure was defined as micrograms of mercury divided by the weight of the child in kilograms at the time of the administration of each vaccine or immune globulin. Individual exposures were summed over the 7-month period.

‡ Estimates in this category are given as odds ratios. We estimated odds ratios for a 2-SD increase in mercury exposure. A lower odds ratio is associated with a better outcome.

"Our study had several limitations. A majority of the selected families declined to participate or could not be located, and we were able to enroll only 30% of the subjects included for recruitment. Therefore, our findings may have been influenced by selection bias. In addition, we were not able to control for interventions, such as speech therapy, that may have ameliorated the potential negative effects of thimerosal exposure and could have biased the results toward the null hypothesis. Given that parents were not trained to assess tics, the parental ratings of tics may have been less reliable than the ratings by trained evaluators. We did not assess exposure to thimerosal beyond 214 days. Finally, the information available for some potential confounding factors, such as family income, which may have resulted in unmeasured residual confounding, was imprecise. Our study did not examine the possible association between autism and exposure to mercury from vaccines and immune globulins."

Though, after "discussing" "*Thompson, et al (2007)*", the authors of the document submitted to the UNEP state:

"*In summary, the consistent findings in studies by Fombonne, et al. (2006), Thompson, et al. (2007), and Schechter, et al. (2008), provide further support that thimerosal exposure of children from vaccines is not associated with neurodevelopmental disorders, including autism*",

this reviewer observes that:

- When the obvious errors in "*Fombonne, et al. (2006)*" are addressed, the data for grades "10" through "1" clearly supports a causal relationship between Thimerosal exposure level and "*neurodevelopmental disorders, including autism*"[97],
- As the researchers in "*Thompson, et al. (2007)*" clearly stated, "*Our study did not examine the possible association between autism and exposure to mercury from vaccines and immune globulins*", and
- The finding in "*Schechter, et al. (2008)*"of increasing numbers of children with a diagnosis in the autism spectrum is valid but the presumption that the level of Thimerosal exposure was decreasing (the researchers in this study made no attempt to assess the actual exposure levels of the children) is a false presumption because the actual ***maximum*** level of Thimerosal exposure did not decrease during the period of their study.

Thus, it is clear that the apparently valid data from two of these three studies, "*Fombonne, et al. (2006)*" and "*Schechter, et al. (2008)*", do seem to support a causal association between the level of Thimerosal exposure and the risk of "*neurodevelopmental disorders, including autism*".

Since "*Thompson, et al. (2007)*" "*did not examine the possible association between autism and exposure to mercury from vaccines and immune globulins*", it should be obvious that, contrary what the authors state, there can be, and were, no consistent findings in the three studies cited by the authors with respect to Thimerosal exposures and the risk of neurodevelopmental disorders, including autism.

With respect to the authors closing statements (emphasis added):

> "*In addition, a recent study conducted by the CDC showed that prenatal and infant exposure to vaccines that contain thimerosal preservative does not increase risk for autism spectrum disorders (ASD). This study found that children with any ASD conditions and those without ASD had similar ethylmercury exposures at the end of each exposure period from pregnancy to 20 months of age. Exposure to ethylmercury from thimerosal-containing immunizations during pregnancy, or as a young child, was not associated with ASD outcomes Price et al. (2010).*"

this reviewer simply points out that this study is based on a false premise – that exposure alone determines the outcomes observed.

Previously, tobacco-industry sponsored numerous studies of the link between cigarette smoking and lung cancer that used this same simplistic, but false, premise to claim that cigarette smoking does not cause lung cancer because everyone who smoked the same number of cigarettes daily for some time period did not get lung cancer.

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97 http://mercury-freedrugs.org/docs/060827_PGKsCmmnts_CanadianEpidemioStudy_Pediatrics-Full-b.pdf

When this deception was exposed by an industry insider, this type of "scientific" study was labeled "tobacco science"

Thus, "*Price et al. (2010)*" is but another deeply flawed study, which some, including this reviewer, recognize as "tobacco science".

"***Recent United States Court Decisions***

Over the last decade, petitions have been filed for compensation with the U.S. Secretary of Health and Human Services (HHS) under the National Vaccine Injury Compensation Program

Page 10

(VICP) alleging that some childhood vaccines may either cause or contribute to ASD. The allegations are specifically that cases of ASD may be caused by either the measles-mumps-rubella (MMR) vaccine or thimerosal-preservative-containing vaccines or from both when administered together. On February 12, 2009, after a series of hearings on causation, the U.S. Court of Federal Claims ruled that the MMR vaccine, either administered alone or in conjunction with thimerosal-containing vaccines, is not a causal factor in the development of ASD. After another series of extensive reviews, on March 12, 2010, the court ruled that thimerosal-containing vaccines are not a causal factor in the development of ASD. http://www.hrsa.gov/vaccinecompensation/omnibusproceeding.htm."

First, this reviewer must note that, though the authors repeatedly use the word "court", all of the bodies to which they refer are administrative bodies of the US federal government that answer to the executive branch of government and not judicial courts, where there are plaintiffs and defendants who still have most of the other legal rights granted them by the Constitution of the United States of America.

Thus, unlike a legal civil court where there are plaintiffs who sue defendants to recover for the damages that the defendants have purportedly caused the plaintiffs, the role of the judge is to maintain order and supervise the trial, and a jury decides the case and, if they find in favor of the plaintiffs, award them compensation, in these US federal administrative proceedings:

- Petitioners beg these governmental bodies for some compensation for the damages suffered,
- Administrators, called "special masters", who are administrative employees of the executive branch of the US government, review the petitions and decide which, if any, of the petitioners' petitions they will hear and when they will hear them, and
- Respondents, who are US federal administrative attorneys, oppose the petitioners' petitions for compensation from a fund that is supported by a tax on every vaccine dose.

In general, the legal "rules of evidence" do not apply, the petitioners have no right of discovery, each petition is supposed to be heard "*de novo*" (without regard to the findings in any previous hearing), and the respondents adversarially oppose most all of the small percentage of petitions that the special masters do hear.

Finally, since the general administrative proceedings conducted by the special masters in "omnibus proceedings", are not *de novo* hearings of individual cases as the statutes intended (42 U.S.C. 30aa-10 et seq.) but rather "test case" hearings to make rulings that will be applied globally, technically these "proceedings" are "extra legal" proceedings.

Against the preceding background, this reviewer understands that, faced with more than 5,000 petitions with potential costs in the hundreds of billions of dollars, the decisions made by the special masters in these "test case" proceedings involving "Thimerosal preserved" vaccines and "autism" were political, not science-based decisions

As a scientist, this reviewer must repudiate the decisions of the special masters because the unbiased epidemiological, toxicological, case and case-control studies have clearly established that, for mercury-poisoning-susceptible individuals[98], there is a causal link between the level of Thimerosal exposure during the development of the child and the risk of a diagnosis of a neurodevelopmental disorder, including autism.

"***Conclusion***

In summary, licensed vaccines containing thimerosal preservative have been determined to be safe and effective under the applicable U.S. statutory and regulatory requirements and therefore are approved for use in the United States."

Here, this reviewer notes that, contrary to the authors' statement, all FDA-licensed vaccines were, in effect, determined to be essentially "unavoidably unsafe" or simply inherently "unsafe" by the US Supreme Court in *Brusewitz v. Wyeth (No. 09–152. Argued October 12, 2010—Decided February 22, 2011)*.

Similarly, since the FDA approves vaccines based on vaccine efficacy as determined by antibody titers in a clinical trial and not based their in-use effectiveness in preventing the vaccinees from contracting a disease when exposed to it some time after being fully inoculated with the vaccines, most of today's vaccines have not been determined to be "*effective*".

Thus, *at the present time*, the general reality is that all FDA-approved vaccines are inherently "unsafe" (as per the US Supreme Court in *Brusewitz v. Wyeth*) and almost all of the current FDA-licensed vaccines meet industry-agency agreed upon efficacy standards but have not truly "*been determined to be … effective under the applicable U.S. statutory and regulatory requirements*".

Further, the authors' careful wording in this part of this submission to the UNEP has cleverly avoided addressing the reality that, when Thimerosal is used as a preservative in a vaccine at some level, the US law, as set forth in 21 CFR § 610.15(a), requires the manufacture to prove this preservative is "sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient".

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98 Shandley K, Austin DW. Ancestry of pink disease (infantile acrodynia) identified as a risk factor for autism spectrum disorders. ***J Toxicol Environ Health A***. 2011 Sep 15; **74**(18): 1185-1194.

To date, the vaccine makers have failed to prove that the level of Thimerosal used as a preservative in their FDA-licensed "Thimerosal preserved" vaccine formulations is "sufficiently nontoxic …", the current good manufacturing practice (CGMP) minimum set forth in 21 CFR § 610.15(a).

Moreover, the authors have failed to disclose that, in the US, the failure of a vaccine manufacturer to prove the safety of its vaccine, a biological drug product, to any CGMP standard, including 21 CFR § 610.15(a), renders that vaccine an adulterated drug under 21 U.S.C. § 351(a)(2)(B).

End of the Review

About the Reviewer

In addition to the general information available on his web site, http://www.dr-king.com/, Paul G. King is a consultant, science advisor to various groups, and the Science Advisor and the current Secretary for the Coalition for Mercury-Free Drugs (CoMeD, Inc., a 501(3)(c) corporation), http://www.mercury-freedrugs.org/.

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"Page 11

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