Respondent's Exhibit L

Toxicology Associates, Prof. LLC

Dedicated to Patient Care, Research, and Teaching in Medical Toxicology

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Vincent J. Matanoski
Assistant Director
Torts Branch, Civil Division
U.S. Department of Justice
P.O. Box 146
Ben Franklin Station
Washington, DC 20044

RE: Cedillo v. Sec'y HHS, Fed. Cl. No. 98-916V

Dear Mr. Matanoski,

I am a physician and a clinical professor of pediatrics and internal medicine at the University of Colorado Health Sciences Center (UCHSC). I hold sub-specialty board certification in medical toxicology – a sub-specialty recognized by the American Board of Medical Specialties – and I maintain a private medical practice in that field through my work at Toxicology Associates. As a medical toxicologist, I specialize in the assessment, diagnosis, and treatment of adverse effects of pharmaceuticals, non-therapeutic chemicals, and other potential toxins on humans. At present there are less than 250 physicians in the United States holding sub-specialty certification in medical toxicology.

In addition to my M.D., I have earned a Ph.D. in biochemistry. My doctoral research focused on potential toxic effects of medicinal agents. Upon completion of my Ph.D. program at Mt. Sinai School of Medicine, I served as a post-doctoral fellow at the Institute of Cancer Research at Columbia University, College of Physicians and Surgeons.

Following completion of this Fellowship, I attended medical school at the State University of New York School of Medicine at Buffalo and was awarded an M.D. I then completed an internship in general surgery at the Harvard Fifth Surgical Service in Boston, Massachusetts, followed by a primary residency in emergency medicine at Emory University School of Medicine in Atlanta, Georgia. Upon completion of my residency, I became a Fellow in medical toxicology at the UCHSC and the Rocky Mountain Poison Center. After completion of this two year Fellowship, I was invited to join the faculty of both institutions, and ultimately became Director of the medical toxicology fellowship program, a position I held until 1993. Since my initial appointment in 1987, I have continuously remained on the UCHSC faculty. At

UCHSC, and at my private practice at Toxicology Associates, I devote most of my time to patient care, research, writing, editorial activities, and teaching in the area of medical toxicology.

During the course of my career as a medical toxicologist, I have had the unique opportunity to evaluate, consult on, diagnose, and treat hundreds of patients for heavy metal poisoning, including mercury toxicity.

In addition to teaching and patient care, I have been active in the research arena throughout my career. My research focuses on the adverse effects of, or poisoning by, pharmaceuticals and environmental or other toxins. I have been an author on over 200 peer-reviewed publications, invited articles, book chapters, abstracts, and other publications.

I have served as Editor-In-Chief of *Toxicological Reviews* and I am currently a Senior Editor of *Clinical Toxicology*, which is the largest circulation peer-reviewed journal in the world devoted to this discipline. I have been Section Editor for environmental toxicology of one toxicology text and am Senior Editor of a major recent text entitled *Critical Care Toxicology – The Diagnosis and Management of the Critically Poisoned Patient*. I serve as a peer-reviewer for a number of medical journals including the *New England Journal of Medicine*, the *Journal of the American Medical Association*, the *Journal of Emergency Medicine*, *Annals of Emergency Medicine*, *Academic Emergency Medicine*, *American Journal of Emergency Medicine*, *Archives of Internal Medicine*, *Clinical Toxicology*, *Critical Care Medicine*, *Journal of Medical Toxicology*, and the *American Journal of Kidney Disease*.

I am a Past President of the American Academy of Clinical Toxicology, which is the largest professional society in the world devoted to this discipline. Its membership includes virtually all medical toxicologists and poison control center directors in the U.S. and Canada and a large proportion of those worldwide. Presently, I am a member of the Board of Directors of the American College of Medical Toxicology, which is the organization composed of physicians who are sub-specialty qualified in medical toxicology.

I have acted as a consultant to various federal agencies, the World Health Organization, and various district attorneys' offices throughout the country. As listed in my Curriculum vitae, I have received numerous national and international honors and awards in the area of clinical toxicology and have lectured extensively, both nationally and internationally, on mercury and other topics in the field of clinical toxicology.

A more detailed recitation of my experience and qualifications can be found in my Curriculum vitae, which is attached to this report as Respondent's Exhibit M.

SUMMARY OF OPINIONS

In this case, I have been asked to render an opinion regarding the existence of a causal link between the administration of thimerosal-containing vaccines to infants and children and the subsequent development of either autistic spectrum disorders (ASDs) or mercury toxicity. In addition, I have been asked to review the medical records of Michelle Cedillo and to express an opinion regarding the claim that her receipt of thimerosal-containing vaccines contributed in any way to her abnormal development.

After a thorough and careful review of the existing body of literature bearing on the subject and the application of the basic principles of toxicology, I have concluded that there is no reliable scientific evidence to support the claim that exposure to thimerosal-containing vaccines administered in accordance with the recommended childhood immunization schedule is causally associated with the development of either mercury toxicity or ASDs. It is thus my opinion that, to a reasonable degree of medical and scientific probability, thimerosal-containing vaccines are not implicated in the etiology of ASDs in general, and did not cause and were not contributory to Michelle Cedillo's condition.

Based on my review of the relevant reliable scientific evidence, and on my knowledge, experience, and training as a medical toxicologist, I have concluded that the dose of mercury to which Michelle Cedillo was exposed from thimerosal-containing vaccines was enormously lower than that which would have resulted in toxicity. Michelle Cedillo does not display, and there is no indication that she ever displayed, any of the characteristic signs or symptoms of mercury poisoning. It is therefore my opinion that, to a reasonable degree of medical and scientific probability, the thimerosal in vaccines administered to Michelle Cedillo did not lead to mercury toxicity or contribute to her condition.

I have carefully reviewed and considered the medical records and laboratory reports pertaining to Michelle Cedillo; the 2001 and 2004 U.S. National Academy of Sciences Institute of Medicine (IOM) reports addressing and refuting the hypothesis that exposure to thimerosal-containing vaccines can cause autism or other neurodevelopment disorders, transcripts of these proceedings and related slide presentations; and the expert reports of Drs. Byers, Krigsman, Kinsbourne, and Aposhian.

SCIENTIFIC BASIS FOR OPINIONS

Mercury poisoning does not manifest as autism spectrum disorders

In my practice as a medical toxicologist, I have consulted on, and personally treated, children suffering from mercury poisoning and I am very familiar with the clinical presentation of mercury toxicity. In addition, I have experience with a number of children with ASDs who have been brought to me for toxicological evaluation and treatment. Based on this clinical experience, I can say with a very high degree of

medical probability that ASDs and mercury poisoning are two very different and distinct clinical syndromes, each with its own characteristic signs, symptoms, and laboratory findings.

Exposure to ethylmercury causes characteristic signs and symptoms that include visual field constriction, ataxia (i.e., uncoordination of movement), dysarthria (poor articulation [slurred speech] due to poor motor control of speech-related muscles), peripheral neuropathy (i.e., abnormal sensation due to damage of peripheral nerves, particularly in the extremities), characteristic abnormalities of renal function, and tremors. None of these is characteristic of ASDs (Nelson and Bauman 2003).

While not specialized in the diagnosis of ASDs, I have seen, evaluated, and treated a number of autistic children in my medical toxicology clinical practice, and am familiar with the characteristic signs and symptoms of this disorder, which include lack of eye contact and other impairments in social reciprocity, speech delays, speech/language deficits, and repetitive and stereotypical behaviors. The fact that some autistic children may also exhibit a variety of other non-specific neurological signs and symptoms that occur in any number of disorders, in the population in general, or even in some people who have been exposed to a mercury-containing substance, is neither surprising nor indicative that the child is suffering from something other than an ASD. Given the clear differences between the core signs, symptoms, and laboratory findings of the two disorders, no informed physician could reasonably confuse mercury poisoning with ASDs, or vice versus, resulting in misdiagnosis. In fact, there are no case reports in the medical literature suggesting that such confusion has occurred.

I have reviewed the article by Bernard et al. (2001), reporting to find substantial similarities and overlap between signs and symptoms of mercury poisoning and those of ASDs and concluding, therefore, that autism is a "novel" form of mercury poisoning. This conclusion is wholly insupportable.

In making their comparison between the two outcomes, Bernard et al. apparently reviewed the entire body of published literature addressing the issues of mercury exposure and ASDs and extracted from these articles every sign or symptom that has ever been reported to anyone who was exposed to mercury in any form and in any dose, and every sign or symptom ever reported to have been exhibited by anyone with ASD. Such an approach to the issue is wholly unscientific and cannot support the author's ultimate conclusion. Moreover, most of the symptoms of mercury toxicity used by Bernard et al. are from cases exposed to elemental and methylmercury, not ethylmercury. The differences between these two compounds and their respective potential toxic effects on the body are discussed below.

In addition, a number of articles referenced by Bernard et al. do not support their characterizations of the symptoms reported. For example, for "social deficits, shyness, social withdrawal" Bernard cites Vroom and Greer (1972), which is a case series of mine workers exposed to mercury vapor; no symptoms of social deficits,

shyness, or withdrawal are documented. Most problematic, however, is that the "traits of mercurialism" identified by the authors go far beyond what is generally accepted as being the characteristic signs and symptoms of mercury poisoning. As documented in the medical literature, mostly in the form of case reports and case series, a person with mercury poisoning may exhibit a variety of signs and symptoms, whether related to mercury exposure or not, that are neither characteristic of, nor specific to, a diagnosis of mercury poisoning.[1] Despite this variation, however, virtually all patients with mercury toxicity present with some or all of the core set of signs and symptoms set forth above.

Bernard et al.'s claim of overlapping of similar signs and symptoms in both mercury poisoning and ASD is blatantly incorrect – an observation that has been made independently by investigators from the U.S. National Institute of Neurological Diseases and Stroke and the Children's Neurology Service at Harvard Medical School (Nelson and Bauman 2003). The clinical characteristics of mercury poisoning are so different from ASDs that it is inconceivable that any competent physician could confuse the two.

Michelle Cedillo does not have mercury poisoning

As noted earlier in this report, there is a characteristic constellation of signs, symptoms, and laboratory findings that are used for the diagnosis of ethylmercury poisoning. My review of Michelle Cedillo's medical records revealed no evidence of mercury poisoning, no blood or urine studies showing elevated mercury levels, and none of the petitioners' experts has diagnosed Michelle Cedillo with mercury poisoning or pointed to any findings that suggest that she has mercury poisoning.

It is thus my opinion as a medical toxicologist with a great deal of experience in mercury poisoning that, to a reasonable degree of medical probability, Michelle Cedillo is not, and was not at any time, suffering from mercury toxicity and her exposure to thimerosal-containing vaccines did not cause or contribute to her current medical conditions

SCIENTIFIC METHODOLOGY IN THE ASSESSMENT OF CAUSATION

As a medical toxicologist, one of the things I am repeatedly required to do is to apply basic scientific and epidemiologic principles to the assessment of whether a medication or other chemical substance is capable of causing a particular adverse

[1] Case reports and case series are simply published reports of a physician's clinical experience in the treatment of a single patient or a series of individual patients. Because of the constraints inherent in the clinical study in which they arise, case reports and case series are not controlled in any way. Nor are they studies that can test a causation hypothesis because there is no basis on which to distinguish whether the observed outcomes/symptoms are attributable to the background rate of occurrence in the general population, the exposure in question, and underlying disease or disorder, or concomitant medication. It is thus generally accepted in the medical and scientific communities that case reports and case series do not constitute proof of a hypothetical causal relationship between an exposure and a subsequent adverse effect.

outcome. It is not until this fundamental question has been answered in the positive that it is scientifically or medically appropriate to move to the next step and to ask whether the agent in question actually caused the outcome in any particular patient.

In applying such principles, the first step in assessing whether a patient's presenting signs or symptoms were caused by an exposure to a particular chemical is to determine if there is sufficient evidence to allow me to assess if that substance is capable of causing the outcome in question, and if so, whether it can do so at the dose to which the patient was exposed. The latter is a reflection of the fundamental toxicological concept embodied in the adage: "The dose makes the poison." At the heart of this principle is the recognition that every chemical substance – including those that are vital to the sustenance of life and those that we come in contact with on a daily basis – can be toxic. What makes any substance toxic, benign, or beneficial is the dose that is delivered to the site of action. So, for example, low to moderate doses of N-(4-hydroxyphenyl) acetamide – commonly known as acetaminophen (Tylenol®) – is an effective pain reliever; however, at high doses, it is very toxic to the liver. It is therefore inappropriate and misleading to say, categorically, that any given substance is "toxic" *per se* and to conclude that exposure to that substance at any dose whatsoever can result in toxicity. Indeed, Dr. Aposhian begins his report by seemingly acknowledging the importance of dose: "All forms [of mercury] **can** be toxic to humans." (p. 2, emphasis added)

In addition to dose, the toxicity of any substance will depend on the particular chemical form of the substance, the route of exposure, the duration of exposure, and the age/developmental stage of the target organ at the time of the exposure. These fundamental principles and their application to the questions presented in this case – i.e., whether exposure to thimerosal-containing vaccines can contribute to ASDs or mercury poisoning and whether such exposure actually was a contributing cause of Michelle Cedillo's condition – are discussed below.[2]

***In vitro* studies do not provide sufficient scientific basis to conclude that a particular substance is a potential cause of any specific toxic effect in humans**

An *in vitro* study is one that is carried out in isolation from the complex environment of the intact living organism. It consists of experiments performed on cells or tissue grown in a petri dish in an artificial culture medium, or on cell or tissue homogenous

[2] Different chemical forms of mercury (Hg), including elemental (Hg^0), ionic (e.g., Hg^{2+}) and organic (e.g., methylmercury, ethylmercury, and thimerosal) have different toxicological properties and affect different organs. For example, at sufficient doses, exposure to elemental mercury vapor affects both kidneys and the central nervous system, while toxic exposure to ionic mercuric salts primarily causes kidney damage. Even within these broad classes, there are toxicological differences between specific substances. The primary target organ for the organic mercurial methylmercury is the brain (i.e., the central nervous system), while the chemically similar ethylmercury can have, at sufficient doses, both reno- and neurotoxic consequences. Thimerosal is the sodium salt of ethylmercury thiosalicylic acid. In the body, thimerosal is rapidly metabolized to ethylmercury. (Clarkson, 2002)

– i.e., a slurry produced by the mechanical disruption (e.g., grinding) that destroys the cell-tissue membrane structure. Such studies are not sufficient to reach conclusions regarding toxicity in the human body. However, they can be useful for generating specific hypotheses to be tested or for studying potential mechanisms by which an established cause and effect relationship might occur.

Before a causal relationship between an exposure and a particular outcome can be inferred, there must first be reliable scientific evidence of an association between exposure at the dose of concern and the particular outcome of interest. In the absence of an established association, discussion of a biological mechanism is a *non sequitur*. *In vitro* studies have a number of inherent limitations that severely diminish their utility in the assessment of whether a causal relationship exists between human exposure to a substance tested and the subsequent development of a clinical condition. If what happens in a petri dish were, in fact, predictive of a human response to the tested substance, then there would be no need for clinical trials or epidemiologic studies to establish the efficacy of drugs or the deleterious effects of toxins. Clearly, this is not the case.

Due to the artificiality of the *in vitro* environment, the response of tissues or cells to an exposure *in vitro* will very often differ from the response in the intact organism. For example, when one is investigating the potential effect of a substance on brain structure and/or function, it is of limited utility to know that the substance investigated will kill petri dish cultured neurons at a particular concentration, unless you know the dose that must be administered to a human before the toxic concentration can be achieved at the neurons in the brain. This is especially significant with regard to the brain because it is protected from toxic insults by an anatomical barrier called the blood-brain barrier, which prevents or hinders the passage of many substances from the blood into the brain.[3] Moreover, most tissue cultures are composed of a single cell type, perhaps with some impurities; as such, the reductionist approach of tissue culture negates the "cross-talk" and homeostatic control that is inherent to *in vivo* conditions.

In addition to this difference in effective dose, the form in which the substance is present *in vivo* may be markedly different from that which exists *in vitro*. For example, *in vivo*, many substances are bound to extracellular proteins and other molecules and thus could not be taken up by target cells. If these binding substances are not included in the *in vitro* incubation mixture, the *in vivo* exposure will not be replicated. The form that the substance takes in the blood is also critical in determining how much, if any, will cross tissue and cell barriers.

[3] The blood-brain barrier is a lipid membrane that permits the passage of small lipid-soluble substances into the brain via diffusion. Ionic and other water soluble substances do not readily cross the blood-brain barrier by simple diffusion. However, there are a number of highly selective mechanisms for transport of essential nutrients into the brain that would otherwise be excluded.

Cells are further protected from potentially toxic substances by a number of biochemical and physiological defense mechanisms. These natural detoxification processes are an essential part of how our bodies deal with many potentially toxic substances to which we are exposed on a daily basis. Because *in vitro* models cannot duplicate, and typically do not account for, these complex defense systems, cell responses *in vitro* may be markedly exaggerated and thus inaccurate representations for what actually occurs *in vivo*.

Both Drs. Byers and Aposhian cite studies by Goth et al. (2006) and Agrawal et al. (2007) as evidence that vaccines can modulate the activity of the immune system. However, such conclusions cannot be validly gleaned from these studies.

As Dr. Aposhian notes in his report (p. 3), thimerosal is "metabolized quickly to ethylmercury" *in vivo* after immunization. The Goth et al. and Agrawal et al. studies, however, are *in vitro* experiments using thimerosal. There is no evidence that the thimerosal they administered in their study was converted to ethylmercury. Therefore, no inferences can be made from their study regarding exposure to ethylmercury as would occur *in vivo* following vaccination.

Moreover, because these *in vitro* studies did not have the normal mercury-protective endogenous molecules present, as would be *in vivo,* and given the lack of the presence of the normal red blood cells that bind mercury in the body, the effective concentration of thimerosal that these cells were exposed to was undoubtedly far greater than the nominal concentration of it in their studies. For example, both studies used ranges of thimerosal concentrations that included 50 nanomolar (nM). Exposing cells *in vitro* to this concentration, even if it was ethylmercury, causes them to receive a much larger effective dose than those *in vivo* when the blood concentration is 50 nM. The reason for this is that when ethylmercury is circulating in the blood it is bound to red blood cells, proteins, and other molecules (e.g., glutathione) that render it unavailable to interact with other cells. It is only the small fraction of unbound ethylmercury that is biologically active *in vivo.* In the Goth et al. and Agrawal et al. experiments, the entire amount of material (which in their case thimerosal) is free and thus available for cellular interaction.

Even if the reported effects by the Goth et al. and Agrawal et al. studies did occur in the body (and there is no evidence that they do), the short half-life of ethylmercury following vaccination would render any such effect very short-lived and unlikely to be clinically consequential. For example, Michelle Cedillio's last exposure to thimerosal from a vaccine was approximately 9 months before the MMR vaccination being implicated by petitioners' experts. Because the half-life of ethylmercury is approximately 7 days (Pichichero et al, 2002), ethylmercury blood levels rapidly fall post-vaccination. As such, even if there were a transient effect on the immune system from ethylmercury following receipt of a thimerosal-containing vaccine (and none has been demonstrated), ethylmercury blood levels fall so fast that the effect would be very short-lived. There is thus no reasonable way that the dose of ethylmercury given

nine months prior to her MMR could have influenced her reaction to the latter vaccination.

For these reasons, *in vitro* studies, such as the ones on which petitioners' expert witnesses rely, cannot be used to assess whether thimerosal or ethylmercury is capable of causing a specific biological effect *in vivo* – let alone assess whether thimerosal or ethylmercury is capable of causing a specific medical condition such as mercury toxicity or ASD. Such *in vitro* studies were presented to and considered by the 2004 IOM panel, which found that they did "not readily translate into a physiologic argument." (2004 IOM Report, p. 140)

Because of the inherent limitations of *in vitro* studies, and the specific flaws in those studies purporting to establish an association between thimerosal-containing vaccines and neurodevelopmental disorders, the *in vitro* studies cited by petitioners' expert witnesses do not provide support for their causal hypotheses.

Despite the limitations of the Goth et al. and Agrawal et al. studies, Dr. Aposhian states in his report: "While excellent review articles exist about 'Mercury-the metal of mystery' [Cites], they must be viewed cautiously as current scientific investigations have rendered some of their findings false and the conclusions they have drawn as inaccurate or outdated." (p. 4) Yet, a search of the current medical and scientific literature fails to reveal any such new articles negating the conclusions of recent reviews regarding the lack of a relationship between thimerosal administration and ASDs. Indeed, Dr. Aposhian fails to provide any specific examples of studies that have shown these review articles' conclusions to be "inaccurate or outdated."

The most recent of the four "outdated" reviews cited by Dr. Aposhian is the paper by Clarkson and Magos (2006). Dr. Aposian cites only 4 papers in his report that were published in 2006 – 2007, two of which are the Goth et al. and Argawal et al. studies. As described in detail above, neither of these would render "the conclusions they [the reviews] have drawn as inaccurate or outdated." The other two recent studies cited by Dr. Apsohian would similarly have no impact on those reviews finding a lack of a relationship between thimerosal administration and ASDs. He cites a paper by Transande et al. (2006), which deals with methylmercury, does not address ASDs or thimerosal, and provides no new data that would render current thinking obsolete in any way. The final recent paper cited by Dr. Aposhian is that of Ashwood et al. (2007). That paper deals primarily with immunological studies in ASD and not with mercury. However, in the short section of the Ashwood paper discussing the thimerosal/ASD allegation, they review the data set forth in support of this hypothesis and conclude: "[T]he overwhelming majority of epidemiological, population studies indicates there is no established correlation between vaccinations and autism."

<u>It is scientifically unsound to draw conclusions regarding the</u>

toxicity of ethylmercury or thimerosal from data on the toxicity of methylmercury or any other form of mercury

It is not scientifically reasonable or accepted to assume that the toxicological properties of any specific compound are the same as those of a different compound, even if the two are in some way chemically similar substances. For example, methyl alcohol (methanol or wood alcohol) and ethyl alcohol (ethanol), which are chemically very similar, have dramatically different toxicological properties. At moderate to high doses, ethanol, the alcohol in spirits, causes acute alcohol intoxication (i.e., drunkenness), but very low doses of methanol can cause acute multi-system dysfunction, often death, and in survivors, blindness.

The minor difference in chemical structure between methanol and ethanol is precisely the same as the chemical difference between methylmercury and ethylmercury. There are many studies that show that in the body methylmercury and ethylmercury behave differently (*e.g.*, Magos et al., 1985; Harry et al., 2004; Burbacher et al., 2005). These same considerations apply to the applicability of data from other chemical substances that are in some way related to, but not, ethylmercury.

The recognition that that which is applicable to one form of mercury does not necessarily apply to other forms is well accepted and broadly articulated in the medical and scientific literature. For example, in Casarett and Doull's very well respected book *Toxicology – The Basic Science of Poisons* (2001; Klaassen, ed.) it is stated: "*No other metal better illustrates the diversity of effects caused by different chemical species than does mercury*" (p. 834). Similarly, the United States Centers for Disease Control and Prevention (CDC) makes that point several times. For example, the Agency for Toxic Substances and Disease Registry (ATSDR), a component of the CDC, states in its toxicological profile on Mercury (1999): "*Exposure to mercury, however, does not necessarily mean that adverse health effects will result. Health effects depend on the amount of exposure, the form of mercury, and the route of exposure. Each form and route leads to different effects*" (pp. 29-30).

Dr. Aposhian recognizes the differences between ethylmercury and methylmercury several times throughout his report. In fact, he calls them different "species" (p. 2) and writes that they have "different toxicological properties" (p. 2) with "markedly different" toxicokinetics (p. 9). However, despite his recognition of these differences, Dr. Aposhian relied very heavily on methylmercury-related data to hypothesize about the adverse effects of ethylmercury.

Petitioners' hypothesis that post-natal exposure to ethylmercury in thimerosal-containing vaccines can cause ASDs or mercury poisoning in children is based, in part, on the proposition that an infant who is vaccinated in accordance with the recommended childhood immunization schedule could be exposed to quantities of ethylmercury that exceed the U.S. Environmental Protection Agency's (EPA's)

reference dose (RfD) for methylmercury (e.g., Dr. Aposhian report, p. 9).[4] However, as discussed below, the assumptions underlying this hypothesis are fundamentally flawed.

The EPA RfD of 0.1 ug/kg/day is not a threshold exposure dose above which toxicity is reasonably likely to occur. Rather, it is an estimate of the average daily oral exposure that is likely to be without an appreciable risk of adverse effects if continued over a person's lifetime. In calculating the RfD, the EPA chose as its starting point the level of *in utero* exposure to methylmercury associated with a predefined level of risk of subtle, sub-clinical, neurodevelopmental deficits;[5] ASD was not an endpoint in this study from which the RfD was derived. The EPA's recommended safe intake level is thus inherently designed to protect those who are arguably the most sensitive to methylmercury – developing fetuses. In addition, once the dose that was observed to create this increased risk of harm was determined, the dose at the lower limit of the 95% confidence interval around that dose was further reduced by a factor of 10 to account for the possibility that some people might be even more susceptible to methylmercury neurotoxicity and to account for the possibility that other unrecognized effects might occur at a lower dose. The RfD, which was calculated to

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[4] Like the EPA, the FDA, the ATSDR, and the World Health Organization (WHO) have all issued safety guidelines for methylmercury consumption. Exposure to mercury (in the form of ethylmercury) from thimerosal-containing vaccines does not exceed any of these other guidelines – with a single exception of an infant in the 5th percentile for body weight, whose cumulative mercury dose would exceed the ATSDR guidelines (Ball et al., 2001).

[5] The RfD for methylmercury was derived from data gathered during the course of a long-term study on the risk of harm posed by *in utero* exposure to methylmercury via mother's regular consumption of contaminated seafood and episodic consumption of whale meat, which is known to have a very high methylmercury content. In this Faroe Island Study, such prenatal methylmercury exposure was found to be associated with subtle, sub-clinical, deficits in the area of learning, memory, and language, as measured by various neuropsychological tests. Using the Faroe Island data (Rice et al., 2000), EPA determined the concentration of mercury in cord blood that, for each test, was associated with the doubling of the number of children with a response at the 5th percentile. This is known as the Benchmark Dose. The lower limit of the 95th confidence interval surrounding this Benchmark Dose – known as the Benchmark Dose Lower Limit (BMDL) was then chosen as a so-called point of departure dose. Then, to account for the fact that some unrecognized adverse event might occur at a dose lower than the BMDL, and recognizing that, due to differences in pharmacokinetics (e.g., impaired mercury elimination) and pharmacodynamics, some people in the population might be more susceptible than others to the adverse effects of mercury, the BMDL of 58 parts per billion (ppb) were divided by a factor of 10. Thus, the level of continuous mercury exposure considered safe to the unborn fetus was determined to be 5.8 ppb (which is the same as 5.8 ug/L). It was then determined that to reach this steady state concentration of mercury in the umbilical blood, a pregnant woman would have to consume an average of 0.1 ug/Hg/kg body weight/day and throughout her pregnancy. This calculation is based, in part, on the half-life of mercury in the blood following dietary methylmercury exposure. It should be noted that in a similar study in another similarly exposed fish-eating population (Seychelles Island) no neurodevelopmental effects were found following fetal exposure to methylmercury (Myers et al., 2003; Davidson et al., 1998). While it has been suggested that the difference between the two studies might be attributed to the so-called "bolus dose" exposure to the fetus as a result of the mother's periodic consumption of whale meat, which contained extremely high levels of methylmercury and resulted in repeated spikes in exposure, the Faroe Island investigators tested this hypothesis and found no support for such a bolus effect (Grandjean et al., 2003).

protect sensitive populations from the first instance, thus incorporates an additional substantial margin of safety for both childhood and adult exposures to methylmercury. There is thus a substantial difference from a presumptively safe daily dose described by the RfD and the dose believed to give rise to toxicity.

Moreover, because the RfD is expressed as the ***average*** daily exposure that is presumptively safe if continued ***over a lifetime***, short-term exceedances of the RfD are anticipated and are not expected to result in adverse consequences; the key is that the RfD defines a chronic exposure that results in a steady state blood level. If the RfD were a toxicity threshold, then one would expect that a child's or nursing mother's periodic consumption of fish or seafood would give rise to neurotoxicity in the child. This is clearly not the case. Consequently, even when considering exposures to methylmercury, the fact that the RfD is exceeded for a brief period is not indicative of toxicity.

Furthermore, in establishing the RfD, EPA evaluated only dietary exposure; *i.e.,* oral exposure through the ingestion of contaminated fish and seafood. As demonstrated in a recent study conducted by the National Institute of Environmental Health Sciences (Harry et al., 2004), the concentration of mercury in the blood and brain following oral exposure to methylmercury is considerably higher than the concentrations resulting from intramuscular exposure to either methylmercury or thimerosal. Given this difference in absorption and distribution between oral and intramuscular exposures, it is reasonable to conclude that the RfD actually overestimates the risk potentially associated with intramuscular exposure. In other words, if an RfD were to be calculated for intramuscular exposure to methylmercury, it would likely be higher than the present RfD for dietary exposure.

In addition to the fact that the RfD was derived from data generated as a result of a route of exposure (ingestion) that was not at issue with the administration of thimerosal-containing vaccines (intramuscular), the RfD is also reflective of continuous, long-term exposure to methylmercury and essentially steady state blood concentrations. Vaccines, on the other hand, are administered approximately once every two months over a six-month period, and then again, approximately one year later. Therefore, because the ethylmercury from episodic vaccinations is rapidly eliminated, the exposure is not continuous nor is it cumulative. Thus, the cumulative dose of fetal exposure would be significantly higher than an infant's post-natal exposure due to bimonthly inoculation with thimerosal-containing vaccines. This difference in dose between cumulative, chronic exposure to methylmercury from seafood in the Faroese Cohort and the infrequent ethylmercury exposures from vaccines renders the comparison between the two situations meaningless. Clearly there is a much greater dose of methylmercury from seafood in the Faroese Cohort than there is in ethylmercury/thimerosal from the vaccination of children.

Second, even if the RfD could be viewed as a toxicity threshold for intramuscular administration of methylmercury, application of that threshold to

thimerosal/ethylmercury exposures would be valid only if the neurotoxicity of ethylmercury were quantitatively the same as that of methylmercury. It is not.

Animal studies have shown, for example, that with equivalent exposures – *i.e.,* equal doses of mercury delivered by the same route of administration – thimerosal/ethylmercury-exposed animals have less mercury in their brain than those exposed to methylmercury (Magos et al., 1985; Harry et al., 2004). It has further been demonstrated that mercury clears from both blood and brain much more quickly following intramuscular thimerosal exposure than it does following dietary methylmercury exposure (Pichichero et al., 2002; Suzuki et al., 1973; Burbacher et al., 2005). Because the neurotoxic potential of any substance will depend on how much of the substance reaches the brain in toxic form, these studies indicate that thimerosal/ethylmercury is quantitatively less neurotoxic than methylmercury.

The study by Burbacher et al. (2005) was designed to evaluate whether the RfD for methylmercury provides an accurate assessment to the risk of children from administration of thimerosal-containing vaccines. In this study, newborn macaque monkeys were administered equivalent doses of thimerosal-containing vaccines via intramuscular injection and methylmercury via dietary exposure on a schedule designed to mimic the childhood vaccination schedule. Each dose was 20 ug Hg/kg body weight, which is substantially higher than the dose administered at any point in the recommended childhood immunization schedule.[6]

Blood mercury levels were measured 2, 7, and 14 days after the initial dose; 7 and 14 days after each subsequent dose; and 28 days after administration of the last dose. Brain mercury levels were measured only during the 28-day period after administration of the last dose.

The results of this investigation demonstrate that in macaque monkeys: 1. the half life of mercury in the blood is nearly 3 times shorter following the intramuscular thimerosal exposure than it is following dietary exposure to methylmercury;[7] 2. although initial blood mercury levels were approximately the same in the two treatment groups following the first dose, mercury accumulated in blood between successive doses of methylmercury, but not between successive doses of thimerosal-containing vaccines, so that at the end of the dosing period, the thimerosal-treated group had blood mercury levels that were approximately 1/4 the level observed in the methylmercury-treated group; 3. brain levels of mercury were approximately 3 times higher following dietary methylmercury exposure, as compared to intramuscular exposure to thimerosal-containing vaccines; and 4. mercury cleared from the brain approximately 2 times faster in the thimerosal-treated monkeys.

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[6] The dose was chosen for technical experimental reasons and was not meant to reproduce the dose received by children at the time of vaccination. (Sager, oral presentation, February 9, 2004)

[7] This short blood half-life is consistent with the findings of Pichichero et al. (2002), who calculated a blood mercury half-life of approximately 7 days in infants administered thimerosal-containing vaccines. This is in contrast to the 50-70 day half-life associated with dietary exposure to methylmercury in humans.

One observation in the Burbacher et al. study emphasized by Dr. Aposhian in his report is that the rate of demethylation of mercury in the brain is faster for ethyl than for methylmercury. However, this is of no known toxicologic consequence. It is well known that all humans and animals accumulate small amounts of mercury in the brain that increase over time. This can come from multiple sources including diet, infant breast-feeding, and, because mercury is present in the air we breath, simply the act of breathing. Because of this natural mercury accumulation, organs of the body, including the brain, have multiple well-developed and highly effective protective mechanisms to detoxify and inactivate mercury, rendering it biologically innocuous. (Clarkson and Magos, 2006) It is only under circumstances of excessive exposure, where the natural detoxifying systems are overwhelmed, that adverse effects from mercury accumulation may occur. This occurs only at doses of mercury vastly exceeding those that would be associated with vaccination. For example, the cumulative dose of mercury to infants from vaccinations in approximately half as much as that received from breast-feeding. (Marques et al, 2007)

Burbacher et al. concluded, based on these differences in the pharmacokinetic properties of oral methylmercury administration and intramuscular thimerosal administration, that applying the RfD for methylmercury would overestimate the potential for toxicity following the administration of thimerosal-containing vaccines (Burbacher et al., 2005).

For all the reasons stated above, it is not scientifically valid to use the methylmercury RfD as the basis for predicting the potential neurotoxicity of the ethylmercury exposure resulting from the administration of thimerosal-containing vaccines. In fact, the demonstrated differences in the route of administration and the relative pharmacokinetic properties of the two compounds indicate that ethylmercury is a less potent neurotoxin than methylmercury; the safe intake level for ethylmercury would be expected to be higher than the current methylmercury RfD. Even if the RfD for methylmercury were applicable for thimerosal/ethylmercury, exceeding this dose, either cumulatively or on any given day, would not be considered a risk factor for any of the subtle neurological endpoints considered in the Faroe Island study and certainly not for ASD.

For all the reasons stated above, it is scientifically unreasonable to claim that thimerosal is toxic at doses that meet or exceed the RfD for methylmercury. What can be said with confidence, however, is that there is no scientific basis for the claim that thimerosal causes mercury toxicity or ASDs at the doses delivered by thimerosal-containing vaccines.

Dr. Aposhian claims in his report that the study by Hightower and Moore (2003) of individuals whose diet was such that they ate fish "almost exclusively as their protein source" and have "central nervous system complaints," found that "[a]fter six months on a seafood-free diet they returned to normal health." This is a gross mischaracterization of the Hightower and Moore study for many of reasons. First, the

study did not assess whether decreasing seafood had any effect on symptoms or any other measure of health status; it only determined serial blood mercury concentrations in these individuals. Second, the study population consisted of individuals who ate a high seafood diet and/or had a variety of symptoms, some of whom had central nervous system complaints. These patients were studied as an aggregated group and there was no attempt to segregate those with symptoms from those who were enrolled simply on the basis of eating a high seafood diet. Third, the study population had a range of diets and did not eat fish "almost exclusively as their protein source." Fourth, the subjects in this study were not put on a "seafood-free" diet. Rather, they were asked to either "stop all fish for 6 months or eat only fish known to be low in mercury."

Dr. Aposhian makes reference to yet another form of mercury in his report – dimethylmercury. Even in small doses, this is a very potent neurotoxin that has toxicological properties radically different from either methylmercury or ethylmercury (Nierenberg et al., 1996). There is incontrovertibly no similarity between poisoning by dimethylmercury and the tiny dose of thimerosal/ethylmercury in childhood vaccines. Rather, the discourse concerning dimethylmercury dramatically illustrates the potentially profound differences in the effects of even closely chemically related forms of mercury.

Dr. Aposhian also discusses mercury from dental amalgam in his report. Dental amalgam contains still another form of mercury – elemental mercury. The toxicology of elemental mercury, like that of dimethylmercury, is so different from that of ethylmercury that the discussion of this topic sheds no light on the question of the relationship, or lack thereof, of thimerosal administration and the development of ASDs. Further, Dr. Aposhian's discussion of the alleged adverse effects of dental amalgam is profoundly at variance with the conclusions of the U.S. Public Health Service, the European Commission, the Health Agencies of Canada, Quebec, and Australia, the World Health Organization, the American Dental Association, the Canadian Dental Association, and the National Multiple Sclerosis Society. It also completely ignores two recently published pivotal randomized clinical trials demonstrating the safety of amalgams (Bellinger et al., 2006; DeRouen et al., 2006).

There is reliable scientific evidence that thimerosal is not toxic to humans, including infants and children, at doses delivered either individually or cumulatively, by thimerosal-containing vaccines

As indicated above, one of the basic tenants of toxicology is that there are no such things as toxic substances – there are only toxic doses. Therefore, the fact that high dose exposure to a particular substance might lead to toxicity does not imply that toxicity will also result in doses that are substantially lower.

In Dr. Aposhian's report (p. 9), he states: "Mercury contained within the vaccines are administered as a bolus injection resulting in an exceedingly high mercury compound [sic] being injected at one time." However, Dr. Aposhian offers no reference or study

for how he defines "exceedingly high." In fact, as will be described in this section, the highest blood mercury concentration measured in term infants in two studies was 4.13 ug/L (Stajich et al., 2001; Pichichero et al., 2002). This is well within the range of blood mercury concentrations in the general population. There has never been any adverse effect associated with blood mercury concentrations in this range.

The available evidence regarding human exposures to thimerosal indicates that the doses of ethylmercury administered as a result of routine administration of thimerosal-containing vaccines are orders of magnitude less than those doses reported to be associated with neurotoxicity in either adults or children. Even under conditions where the dose is sufficient to cause neurotoxicity, the outcome is not ASD.

For example, in a study by Haeney et al. (1979), 26 patients, including young children, were treated with thimerosal-preserved immunoglobulin administered intramuscularly, typically on a weekly basis, for up to 17 years. The youngest patients had received these injections for a minimum of 6 months and up to 4 years. The amounts of thimerosal-derived mercury administered ranged from 4-734 mg (i.e., 4,000-734,000 ug) as compared to the maximum of 187.5 ug delivered by thimerosal-containing vaccines over 6 months, or 237.5 ug over 18 months. Yet, the Haeney et al. investigators reported that not one of their 26 patients exhibited clinical evidence of mercury toxicity.

The literature also contains a report of a 6-week old infant who had been administered intramuscular injections of thimerosal containing a minimum of 12,750 ug of mercury. This infant showed no signs of mercury toxicity during a two month followup period (Axton, 1972).

While there are reports in the peer-reviewed scientific literature of thimerosal-related toxicity in humans, these uniformly involved doses far in excess of those delivered by thimerosal-containing vaccines and in some, the diagnosis or implication of mercury poisoning was questionable. There has not been a single case report of even high dose methylmercury or ethylmercury exposures resulting in ASDs.

For example, there is a report in the literature of an 18-month old infant who had been administered a thimerosal solution for treatment of otitis media (Rohyans et al., 1994). Over a one month period she received 600,000 ug of mercury which, due to the way in which the thimerosal solution was administered, was ultimately swallowed. This is more than 2,500 times the maximum cumulative amount of mercury delivered by vaccines over an 18 month period and approximately 3,200 times more than the 6 month vaccination schedule. Signs of neurotoxicity quickly developed; she also developed signs of renal toxicity, which is characteristic of high dose ethylmercury exposure. Her plasma mercury concentration was 1,630 ppb (1,630 ug/L).[8] This child's whole blood mercury level would have been much greater

[8] Because ethylmercury in the body is primarily bound to hemoglobin in red blood cells, plasma mercury concentrations would be expected to be significantly lower than whole blood concentrations.

than her plasma level, yet the latter is at least 70 times higher than the highest whole blood mercury level ever observed following administration of thimerosal-containing vaccines.[9] In addition, her exposure continued over a prolonged period of time compared to that of the vaccines.

Suzuki et al. (1973) reported on a 13-year old boy with a serious condition known as protein-losing enteropathy in which plasma proteins are lost from the blood and enter the intestines and excreted. The treatment for his illness consisted of frequent plasma transfusions, often using thimerosal-preserved human plasma. During the last three months of his life, the child was administered a total of 283,500 ug mercury – over 15,000 times more than a child could receive in 6 months from thimerosal-containing vaccines. Although the authors did not contend that the boy died of mercury poisoning and did not note any signs of neurotoxicity, they did note that his blood mercury concentration 3-4 days prior to his death was 7,000 ug/L. This is nearly 300 times greater than the highest blood level observed following administration of thimerosal-containing vaccines.

One case report cited by Dr. Aposhian in his expert report involved an infant whose umbilical hernia[10] had been treated by topical application of a thimerosal tincture (Fagan et al., 1977). Although this article gives no information regarding the dose of thimerosal administered, it does report that this child's blood mercury level at the time of death[11] was 1,340 ppb (1,340 ug/L). The highest blood mercury level ever observed following the administration of thimerosal-containing vaccines is nearly 600 times lower. In addition, this infant was treated repeatedly and maintained these very high blood levels for a relatively prolonged period of time compared to the rapid fall off of blood mercury levels following the administration of a thimerosal-containing vaccine.

Another report cited by Dr. Aposhian, which like the Fagan study is a clear example of the importance of assessing dose, is the paper by Zhang (1984). This paper reported on an episode in China in which 41 people from 8 families ingested rice contaminated with high concentrations of ethylmercury in the form of a fungicide known as Cersan. Forty of the 41 improved or completely recovered despite the fact

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[9] There are two studies in infants that looked at blood mercury concentrations following administration of thimerosal-containing vaccines. The first is Stajich et al. (2000), which measured the level of mercury in blood a 5 full-term and 15 pre-term infants following administration of a birth dose of hepatitis B vaccine. The vaccine administered contained 12.5 ug of mercury. The term infants had an average post-vaccination blood mercury level of 2.24 ug/L (range: 1.4-2.9); in pre-term infants the mean blood mercury concentration was 7.36 ug/L (range: 1.3-23.6).
Pichichero et al. (2002) measured blood mercury concentrations in 2- and 6-month old infants following administration of thimerosal-containing vaccines. The highest mercury concentration in the blood of the 2-month olds was 4.13 ug/L (ppb), resulting from a cumulative mercury exposure of 37.5-63.5 ug. In 6-month olds the highest measured blood mercury concentration was 1.39 ug/L. In these children, the exposure ranged from 87.5 – 175.0 ug.

[10] This is an abnormal protrusion of internal abdominal contents into a defect in the umbilical area.

[11] Since the tincture used for treatment of the umbilical hernia may have contained up to 99.9% alcohol, the child's death cannot necessarily be attributed to mercury poisoning.

that they received estimated doses between 35,000 and 280,000 ug of ethylmercury. This corresponds to doses of mercury of approximately 30,500 to 244,000 ug. In contrast, children receiving a standard regimen of vaccination in the first 6-months of their lives receive typically less than 200 ug of mercury.

Dr. Aposhian cites a 1975 study by Koller and a 1981 study by Koller and Vos as evidence of immune dysregulation related to mercury exposure. A careful search of the National Library of Medicine database failed to identify any paper by Koller and Vos. The paper by Koller published in 1975 is a study of chronic administration of methylmercury to mice and assessed their susceptibility to two viruses: encephalomyocarditis virus and the Rauscher leukemia virus. Methylmercury, given at doses sufficient to cause mercury toxicity as seen by analysis of the kidney on autopsy, resulted in increased likelihood of mortality from the encephalomyocarditis virus but not from the Rauscher leukemia virus. This study provides little data upon which to support Dr. Aposhian's conclusion that thimerosal administration in vaccines can have any immune modulating effects. Note that this study was on **methylmercury**, not ethylmercury. It was a chronic exposure experiment as opposed to the very short-lived exposures associated with vaccines, and it administered doses that resulted in mercury toxicity. It is certainly not surprising that, in any animal, if given high enough doses of almost any chemical substance such that they are toxic from it, they may have enhanced susceptibility to infection. Dr. Aposhian also cites Petrucciori et al. (1990), which deals with mercuric chloride, and 3 studies by Shenker et al. (1992 x 2 and 1998). The Shenker studies are *in vitro* experiments with mercuric chloride and methylmercury. No conclusions can be gleaned from these studies regarding the effect of ethylmercury *in vivo.*

In footnote 2 of Dr. Aposhian's report, he cites a 1982 FDA determination that thimerosal is not safe. However, this had nothing to do with vaccines. Rather, it dealt with the direct application of thimerosal, in the form of Merthiolate, to open wounds on the skin. This determination had no relationship whatsoever to the minute doses of thimerosal that were given with vaccines.

There is no scientifically reliable evidence that exposure to thimerosal-containing vaccines can cause ASDs

As a medical toxicologist, I routinely rely on epidemiologic data to determine if there is a basis for including a particular exposure in my differential diagnosis. My review of the epidemiologic literature investigating the hypothesis that exposure to thimerosal-containing vaccines is associated with ASD has led me to conclude that there is no scientific or medical basis to conclude that thimerosal-containing vaccines are a potential cause of ASDs. In fact, there is a very impressively large body of reliable epidemiologic evidence that all indicate that there is no association between vaccination with thimerosal and ASDs (Hviid et al., 2003; Andrews et al., 2004; Heron et al., 2004; Jick et al., 2004; Verstraeten et al., 2003; Madsen et al., 2003; Stehr-Green et al., 2003). Upon review of all the then-available epidemiologic and ecologic data, both published and unpublished, the 2004 IOM Panel reached the same

conclusion, finding that "the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism." (2004 IOM Report, pp. 41-65; see also Parker et al., 2004)

I am aware of the studies by Geier and Geier (2003, 2004, and 2006) purporting to find a 2-6 fold statistically significant increase in the risk of developing autism associated with the administration of thimerosal-containing vaccines. These studies are methodologically flawed and nearly impossible to interpret and their results and reported correlation coefficients are highly implausible. In fact, such prestigious bodies as the 2004 IOM (2004 IOM Report, pp. 55-62, 65, Table 9), the American Academy of Pediatrics, the CDC, and the World Health Organization have reviewed the Geier and Geier studies and found them unconvincing and uninformative on the question of the hypothesized association between thimerosal-containing vaccines and ASDs.

THERE IS NO SCIENTIFIC EVIDENCE OF A SUB-POPULATION OF CHILDREN WHO ARE PARTICULARLY VULNERABLE TO MERCURY TOXICITY BASED ON THE INABILITY TO EXCRETE MERCURY FROM THIMEROSAL-CONTAINING VACCINES OR ANY OTHER FACTOR

There is no evidence to suggest that there is a vulnerable sub-population of children who cannot excrete mercury and thus retain and accumulate it in their tissues, including their brains

Dr. Aposhian filed several articles with his expert report that he did not cite to within the body of his report. Two of these – Bradstreet et al. (2003) and Holmes et al. (2003) – are articles that Dr. Aposhian spoke about during his presentation to the IOM in February 2004. Dr. Aposhian used those two studies to hypothesize that autism is caused by a buildup of mercury in a certain sub-population of children who cannot effectively excrete it. According to Dr. Aposhian's presentation, these studies demonstrate that autistic children do not excrete mercury effectively and thus retain more mercury in their bodies than non-autistic children, rendering them vulnerable to mercury toxicity. Such claims are scientifically untenable.

The Holmes et al. study compared first baby haircut samples from autistic children with those of non-autistic "controls." The hair samples were cut when the children were between approximately 1-2 years old. The authors claim to have found a statistically significant lower mercury concentration in the hair of autistic children, indicating a decreased ability of these children to "excrete" mercury into their hair and hypothesized that these children thus retain mercury in their tissues, including their brains. This study, however, is fraught with methodological and analytical flaws, including myriad problems with the recruitment and selection of controls. The following are a few of the more egregious problems.

In 2004, the National Center for Health Statistics of the CDC published the results of its National Health and Nutrition Examination Survey in which they assessed levels

of mercury in U.S. children and women of childbearing age (McDowell et al., 2004). This study reported that the mean mercury level in the hair of children 1-5 years old is 0.2 ppm (with a 95% confidence interval of 0.18 – 0.25 ppm); children in the 95th percentile have a hair mercury level of 0.64 ppm (with a 95% confidence interval of 0.52 – 0.76). In most children who were reported to have consumed fish or seafood 3 or more times during the preceding 30 days the mean hair mercury was 0.40 ppm (with a 95% confidence interval of 0.24 – 0.55); fish consuming children in the 95th percentile were found to have a mean hair mercury level of 2.00 ppm (with a 95% percent confidence interval of 0.39 – 3.62).

In the Holmes et al. study, the mean level of mercury in baby hair of autistic children was 0.47 ppm while that of controls was 3.63 ppm. One thing is immediately obvious from these results. The concentration of mercury in the baby hair of autistic children in this sample was exactly within the range of normal for children in the U.S. On the other hand, the "normal" controls selected to participate in the Holmes et al. study had a mean hair mercury concentration that was more than 15 times the national average and more than 10 times higher the mean observed in children with high fish consumption. These data provide no support whatsoever to the proposition that "excretion" of mercury into hair is somehow impaired in autistic children. In fact, the only thing the Holmes et al. study suggests is that there was either bias in the selection of the control population, such that subjects with unusually high hair mercury concentration were preferentially selected, or there were other methodological or analytical errors.

Moreover, the authors' suggestions that the absorbed difference between autistics and controls in terms of hair mercury concentration is inconsistent with other peer-reviewed studies that directly investigated the hypothesis of differential deposition of mercury in the hair of autistics versus controls.[12]

A study by Ip et al. (2004) evaluated hair mercury levels of autistic children and found that they were the same as non-autistic controls with similar mercury exposures. While the mean age at the time of sampling was higher in the latter study, that should have no bearing on the outcome.

Similarly, a recent study by Kern et al. (2007) assessed the concentration of several metals in the hair of children 1-6 years old with autism compared to non-autistic children. This study found that there was no statistically significant difference in the hair mercury concentrations between the two groups. The children in the Kern study were between 1-6 years of age.

[12] Another study not published in the peer-reviewed literature also finds lower hair mercury in autistics versus controls due to impaired excretion (Hu et al., 2003). However, as with the Holmes et al. study, this article demonstrates nothing more than autistic children have hair mercury levels that are precisely what would be expected in children in the U.S. And like the Holmes et al. study, the choice of both the cases and controls in Hu et al. are suspect.

If the Holmes et al. hypothesis of differential incorporation of mercury into the hair of autistics were true, then there should be a difference between autistic and non-autistic children with similar exposures at all ages. In other words, whatever metabolic or genetic factors that would make autistics different from non-autistics regarding ability to "excrete" mercury into hair would not be expected to change with age. Thus, the Holmes et al. data is not only implausible, but 2 studies now have failed to replicate it.

Another serious problem with the Holmes et al. study is that it did not evaluate anything that might actually signal a difference in the children's ability to excrete mercury. It is well established and generally accepted that the excretion of mercury following exposure to organic species such as ethylmercury or thimerosal occurs primarily in feces and, to a lesser extent, in urine. In fact, Pichichero et al. (2002) demonstrated that infants rapidly excrete mercury into stool following administration of thimerosal-containing vaccines. Hair has never been shown to be a significant route of mercury excretion. Therefore, if one were truly interested in evaluating whether autistic children have impaired ability to excrete mercury, the medium that should be tested is feces. Holmes et al. could have done this; they did not.

The analytical and methodological deficiencies discussed above are merely the tip of the iceberg. They do, however, provide ample basis for rejecting the conclusions of the authors as they are clearly scientifically invalid and insupportable.

The Bradstreet et al. (2003) study is referenced by Dr. Aposhian in tandem with the Holmes et al. study in his 2004 IOM presentation to support the proposition that impaired mercury excretion results in higher mercury retention and buildup in the tissues of vulnerable children, leading to mercury toxicity that manifests as ASDs. Like the Holmes et al. study, however, the Bradstreet et al. study fails to hold up its end of the hypothesis.

In the Bradstreet et al. study, urinary mercury excretion following chelation with succimer (DMSA) was evaluated in 221 children with ASD and unmatched controls. The authors report that the post-chelation mercury concentrations in the urine of the autistic cases was approximately 3 times higher than in controls and that the difference was statistically significant. From this and other sub-analyses, the authors conclude that "children who develop autistic spectrum disorders had significantly greater accumulated mercury than controls," and that this "probably result[ed] from a decreased ability of children with autistic spectrum disorders to excrete mercury, resulting in the retention of potentially toxic mercury levels." (Bradstreet et al., 2003, p. 78) To say that to draw such conclusions from the data presented requires a colossal leap of faith would be an understatement. As with the Holmes et al. study, the Bradstreet et al. study has so many methodological and conceptual errors that it provides no useful information whatsoever.

The first problem with jumping to the conclusions reached by Bradstreet et al. is that urinary excretion following succimer chelation is not an accurate or reliable measure of mercury body burden. This has been demonstrated in multiple studies (e.g., Archbald et al., 2004). Moreover, the authors themselves acknowledge in the article that the higher observed urinary mercury excretion in the autistic cases could merely reflect nothing more than higher current exposure to mercury,[13] rather than increased tissue retention (Bradstreet et al., 2003, p. 79). In fact, given how the controls were recruited, this is likely. The controls used in the Bradstreet et al. study were not randomly selected, but rather, were chosen from a population of children whose parents brought them to Dr. Bradstreet's clinic for elective determination of mercury levels. It is likely that the concern of these parents about potential mercury toxicity lead them to restrict the child's exposure to mercury from seafood in the first instance. This bias in the selection of controls raises serious concerns regarding the validity of the results. No effort was made by Bradstreet et al. to control for this factor.

In addition, since in the Bradstreet et al. study there were no pre-chelation levels reported, it is impossible to tell whether the DMSA had any effect whatsoever on mercury excretion. Moreover, the difference in the mean post-chelation urinary mercury excretion between the cases and controls is not dramatic. And although the authors claim that this difference is statistically significant, their statistical methodology is inadequately described and the authors clearly based their analysis on the premise that the new data is normally distributed. However, they did not demonstrate that the data was, indeed, normal. An inspection of the ranges and standard deviations on the data presented suggest a non-normal distribution. Therefore, the statistical tests used may not have been appropriate. Further, even using their described statistics and assuming a normal distribution, I could not calculate a statistically significant result from their presented data.

The Bradstreet et al. study, whether considered on its own or in conjunction with the Holmes et al. study, provides no information regarding a potential association between thimerosal-containing vaccines – or mercury in any form – and the development of ASDs. Nor do these studies support the hypothesis that children with ASD excrete mercury any differently than normal children. In fact, after considering the Holmes et al. and Bradstreet et al. studies, the 2004 IOM panel concluded they "do not provide evidence of a relationship between vaccines or thimerosal and autism." (2004 IOM Report, pp. 132-134, 140-141)

There has been no sub-population of children with increased susceptibility to mercury ever identified

Dr. Aposhian indicated in his report that Pink Disease, also known as acrodynia, indicates that some children are hypersusceptible to mercury toxicity (p. 9). Pink

[13] The investigators did not report any attempt whatsoever to evaluate either present or past level of mercury exposure in either the cases or the controls.

Disease is a rarely seen condition that was more common in the early part of the last century when children were given mercuric chloride-containing teething powders. Affected children developed this syndrome, which bore no resemblance to ASDs, and consisted of profuse sweating, swollen painful red extremities, rash, weight loss, weakness, insomnia, and photophobia. Because only a small proportion of exposed children developed acrodynia it has been hypothesized that those who got the disease may have an unusual sensitivity to mercuric chloride. However, there has never been a dose-response analysis which would be necessary before one can speculate that this is not simply a dose-related phenomena. In fact, where mercury levels have been assessed in children with acrodynia, they have been elevated, suggesting that rather than an idiosyncratic hypersusceptibility syndrome, it is likely dose related. Mercuric chloride is not thimerosal or ethylmercury. As described above, it is a different compound with very different toxicological properties. The entirety of the world's literature that I can find identifies only one case that may represent acrodynia from ethylmercury exposure. That case is markedly unusual (Matheson et al., 1980). It describes a 15-year old patient who had received multiple gamma globulin injections. Given that acrodynia is not seen with other ethylmercury exposures it is questionable whether the Matheson case actually represents acrodynia. Thus, the data cited by Dr. Aposhian does not represent any credible scientific evidence that there is a hypersusceptible population to developing acrodynia. The latter is related to a completely different form of mercury, and has nothing to do with ASDs.

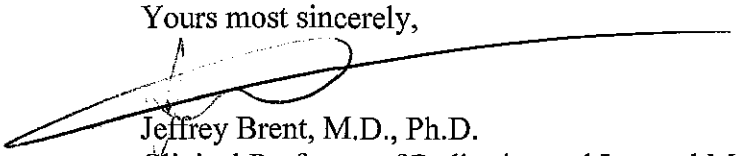
CONCLUSION

In light of the above, and based on my clinical, academic, and research practice, experience, and training, it is my opinion, to a reasonable degree of medical and scientific probability that exposure to thimerosal-containing vaccines does not cause ASDs in any identifiable population. In fact, available epidemiologic evidence from well-controlled studies, collectively and conclusively rule out a finding of an association of any kind between thimerosal administration and ASDs. In the absence of a finding of general causation – i.e., that thimerosal in the doses delivered by childhood vaccines is capable of causing ASDs – it is scientifically and medical unreasonable to conclude that thimerosal-containing vaccines administered to Michelle Cedillo played any causal role in her diagnosed autism.

It is also my opinion that, to a reasonable degree of medical and scientific probability, the dose of mercury administered to Michelle Cedillo in thimerosal-containing vaccines is very far below that which could cause mercury toxicity, and that this dose in fact did not cause mercury toxicity.

Finally, there is nothing in Michelle Cedillo's medical records to suggest that she was, or is, suffering from mercury toxicity.

Yours most sincerely,



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