In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

(E-Filed: March 12, 2010)
No. 03-215V
TO BE PUBLISHED

GEORGE and VICTORIA MEAD, Parents of WILLIAM P. MEAD,	)	Omnibus Autism Proceeding; Test Case; Petitioners' Second Theory of General Causation; Failure to Prove that Thimerosal-Containing Vaccines Cause Autism
Petitioners,	)	
v.	)	
SECRETARY OF HEALTH AND HUMAN SERVICES,	)	
Respondent.	)	

Thomas Powers, Portland, OR, for petitioners.

Lynn Ricciardella, United States Department of Justice, Washington, DC, for respondent.

DECISION[1]

[1] Vaccine Rule 18(b) provides that all of the decisions of the special masters will be made available to the public unless an issued decision contains trade secrets or commercial or financial information that is privileged or confidential, or the decision contains medical or similar information the disclosure of which clearly would constitute an unwarranted invasion of privacy. When a special master issues a decision or substantive order, the parties have 14 days within which to move for the redaction of privileged or confidential information before the document's public disclosure.

In this case, petitioners have elected to waive the 14-day period afforded for redaction requests prior to the public disclosure of an issued decision. In Petitioners' Notice to Waive the 14-Day Waiting Period as Defined in Vaccine Rule 18(b) (Petitioners' Waiver Notice), petitioners state that "none of the information they have furnished in their case is 'private' information." Petitioners' Waiver Notice at 1, filed on 1/26/10. Petitioners add that the "disclosure of any or all information they have furnished

(continued...)

CAMPBELL-SMITH, Special Master

On January 29, 2003, George and Victoria Mead (petitioners or the Meads), as parents of William P. Mead (William), filed a short-form petition[2] pursuant to the National Vaccine Injury Compensation Program[3] (the Act or the Program), 42 U.S.C. § 300aa-10, et seq. With the consent of the Meads, the Petitioners' Steering Committee

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[1](...continued)
would not be an invasion of William Mead's privacy." Id. Noting further that there is significant public interest in the OAP proceedings, petitioners recognize the likelihood "that the public will seek immediate access to the details" of the issued decision. Id. In consideration of the public interest in details of the issued decision and because the furnished information is not private, petitioners have waived the right to seek a redaction of the decision.

Respondent also has elected to waive the right, afforded under the Vaccine Rules, to seek a redaction of the issued decision. See Respondent's Consent to Disclosure at 1, filed on 1/13/10.

[2] As permitted by the Order dated July 8, 2002, petitioners electing to participate in the Omnibus Autism Proceeding (OAP) were permitted to file a short-form "opt-in" petition. See OAP Order of 7/8/02 at 1, 4. Each short form petition would consist of the name of the injured child, the names of the injured child's parents or legal representatives, and an election to opt into the OAP proceeding. Id. at 1. The petition "would not contain a detailed account of the relevant vaccinations and the vaccinee's disorder." Id. Nor would the vaccinee's medical records be required to accompany the petition. Id.

Prior to filing their vaccine claim here, the Meads had filed a civil lawsuit in Oregon state court against a number of pharmaceutical companies alleging that the thimerosal additive in many pediatric vaccines significantly contributed to the development of William's autism. See Petitioners' Post-Hearing Brief (Mead Ps' Brief) at 6. The state court determined that the Meads' thimerosal injury claim was "vaccine-related" as defined under the Vaccine Act, see 42 U.S.C. § 300aa-33(5), and thus, the Meads could not maintain their civil action against the vaccine manufacturers without first seeking a remedy under the National Vaccine Injury Compensation Program. See King v. Aventis Pasteur, Nos. 0201-00126 and 0106-05780, 2003 WL 23531954 (Or. Cir. Mar. 20, 2003) (Stipulation and Order of Dismissal). Accordingly, the state court claim was dismissed to permit the Meads to pursue this claim now before the Office of Special Masters. See id.

[3] Hereafter, for ease of reference, all "section" references to the Vaccine Injury Compensation Act will be to the pertinent subsection of 42 U.S.C. § 300aa (2006).

(PSC) designated this case on November 19, 2007, as one of the three test cases to be heard in the Omnibus Autism Proceeding (OAP) on petitioners' second theory of general causation.[4] See Docket of Omnibus Autism Proceeding (OAP Docket),[5] Order Modifying Schedule for PSC's "Second Theory" of Causation, dated November 20, 2007, at 2. The three test cases designated by the PSC for petitioners' second theory of causation proceeded "on the theory that thimerosal as contained in certain pediatric vaccines was a substantial contributing cause of neurodevelopmental injuries, including autism spectrum disorder, in certain claimants in this proceeding." See Docket of Autism Omnibus Proceeding (OAP Docket), PSC Proposal for Scheduling Additional Test Cases, dated June 25, 2007, at 1.

For the reasons discussed more fully in this decision,[6] the undersigned finds that petitioners are not entitled to Program compensation on either the proposed general theory of causation or the specific theory of causation proposed in William Mead's case.

I. Procedural Background

This case is one of three test cases heard in the OAP addressing the second general causation theory advanced by petitioners. A brief description of the OAP follows.

[4] The Meads' willingness to present their case as a test case in the OAP litigation is very much appreciated.

[5] For complete information concerning the autism proceedings including audio files and transcripts of the hearings on causation, see http://www.uscfc.uscourts.gov/omnibus-autism-proceeding (last visited 3/9/10). The OAP Docket, which includes orders, decisions, and periodic updates issued by the special masters assigned to the autism docket, is available at http://www.uscfc.uscourts.gov/node/2718. Filings by petitioners and respondent are posted on this website.

[6] For ease of reference to the various sections of this decision, the undersigned has attached an outline of the opinion at the conclusion of the decision as an appendix.

A. The Omnibus Autism Proceeding[7]

Vaccine Rule 3(b) tasks a special master with responsibility "for conducting all proceedings, including taking such evidence as may be appropriate, making the requisite findings of fact and conclusions of law, preparing a decision, and determining the amount of compensation, if any, to be awarded." Rules of the Court of Federal Claims (RCFC), Appendix (App.) B, Vaccine Rule 3(b)(1). Vaccine Rule 8(a) permits a special master, after consultation wit the parties, to "determine the format for taking evidence and hearing argument" in a proceeding. RCFC, App. B, Vaccine Rule 8(a). Additionally, the Vaccine Rules counsel that when determining how to conduct vaccine proceedings, a special master shall "endeavor[] to make the proceedings expeditious, flexible, and less adversarial, while at the same time affording each party a full and fair opportunity to present its case and creating a record sufficient to allow review of the special master's decision." RCFC, App. B, Vaccine Rule 3(b)(2).

Consistent with the duties of a special master, set forth in Vaccine Rule 3(b), for determining how to conduct Program proceedings most efficiently, the Chief Special Master issued Autism General Order #1 on July 3, 2002, outlining the procedure for handling the anticipated filing of approximately 3,000 to 5,000 petitions alleging that certain administered childhood vaccines were causing the neurodevelopmental disorder of autism or autism spectrum disorder in children. See OAP Docket, Autism General Order #1 at 1-2. The coordinated proceedings addressing the numerous filed petitions seeking compensation for the alleged vaccine-related autistic disorders are referred to as the Omnibus Autism Proceeding (OAP). The underlying purpose of the OAP has been, and continues to be, to resolve the numerous filed petitions as expeditiously as possible. The procedure adopted for addressing the filed claims resulted from a number of meetings between the Chief Special Master and an informal advisory committee comprised of various petitioners' counsel and legal and medical representatives of the Secretary of the Department of Health and Human Services.

The claims involved in the OAP were assigned initially to a single special master, Special Master George Hastings, for consideration. The adopted procedure for addressing the OAP claims anticipated the conduct of a two-phase proceeding. OAP Docket, Autism General Order #1 at 3. The first phase of the proceeding would inquire into the general causation question of whether certain vaccinations could cause autism and, if so, under what circumstances. Id. at 3-4. The second phase of the proceeding would involve applying the information acquired during the first phase of the proceeding

[7] For complete information concerning the autism proceedings, see http://www.uscfc.uscourts.gov/omnibus-autism-proceeding.

to decide the specific causation question of whether the received vaccinations did cause the autistic condition alleged in each individual case. Id. at 4.

At the request of petitioners' counsel, through the designated PSC (Petitioners' Steering Committee), petitioners were afforded a generous period of time to conduct discovery that would inform their theories concerning causation. During the afforded period of time, the PSC sought documents from various federal agencies, including the Food and Drug Administration (FDA), the Centers for Disease Control (CDC), the Agency for Toxic Substances and Disease Registry (ATSDR). See OAP Docket, Ruling Concerning Motion for Discovery from Merck re MMR Vaccine, dated July 16, 2004, at 4. Numerous documents that were responsive to the PSC's discovery request were obtained and were filed into the case of Taylor v. Secretary of Health and Human Services, No. 02-699V. Id. At the request of the PSC, respondent made officials of the FDA, CDC, and ATSDR available for deposition. Id.

After the afforded time period for discovery and as part of the first phase of the OAP proceedings, the general causation inquiry, petitioners through the designated PSC, proposed that hearings be conducted on three general causation theories. See Petitioners' Proposal Re: General Causation proceedings, dated July 18, 2006, at 2-4. The three general causation theories to be advanced by petitioners were: (1) whether thimerosal-containing vaccines and the MMR vaccine, in combination, can cause autism; (2) whether thimerosal-containing vaccines alone can cause autism; and (3) whether MMR vaccines alone can cause autism. Id. at 3. The PSC, however, refined its initial proposal and proposed conducting a hearing in a test case on the first of the three general causation theories, specifically whether thimerosal-containing vaccines and the MMR vaccine, in combination, can cause autism, in June 2007. See OAP Docket, Petitioners' Second Proposal Re: General Causation proceedings, dated January 9, 2007, at 1-2.

By Notice Regarding Reassignment dated January 11, 2007, the Chief Special Master assigned two additional special masters, specifically Special Master Denise Vowell and the undersigned, to hear and to decide the issues presented in two additional test cases on the first theory of general causation advanced by petitioners. As explained in the Notice of Reassignment, the addition of two special masters to hear test cases was for the purpose of "ensur[ing] that the Federal Circuit has the broadest perspective and clearest understanding of the issues presented to . . . and ultimately resolved by the special masters." Notice of Reassignment, dated January 11, 2007, at 2.

The same three special masters tasked with hearing the three test cases on the first theory of general causation advanced by petitioners were also tasked with hearing the three test cases on the second theory of general causation advanced by petitioners. After the hearings in the three test cases on the second theory of general causation were

conducted, however, the PSC determined that test cases on the third theory of general causation, specifically, whether the MMR vaccine contributes to the development of autism, need not be designated for hearing because the evidence pertaining to this theory was presented during the hearings of the test cases advanced on the first theory of general causation. See OAP Docket, PSC Notice Re "MMR Only" Test Cases, dated August 7, 2008; see also OAP Docket, Autism Update, dated September 29, 2008.

The OAP also contemplates that at any time, a petitioner who previously elected to opt in to the omnibus proceedings may elect to opt out. Upon making such an election, petitioner may move a claim forward by presenting evidence that supports the claim of vaccine-related causation.

The undersigned turns now to address the presentation of petitioners' theories of general causation.

B. The Presentation of Petitioners' First Theory of General Causation: Whether Thimerosal-Containing Vaccines and the MMR Vaccine, in Combination, Can Cause Autism

Each of the three special masters assigned to hear the autism cases heard one test case in which petitioners asserted the first general causation theory. During the test case proceedings on petitioners' first theory of general causation, petitioners presented evidence in support of their claim that thimerosal-containing vaccines caused immunosuppression in certain genetically predisposed children that permitted the MMR vaccine to persist in the children's gastrointestinal systems and, in turn, led to neuroinflammation in the brain that produced symptoms of autism.

Separate trials were conducted. The first test case, Cedillo v. Secretary of Health and Human Services, No. 98-916V, assigned to Special Master Hastings, was heard in Washington, D.C. on June 11-26, 2007. During this hearing, the bulk of the general causation evidence pertaining to the first theory of general causation was introduced. On February 12, 2009, Special Master Hastings issued a decision finding that petitioners had failed to establish both general and specific causation. See Cedillo v. Sec'y of Health and Human Servs., No. 98-916V, 2009 WL 331968 (Fed. Cl. Spec. Mstr.), aff'd, 89 Fed. Cl. 158 (2009), appeal docketed, No. 09-5004V (Fed. Cir. Oct. 7, 2009).

The undersigned conducted a hearing in the second test case in Charlotte, North Carolina, on October 15-18, 2007. On February 12, 2009, the undersigned issued a decision finding that petitioners had failed to establish both general and specific causation. See Hazlehurst v. Sec'y of Health and Human Servs., No. 03-654V, 2009 WL 332306 (Fed. Cl. Spec. Mstr.), aff'd, 88 Fed. Cl. 473 (2009), appeal docketed, No. 09-5128V (Fed.

Cir. Sept. 21, 2009).

The third test case, Snyder v. Secretary of Health and Human Services, No. 01-162V, assigned to Special Master Vowell, was heard in Orlando, Florida, on November 5-9, 2007. On February 12, 2009, Special Master Vowell issued a decision finding that petitioners had failed to establish both general and specific causation. See Snyder v. Sec'y of Health and Human Servs., No. 01-162V, 2009 WL 332044 (Fed. Cl. Spec. Mstr.), aff'd, 88 Fed. Cl. 706 (2009). This case was not appealed to the Federal Circuit.

C. The Presentation of Petitioners' Second Theory of General Causation: Whether Thimerosal-Containing Vaccines Alone Can Cause Autism

Each of the three special masters assigned to hear the autism cases has one test case in which petitioners have asserted the second general causation theory. Assigned to the undersigned for hearing and decision is the instant case, Mead v. Secretary of Health and Human Services, No. 03-215V. Assigned to Special Master Hastings for hearing and decision is the case of King v. Secretary of Health and Human Services, No. 03-584V, and assigned to Special Master Vowell for hearing and decision is the case of Dwyer v. Secretary of Health and Human Services, No. 03-1202V.

During a hearing conducted in Washington, D.C., on May 12-30, 2008, the parties presented general causation evidence on the second theory of causation and presented specific causation evidence in the King and Mead cases regarding whether the administered vaccines had caused the autistic condition of the vaccinated children whose particular cases were being heard.[8] During another hearing conducted in Washington, D.C., on July 21-22, 2008, the parties presented more general causation evidence and specific causation evidence in the Dwyer case. Having heard all of the general causation evidence presented during the May and July 2008 hearings and having heard the specific causation evidence pertaining to William Mead during the May 2008 hearing, the undersigned now bears the sole responsibility for deciding this particular test case. Similarly, Special Masters Hastings and Vowell will individually decide their respectively assigned test cases.

In each of the three test cases, the parties have filed hundreds of medical and scientific articles. Additionally, the parties have presented the written opinions of numerous experts in the three test cases. Many of the experts who submitted written opinions also testified during the hearings. To ensure that the record in each test case includes the most comprehensive evidence, each special master has filed into the record of her or his particular test case, with the permission of the parties, the medical and scientific

[8] The King and Mead cases were tried concurrently.

literature, the general causation expert opinions, and the corrected hearing transcripts[9] from the concurrent King/Mead hearing and from the Dwyer hearing. These filings also inform the independent decisions of the special masters with respect to the specific causation issues presented in each of the three test cases on petitioners' second theory of causation. Moreover, the general causation evidence developed in these three test cases is expected to be helpful in resolving the other autism cases awaiting decision.

The Meads believe that thimerosal-containing vaccines caused William's regressive autism. As explained below, the undersigned finds that the Meads have not presented a scientifically sound theory.

Before addressing the case at hand, the undersigned again thanks the Meads for consenting to have this case heard as a test case in the OAP. The undersigned is mindful that while the Meads have agreed to have their case designated as a test case, the Meads have pursued this vaccine claim on behalf of their son William. The undersigned is further mindful that William's autistic condition has had a profound impact on the Meads and that the Meads, as caring and committed parents–like others who have filed suit on behalf of their children–desire to understand what caused their child to develop an autistic spectrum disorder. This decision does not and cannot offer a determinative explanation. Rather, the task set before the undersigned is to evaluate the presented theory that purports to explain why William developed autism. It is imperative, for William and for all the other families involved in the OAP, that the undersigned analyze this specific theory in great detail. Such analysis compels an extensive discussion of clinical and scientific matters. In the scientific discussion that follows, there may be an appearance of detachment from the highly personal specifics of William's medical history. But that is not the case. While analyzing the wealth of evidence presented, the undersigned has remained mindful that this vaccine claim is a personal one, and the undersigned will address the particulars of William's case after the foundational analysis has been completed.

D. The Record in this Case

The record in this case is comprised of all of the medical records, expert opinions, and referenced literature filed in this case pertaining specifically to William Mead.

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[9] To address the problems with the original transcripts that the parties identified, a procedure to correct the many substantive errors in the transcripts was developed and applied to the three weeks of transcript testimony from the two hearings (specifically, the concurrently heard King and Mead cases and the subsequently heard Dwyer case). Final corrected versions of the transcripts are now filed into the record of this case, and citations for hearing testimony in this decision are to the final corrected version of the transcripts.

Additionally, as stated earlier, the Meads have designated for consideration in this case the general causation evidence introduced in the two other test cases King and Dwyer. See Mead Ps' Brief at 14. Most of the general causation evidence heard on petitioners' second theory was introduced during the concurrently tried King and Mead cases over a period of 14 days, and one transcript was prepared for the simultaneously conducted trials in the King and Mead cases (referred to herein as the Mead transcript). By Order dated October 8, 2009, one CD containing the general causation evidence introduced in the Dwyer case, specifically containing the final corrected transcripts of two days of hearing testimony, the trial exhibits, expert reports, and the curricula vitae of the experts, was filed into this case as well. See Order dated October 8, 2009**.**

Twenty experts filed reports that were considered in this case. More than 1200 exhibits that included medical literature also were filed into the record. This number of exhibits includes the 761 exhibits filed by petitioners, identified by name and designated by sequential number on Petitioners' Master Reference List (PMRL),[10] and the 523 exhibits filed by respondent, identified by name and designated by sequential number on Respondent's Master Reference List (RMRL).[11] Citations to an exhibit first identify the proper reference list, either PMRL or RMRL, and then the corresponding number of the exhibit on the reference list. The specific page references are to the page numbers in the published manuscript and not to the page numbers given to the document when it was designated as a trial exhibit. Exhibits filed at trial by the parties are not included in these numbers and are referenced in this decision by the trial exhibit numbers assigned during trial.

E. The Testifying Experts

In support of their theory that thimerosal-containing vaccines can cause and, in this case, did cause autism, petitioners offered the opinions of five testifying expert witnesses, four of whom offered testimony in support of petitioner's general causation theory. The fifth witness provided testimony about specific causation in each individual case.

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[10] Although petitioners identified 761 exhibits on the PMRL, they did not file five of the referenced articles, specifically PMRL 666-670. Moreover, some of the filings that are identified on the PMRL are not medical literature.

[11] Although respondent filed 523 exhibits, respondent failed to update the RMRL to reflect the filing of the last exhibit, RMRL 523. Respondent also filed medical literature with exhibit letter designations. See, e.g., Exhibit QQ, RR, SS, and TT filed on 5/27/2009.

In refutation of petitioners' theory, respondent offered the opinions of 13 testifying expert witnesses. Respondent filed expert reports from three additional witnesses who did not testify during hearings. These experts included: (1) Manuel Casanova, M.D., a neurologist; (2) Thomas W. Clarkson, M.D., Ph.D., a toxicologist; and (3) Laszlo Magos, M.D., a toxicologist.[12] For ease of reference later in the opinion, the undersigned addresses here the qualifications of the experts[13] and her impressions of the experts as witnesses.

Petitioners' experts included: (1) H. Vasken Aposhian, Ph.D., a toxicologist; (2) Richard C. Deth, a pharmacologist; (3) Sander Greenland, an epidemiologist; (4) Elizabeth A. Mumper, M.D., a pediatrician; and (5) Marcel Kinsbourne, M.D., a pediatric neurologist. The qualifications of the experts are addressed in turn.

1. Petitioners' Testifying Experts

Dr. Aposhian is a Professor of Molecular and Cellular Biology at the University of Arizona in Phoenix, and a Professor of Pharmacology at the College of Medicine,

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[12] Dr. Casanova is a Professor in the Department of Psychiatry and Behavioral Sciences at the University of Louisville. Mead Respondent's Exhibit (Mead R's Ex.) J at 1. He is board-certified in neurology, a reviewer for more than 20 journals, and a member of several professional organizations. Id. at 5, 7-9. He has numerous publications detailing his findings with respect to minicolumnar formation in the brains of individuals with autism. See id. at 20-39; see also RMRL 61-67.

Respondent also provided expert reports from Drs. Clarkson and Magos on the general issue of causation. Drs. Clarkson and Magos were unable to testify during the May 2008 hearing. After the conclusion of that hearing, respondent evaluated the evidence that had been presented and determined that the testimony of Drs. Clarkson and Magos was not necessary. Respondent informed the special masters of her determination. Respondent further determined that the reports filed by Drs. Clarkson and Magos were not necessary for respondent's defense of the case, and withdrew their reports.

The undersigned has reviewed and considered the filed report from Dr. Casanova and finds that his opinion lends support to the conclusions reached in this decision. In reaching the conclusions set forth here, however, the undersigned relies more heavily on the testimony and reports of the experts who were observed and heard during the hearings.

[13] The qualifications of the experts that were set forth in the curricula vitae of the experts and during the experts' trial testimony were summarized ably in the parties' post-hearing briefs.

University of Arizona. PMRL 710 at 1 (Dr. Aposhian's curriculum vitae). With expertise in metals toxicology and mercury toxicology, he has conducted research and taught within his field for more than 30 years. In addition, he has written and edited book chapters and published dozens of articles in peer-reviewed journals. Id. Having acknowledged that he is not qualified to diagnose mercury toxicity and that he has not published any peer-reviewed articles on thimerosal toxicity, ethyl mercury toxicity, or the impact of mercury on the immune system, see Transcript of Mead Hearing (Mead Tr.) at 247-248, Dr. Aposhian testified about the toxicology of mercury and thimerosal-containing vaccines. See Mead Ps' Brief at 15. He specifically addressed how thimerosal-containing vaccines deposit mercury in the brain and how the deposited mercury contributes to neuroinflammation in the brain. Id. at 15-16. The undersigned found that the reliability and, thus, the persuasiveness of Dr. Aposhian's testimony were compromised considerably by his repeated reliance on the limited, favorable aspects of the articles he cited while ignoring the broader, unfavorable aspects of the reported scientific findings.

Dr. Deth is a Professor of Pharmacology at Northeastern University. PMRL 712 at 1. For more than 32 years, he has taught and conducted research at the university where he maintains a research laboratory. PMRL 712 at 1. Among his approximately 60 publications are articles. Id. at 4-8. Since approximately 1998, the major focus of his work has been the biochemistry of autism. See id. at 3-4; Mead Ps' Brief at 16. His research interest in mercury began in either 2002 or 2003. Mead Tr. at 599. He testified about the cellular biochemistry of mercury in the brain. He specifically addressed the oxidative environment created by mercury in the brain, the damaging effects of oxidative stress in the brain, and the subcellular effects of mercury on brain function. See Mead Ps' Brief at 16. Dr. Deth testified earnestly, and he responded to pointed questioning at hearing by acknowledging the limitations of the theory he presented. The undersigned found that the particular limitations that Dr. Deth recognized in his own testimony significantly diminished the weight that could be accorded to the theory he presented.

Dr. Kinsbourne is a pediatric neurologist who conducted research and treated patients for more than 30 years and has authored or coauthored more than 400 medical and scientific articles. PMRL 716 at 1-3. He is currently a Professor of Psychology at the New School University in New York and a Research Professor at Tufts University in Boston. Id. at 2. He testified about the neurological consequences of mercury-induced neuroinflammation and identified inflammation induced by thimerosal-containing vaccines as a potential environmental factor contributing to the development of regressive autism. See Mead Ps' Brief at 16. He also testified about regressive autism and the interplay between genetics and environmental factors in causing autism. Id. Dr. Kinsbourne carefully limited the scope of his testimony by explaining that he was simply identifying a general mechanism by which mercury could be a potential cause of neuroinflammation and, thus, could be included on a differential diagnosis list as a

possible cause of regressive autism. See Mead Tr. at 778-781. His acknowledgment of the limitations of his testimony assisted in exposing critical vulnerabilities in the theory of causation that petitioners put forth.

Dr. Greenland is a Professor of Epidemiology at the University of California at Los Angeles (UCLA) School of Public Health, and a professor of statistics at the UCLA College of Letters and Science. PMRL 714 at 1. With more than 500 publications to his credit that include articles in peer-reviewed journals, letters, abstracts, book chapters, and encyclopedia entries, Dr. Greenland is a co-author of the leading text on epidemiology and statistical methodology in the United States. Mead P's Brief at 16. He testified about the limits of the available epidemiology in assessing any association between thimerosal-containing vaccines and regressive autism. See id. He testified carefully and made plain the limits of his opinion.

Dr. Mumper is a pediatrician with 25 years of experience in private practice. PMRL 718. She is also the Medical Director and Director of Physician Training for the Autism Research Institute, the parent organization of Defeat Autism Now! Id. at 2; see Mead Tr. at 1192, 1197. Her specialty is the care and treatment of children with autism spectrum disorders and other developmental disorders. Mead Ps' Brief at 16. She testified about the differential diagnosis she conducted for William Mead in order to conclude that neuroinflammation induced by thimerosal-containing vaccines was a substantial cause of his autistic regression. See id. Dr. Mumper's discussion and interpretation of William's laboratory test results assisted in disclosing the flaws underlying petitioners' proposed theory of vaccine-related causation.

2. Respondent's Testifying Experts

Respondent's testifying experts included: (1) Jeffrey Brent, M.D., Ph.D., a medical toxicologist; (2) Eric Fombonne, M.D., a pediatric psychiatrist; (3) Steven Goodman, M.D., M.H.S., Ph.D., a biostatistician and an epidemiologist; (4) Jeffrey Johnson, Ph.D., a neurotoxicologist; (5) Dean Jones, Ph.D., a biochemist; (6) Thomas Kemper, M.D., a neuropathologist; (7) Bennett Leventhal, M.D., a pediatric psychiatrist; (8) Catherine Lord, Ph.D., a clinical pediatric psychologist; (9) Richard Mailman, Ph.D., a neuropharmacologist; (10) L. Jackson Roberts, II, M.D., a pharmacologist; (11) Patricia Rodier, Ph.D., a teratologist;[14] (12) Robert Rust, Jr., M.D., a pediatric neurologist; and (13) Sir Michael Rutter, M.D., Ph.D., a pediatric psychiatrist. The experts' qualifications are addressed in turn.

[14] Teratologists specialize in examining toxicological effects on developing animals or humans. See Mead Tr. at 2911-2912.

Dr. Brent is a physician and Clinical Professor of Pediatrics and Internal Medicine at the University of Colorado Health Science Center. Mead R's Ex. H at 1. Holding a sub-specialty board certification in medical toxicology, he is one of 350 board-certified medical toxicologists in the United States. Mead Tr. at 1781, 1797. In addition to his teaching duties, Dr. Brent has a private clinical toxicology practice, which includes the diagnosis and treatment of mercury toxicity. Id. at 1792. He has consulted with government and international agencies, including the U.S. Centers for Disease Control and Prevention, and the World Health Organization. Mead R's Ex. H at 21-22; Mead Tr. at 1784. Dr. Brent is a reviewer for several acclaimed journals, including The New England Journal of Medicine, Clinical Toxicology, and Journal of the American Medical Association. Mead Tr. at 1786. He has authored more than 200 scientific publications and is the recipient of numerous awards for outstanding accomplishment in the field of medical toxicology. Id. at 1783, 1787. Dr. Brent testified cogently and knowledgeably. He capably communicated how the different toxicological principles addressed in this case fit together and, thus, provided an important perspective.

Dr. Fombonne is a Professor of Psychiatry and the Head of the Division of Child Psychiatry at McGill University, in Montreal, Canada. Mead R's Ex. N at 1; Mead Tr. at 3607, 3614. Having worked extensively in the area of childhood pervasive developmental disorders and autism for the last 23 years, he also heads the Department of Psychiatry at Montreal Children's Hospital and is the director of the hospital's Autism Clinic. Mead Tr. at 3614. In addition to his teaching and research responsibilities, he has an active clinical practice. Id. at 3619. Dr. Fombonne diagnoses and treats children with autism and saw between 250 to 300 children in 2007-08. Id. at 3619. Dr. Fombonne is also a trained epidemiologist and has conducted approximately 10 epidemiologic studies of autism. Mead R's Ex. N; Mead Tr. at 3621. He has published more than 160 articles related to childhood developmental disorders and 34 book chapters, is a frequent reviewer for numerous journals, and serves on the editorial board of several journals. Mead Tr. at 3621-3623. Dr. Fombonne has been asked by the American Psychiatric Association to write the chapter on the epidemiology of autism in its upcoming textbook. Id. at 3624. His testimony was well-informed and helpful.

Dr. Goodman is a Professor of Oncology, Epidemiology, Biostatistics, and Pediatrics at the Johns Hopkins School of Medicine. Mead Tr. at 3065. He is board-certified in pediatrics, has a Master's degree in biostatistics, and a Ph.D. in epidemiology. Id. at 3065-3066. He now focuses exclusively on epidemiology and is the director of the division of biostatistics in the Department of Oncology at Johns Hopkins University, where he collaborates with researchers throughout the medical school on large-scale epidemiologic studies. Id. at 3066, 3069. Dr. Goodman has published more than 100 peer-reviewed articles on epidemiology, authored six book chapters on the subject, and wrote the lead chapter in the 2004 Surgeon General's Report on Smoking. Id. at

3069-3071. He is the senior statistical editor for the Annals of Internal Medicine, one of the world's leading medical journals; the editor-in-chief of Clinical Trials; and a frequent reviewer for several other journals. Id. at 3071. Dr. Goodman has served on numerous committees of the Institute of Medicine ("IOM"), and was selected to serve on the prestigious, 13-member panel comprising the IOM's Immunization Safety Review Committee. Id. at 3072-3077. His testimony was careful, clear, and instructive.

Dr. Johnson is a Professor of Pharmaceutical Sciences at the University of Wisconsin, and the Director of the Pharmacy and Toxicology Bachelor of Science Program. Mead Tr. at 2198; Mead R's Ex. Q at 1. The primary focus of his research is on neurodegenerative diseases with a specific interest in the prevention of cell loss and neuronal death in these diseases. Mead Tr. at 2199. Research from his laboratory has been published in numerous peer-reviewed journals. Id.; see also Mead R's Ex. R at 6-9. Dr. Johnson served on a National Institutes of Health ("NIH") Study Section for five years, and is a frequent reviewer for numerous journals. Mead Tr. at 2200, 2202-2203. An expert in neurotoxicology, see Mead Tr. at 4314, Dr. Johnson testified knowledgeably. His testimony concerning the effects of chronic cell dysfunction helpfully called attention to the implausibility of that aspect of petitioners' proposed biological mechanism of harm.

Dr. Jones is a Professor of Medicine at Emory University and the Director of the Clinical Biomarker Laboratory. Mead Tr. at 2692, 2695. His laboratory specializes in the measurement of oxidative stress markers, inflammatory markers, and cytokine measurements. Id. at 2695. Of his more than 325 peer-reviewed publications, more than 100 have involved original research on oxidative stress. Id. at 2696-2697. Dr. Jones has recently received several major grants to examine oxidative stress mechanisms. Id. at 2695. He has chaired an NIH Study Section, and is a regular manuscript reviewer for several journals, including Science, Nature, and Toxicology. Id. at 2694. Dr. Jones testified knowledgeably and understandably. He identified a number of key departures from scientifically sound principles in the causation theory presented by Dr. Deth.

Dr. Kemper is a Professor in the Departments of Anatomy and Neurobiology, Neurology, and Pathology at Boston University School of Medicine. Mead Tr. at 2793-2794. In more than 30 years of professional experience, Dr. Kemper has published 170 articles, of which 30 are specifically related to autism. Id. at 2795. He has dedicated a substantial portion of his professional career to studying the neuropathogenesis of autism, specifically focused on the structural presentation of the disease in the brain.[15] Id. at 2797, 2799. He and his colleague, Margaret Bauman, M.D., were pioneers in autism research,

[15] Dr. Kemper defined neuropathology as the study of the diseased brain, nerves, and muscles. Mead Tr. at 2796; see also Dorland's at 1174 (defining neuropathology as the branch of medicine that deals with the morphological (structural) features as well as other aspects of disease of the nervous system).

publishing their first article in 1985. Id. at 2798. Dr. Kemper has also been a frequent reviewer for multiple, reputable journals. Id. at 2795. His testimony was well-informed, amply supported by the scientific literature, and helpful.

Dr. Leventhal is a Professor of Psychiatry and the director of the Center for Child Mental Health and Developmental Neuroscience Institute for Juvenile Research at the University of Illinois College of Medicine in Chicago, Illinois.[16] See Transcript of Dwyer hearing (Dwyer Tr.) at 206; Dwyer R's Ex. CC. Over the course of his 30-year career, Dr. Leventhal has diagnosed thousands of children with autism spectrum disorders and currently sees between 50 to 200 new cases a year. Dwyer Tr. at 212-213. In addition to his teaching and clinical duties, Dr. Leventhal has a large and active research practice. Id. at 216. His center is currently one of five "Centers of Excellence" selected by NIH to receive large grants to research autism. Id. at 216-217. Dr. Leventhal is also one of the co-authors of the Autism Diagnostic Observation Schedule ("ADOS"). Id. at 217. He has published more than 120 peer-reviewed articles on child psychiatry and ASDs, serves on the Panel of Professional Advisors to the Autism Society of America, and is a reviewer for numerous journals, such as The New England Journal of Medicine, Journal of the American Medical Association, Pediatrics, and the American Journal of Psychiatry. Id. at 219-220. Dr. Leventhal's testimony was considered and direct.

Dr. Lord is a Professor of Psychology, Psychiatry, and Pediatrics at the University of Michigan, and director of the Autism and Communication Disorders Center there. Mead R's Ex. W at 1; Mead Tr. at 3535; see also Mead R's Ex. X. Dr. Lord has dedicated her more than 30-year career to the research, diagnosis, and treatment of autism. See generally Mead R's Ex. X at 1-2. She has co-authored standardized instruments used to diagnose autism, including the Autism Diagnostic Interview – Revised (ADI-R), and the ADOS, which "have become the gold standard[s] for autism research." Mead R's Ex. W at 2; Mead Tr. at 3548-3551. She is on the planning committee for autism and related diagnoses for the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders ("DSM"), and was on the corresponding panel for the DSM-IV.[17] Mead Tr. at 3538-3539. Dr. Lord has diagnosed thousands of children with autism, and she currently follows and treats children, adolescents, and adults with the disorder as part of her clinical and research practices. Id. at 3542-3543. She serves on the editorial boards of six child psychology and autism-related journals. Id. at 3553. She has published more than 125 peer-reviewed articles, 61 chapters, and nine books, the majority

[16] Dr. Leventhal submitted an expert report and testified for respondent in the Dwyer case.

[17] Am. Psychiatric Ass'n, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (1994).

of which pertain to ASDs, and many to regression in autism, in particular. Id. at 3552-3554. At hearing, Dr. Lord testified knowledgeably and persuasively.

Dr. Mailman is a distinguished neuropharmacologist with advanced training in the fields of physiology, toxicology, and neurobiology. Mead R's Ex. AA at 1; R's Ex. BB at 1; see also Mead Tr. at 1975-77. At the time of the May 2008 hearing, Dr. Mailman was a Professor in the Departments of Psychiatry, Pharmacology, Neurology, and Medicinal Chemistry at the University of North Carolina School of Medicine.[18] Mead R's Ex. AA at 1; R's Ex. BB at 2; Mead Tr. at 1975. He is on the editorial boards of numerous scientific journals, and has received multiple awards for his scientific contributions, including the Burroughs-Wellcome Scholar in Toxicology Award from the Society of Toxicology. Mead R's Ex. AA at 1-2; R's Ex. BB at 2-3. His research "interest is in the structure, function and signa[l]ing of dopamine receptors," and he has published extensively on the subject of dopamine receptors. Mead Tr. at 1976-1977. Dopamine is one of the neurotransmitters that petitioners' pharmacologist, Dr. Deth, discussed as part of his theory of causation. Dr. Mailman testified plainly and informatively.

Dr. Roberts is a Professor of Pharmacology and Medicine at Vanderbilt University, where he holds an endowed chair. Mead Tr. at 2155. He completed a fellowship in clinical pharmacology after he received board certification in internal medicine. Id. at 2154. Since 1990, nearly all of his publications have been about oxidative stress, and of his more than 340 articles in peer-reviewed journals, abstracts, and book chapters, approximately 180 are in this specific subject area. Id. at 2160. He receives funding from multiple grants to research oxidative stress, and holds several patents related to oxidative stress or oxidative injury. Id. at 2158-2160; Mead Respondent's Trial Exhibit (Mead R's Trial Ex.) 6 at 2-3. Dr. Roberts is the Associate Editor of the journal of Free Radical Biology in Medicine. Mead Tr. at 2157-2158. His area of expertise is oxidative stress and oxidative damage as it relates to various diseases. Id. at 2166. The inducement of oxidative stress is an important component of the opinions of vaccine-related causation that petitioners' experts, Drs. Deth and Kinsbourne, presented. Dr. Roberts testified very knowledgeably.

Dr. Rodier is a Professor of Obstetrics and Gynecology at the University of Rochester. Mead Tr. at 2911. She received her doctoral degree in experimental psychology, and has spent most of her professional career researching issues related to the development of the nervous system. Id. at 2911-2912. As a result of her research interest in how disturbances to the nervous system can lead to "aberrant behavior," she has developed particular knowledge regarding "what difference it makes when an injury

[18] Dr. Mailman has since become a Professor and Distinguished Senior Scholar in Pharmacology and Neurology at Pennsylvania State University College of Medicine.

occurs at one time versus another in development." Id. at 2912-2913. She has published extensively and is a reviewer for numerous journals. Id. at 2913-2914. She is the only expert in this case who has research experience with both autism and mercury toxicity. Id. at 2914-2919. Dr. Rodier was well-informed by her own research experiences and the body of relevant scientific literature. Her testimony was careful, focused, and understandable.

Dr. Rust is a Professor of Epileptology, Neurology, and Pediatrics at the University of Virginia School of Medicine, where he is also the co-director of the Epilepsy and Child Neurology Clinic. Mead R's Ex. JJ; Mead Tr. at 2351. Dr. Rust is board-certified in pediatrics and neurology, with special qualifications in child neurology. Mead R's Ex. JJ at 2; Mead Tr. at 2352. He has served on the editorial boards of several journals, including the Journal of Child Neurology and Pediatric Neurology, and has been a reviewer on an additional 17 journals. Mead R's Ex. JJ at 9-10. He has authored or co-authored approximately 50 peer-reviewed published articles, and written approximately 50 book chapters and reviews. Id. at 30-38. Dr. Rust has diagnosed and treated many hundreds of children with autism. Mead Tr. at 2355. In 2007, Dr. Rust received an award from the Child Neurology Society that recognized him as the person who has made the most distinguished contribution to child neurology. Mead R's Ex. JJ at 5. A seasoned and knowledgeable clinician and researcher, Dr. Rust's testimony was insightful.

Dr. Rutter is a Professor of Developmental Psychopathology at the Institute of Psychiatry, Kings College, London. Mead Tr. at 3236. Dr. Rutter is a world-renowned authority in child psychiatry, and, particularly, in ASDs. In 1992, the United Kingdom honored him as a Knight Baronet for his extraordinary research and teaching contributions in the field of child psychiatry.[19] Id. at 3248-3249; see also Mead R's Ex. HH. He has more than 50 years of clinical and teaching experience, and is board-certified in psychiatry and internal medicine with additional training in neuroanatomy and neuropsychology. Mead Tr. at 3237-3238, 3246-3247. Since 1966, Dr. Rutter has held a consultant appointment in the National Health Service in Great Britain, and, in 1984, he established the Medical Research Council Child Psychiatry Unit.[20] Id. at 3239. Dr. Rutter's pioneering research spans many decades and categories. He is the clinical Vice President of the Academy of Medical Sciences, co-author of the ADI-R and ADOS, and

[19] Dr. Rutter has also earned numerous international honors. For example, he was elected to the British Royal Society and the Institute of Medicine, and he received the Helmut Horten Prize (an award regarded as "one of the big prizes in medicine") for his work on autism. Mead Tr. at 3248.

[20] The Medical Research Council is equivalent to the NIH in the United States. Mead Tr. at 3239.

one who helped to formulate the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the International Classification of Diseases (ICD-10). Id. at 3240, 3242. Dr. Rutter conducted the first systematic psychiatric epidemiologic study in childhood, examining mental disorders, undertook the first epidemiologic study to analyze interconnections between neurological disorders and psychopathology, and researched the potential contribution of toxins to mental disorders. Id. at 3240-3241; Mead R's Ex. GG (Introduction) at i-ii. He has further investigated the genetics of mental disorders, specifically the interplay between genetic and environmental factors, and is involved with molecular genetic studies of autism. Mead Tr. at 3244-3245. Dr. Rutter has published 400 peer-reviewed articles, 200 book chapters, and more than 40 books, the majority of which pertain to ASDs. Id. at 3245-3246. He has served on the editorial boards for numerous scientific journals, including The Journal of Child Psychology and Psychiatry and Allied Disciplines and Autism. Id. at 3246. Dr. Rutter carefully limited the scope of his testimony to those areas in which his significant and internationally-renowned expertise lies. He testified clearly, knowledgeably, and persuasively.

The undersigned observes that while petitioners' experts were qualified, they lacked the specialized qualifications that distinguished respondent's experts. The focus of the extensive research conducted by respondent's witnesses coupled with the significant clinical experiences of respondent's witnesses provided well-informed guidance concerning the various aspects of petitioners' theory of vaccine-related causation. The testimony of respondent's witnesses made clear that petitioners' presented theory of causation was biologically implausible and scientifically unsupported. Petitioners' experts openly conceded the limitations of their expertise during cross-examination, and the testimony given by petitioners' experts showed both internal inconsistencies and notable external inconsistencies with established scientific principles. These inconsistencies in the testimony of petitioners' experts–that were exposed, in part, through the testimony of respondent's experts–diminished the persuasiveness of the opinions that petitioners' experts offered, and, in the view of the undersigned, called into question the soundness of the positions that they offered.

F. The Parties' Post-Hearing Briefing

The parties have submitted post-hearing briefing in each of the test cases addressing both the general and specific causation evidence presented during the hearings conducted for the three test cases.[21] This case is now ripe for decision.

[21] After the conclusion of the hearing in the Dwyer case on July 22, 2008, the parties filed supplemental expert reports. On July 28, 2008, petitioners provided a supplemental report from Dr. Aposhian. In response, respondent submitted an additional report from Dr. Brent on October 7, 2008. The last post-hearing brief was filed on July 2, (continued...)

II. The Applicable Legal Standards

A. Proving a Vaccine Claim

In determining whether petitioners are entitled to compensation under the Vaccine Program, special masters must consider, "as a whole," the record "established . . . in a proceeding on a petition." 42 U.S.C. § 300aa-13(a)(1), 13(c). The Vaccine Act prohibits a special master from making a finding of entitlement to compensation based on the "unsubstantiated" claims of petitioners. See 42 U.S.C. § 300aa-13(a)(1). Petitioners' claims must be supported by the filed medical records or by the offered medical opinions. See id.

There are two methods of establishing entitlement to compensation under the Vaccine Act. Petitioners may show that the vaccinee received a vaccine listed on the Vaccine Injury Table, that the vaccinee suffered an injury listed on the Vaccine Injury Table, and that the injury occurred within the prescribed time period on the Vaccine Injury Table.[22] 42 U.S.C. § 300aa-14(a) (initial Table); 42 C.F.R. § 100.3 (updated Table). Petitioners seeking to establish entitlement by this method assert what is commonly referred to as a "Table" claim in the Vaccine Program. See 42 U.S.C. § 300aa-14(a). A rebuttable presumption of causation attaches when petitioners establish a Table claim. Id.

If, however, the vaccinee suffered an injury that is not listed on the Vaccine Injury Table or suffered an injury that did not occur within the prescribed time period on the Table, petitioners may assert a claim that the administered vaccine "caused" or "significantly aggravated" the vaccinee's injury or condition. 42 U.S.C. § 300aa-11(c)(1)(C)(ii)(I). Petitioners seeking to establish entitlement by this method assert what is commonly referred to as an "off-Table" claim in the Vaccine Program. See id. No presumption of causation attaches when petitioners assert an off-Table claim.

Petitioners' burden of proof is the same for both methods of establishing entitlement to compensation under the Vaccine Program. In both instances, petitioners bear the burden of proving their claim by a preponderance of the evidence. 42 U.S.C. §

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[21](...continued)
2009. By Order dated July 27, 2009, the undersigned closed the evidentiary record in this case.

[22] Additionally under the Act, petitioners must establish that the vaccine was administered in the United States (or meets a narrow list of exceptions) and that the claimed condition has persisted for at least six months, with an exception not pertinent here for surgery. See 42 U.S.C. § 300aa-11(c)(1)(B). There is no dispute in this case that petitioners' claim satisfies these requirements.

300aa-13(a)(1)(A). That burden of proof is assisted in Table cases by a rebuttable presumption of causation. In off-Table cases, petitioners satisfy this evidentiary standard by demonstrating that the vaccine in question more likely than not caused the vaccinee's injury. See In re Winship, 397 U.S. 358, 371-372 (1970) (Harlan, J., concurring) (The fact finder must "believe that the existence of a fact is more probable than its nonexistence before [she] may find in favor of the party who has the burden to persuade the [factfinder] of the fact's existence.") (internal quotation and citation omitted); see also Althen v. Sec'y of Health and Human Servs., 418 F.3d 1274, 1279 (Fed. Cir. 2005) (The Federal Circuit "has interpreted the 'preponderance of the evidence' standard referred to in the Vaccine Act as one of proof by a simple preponderance, of 'more probable than not' causation.") (internal citation omitted). Offered opinions that reflect mere conjecture or speculation do not satisfy the preponderance standard. See Moberly v. Sec'y of Health and Human Servs., 592 F.3d 1315, 1322 (Fed. Cir. 2010) (stating that the "more likely than not" standard is not satisfied by proof of a "plausible" or "possible" causal link between the vaccine and the injury, but requires proof that meets the traditional tort standard of "preponderant evidence"); Doe v. Sec'y of Health and Human Servs., 19 Cl. Ct. 439, 450 (1990) (stating "an assertion that something is 'highly possible' does not rise to the level necessary to establish causation by a preponderance of the evidence").

Petitioners are not required to present particular types of evidence, such as "epidemiologic studies, [evidence of] rechallenge, the presence of pathological markers or [a] genetic disposition, or general acceptance in the scientific or medical communities" because "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." Capizzano v. Sec'y of Health and Human Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006) (emphasis omitted). Nor must petitioners file medical literature in support of their theory. Id. But if petitioners do file medical literature in support of their claims, the reliability of the literature must be considered. See Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 590 (1993) (stating that scientific knowledge requires "more than subjective belief or unsupported speculation"); Althen, 418 F.3d at 1278 (stating that proof of a logical sequence of cause and effect by a "reputable medical or scientific explanation" supports a finding that the presented medical theory is a persuasive one) (quoting Grant v. Sec'y of Health and Human Servs, 956 F.2d 1144, 1148 (Fed. Cir. 1992)).

Formal evidentiary rules, including the Federal Rules of Evidence, do not apply in Program proceedings. See 42 U.S.C. § 300aa-12(d)(2)(B) (stating that the Vaccine Rules "shall . . . include flexible and informal standards of admissibility of evidence"); RCFC App. B, Vaccine Rule 8(b) (providing that "[i]n receiving evidence, the special master will not be bound by common law or statutory rules of evidence"). However, the Federal Circuit has declined to find an abuse of discretion when special masters rely on the

decision of the Supreme Court in Daubert, 509 U.S. at 594, "as a tool or framework for conducting the inquiry into the reliability of the evidence." Terran v. Sec'y of Health and Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999) (emphasis added). As the Supreme Court in Daubert noted, scientific knowledge requires "more than subjective belief or unsupported speculation." Daubert, 509 U.S. at 590. An expert's opinion must be grounded "in the methods and procedures of science." Id.

The Federal Circuit has instructed that in appropriate circumstances, it may be sufficient for petitioners to present only a medical opinion and circumstantial evidence of a vaccine-related cause and effect to prove causation under the Vaccine Act. See Althen, 418 F.3d at 1279. Identification and proof of specific biological mechanisms are not required. Knudsen v. Sec'y of Health and Human Servs., 35 F.3d 543, 549 (Fed. Cir. 1994). However, special masters must examine the soundness and reliability of the offered medical or scientific explanations. See Althen, 418 F.3d at 1278; Knudsen, 35 F.3d at 548; see also RCFC App. B, Vaccine Rule 8(b) (instructing special masters to ensure that the considered evidence is "relevant and reliable").

The Federal Circuit has instructed that the testimony of an expert may be rejected when a reasonable basis supports such a rejection. See Burns v. Sec'y of Health and Human Servs., 3 F.3d 415, 417 (Fed. Cir. 1993). In addition, the testimony of an expert may be rejected when the reasons underlying the expert's opinion are unsound. See Perreira v. Sec'y of Health and Human Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) ("An expert opinion is no better than the soundness of the reasons supporting it.").

Petitioners need not show that the vaccine was the sole cause or even the predominant cause of the suffered injury or condition. Shyface v. Sec'y of Health and Human Servs., 165 F.3d 1344, 1352 (Fed. Cir. 1999). Rather, petitioners must show that the vaccine was a "substantial factor" in causing the condition and was a "but for" cause of the condition. Id.; see also Pafford v. Sec'y of Health and Human Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006) (requiring petitioners to establish that the received vaccines were a substantial factor and that harm would not have occurred in the absence of the vaccinations).

Petitioners here allege that William developed regressive autism as a result of the vaccines he received in his first couple of years of life. Because autism is not a listed injury on the Vaccine Injury Table, the Meads must assert an off-Table claim.

B. Proving an "Off-Table" Claim

Because petitioners assert an off-Table claim for compensation in this case, petitioners must prove, by a preponderance of the evidence, that the administered vaccines

"caused" William's regressive autism. Petitioners satisfy this burden of proof by presenting: (1) "a medical theory" that causally connects William's vaccinations and his autism; (2) "a logical sequence of cause and effect" that shows that William's vaccinations were the "reason" for his injury; and (3) evidence of "a proximate temporal relationship" between William's vaccinations and his injury. Althen, 418 F.3d at 1278. Guided by the three Althen factors, a special master decides the issue of causation "based on the circumstances of the particular case." Knudsen, 35 F.3d at 548. No particular "diagnosis, conclusion, judgment, test result, report, or summary" is binding on a special master. 42 U.S.C. § 300aa–13(b)(1). Instead, the Vaccine Act contemplates that a special master will "consider the entire record and the course of the injury" and will weigh all of the evidence presented when making a decision on entitlement. Id.

1. The First Althen Factor: A Medical Theory of Causation

Petitioners satisfy the first Althen factor by offering a medical theory of causation that causally links the vaccination to the injury. Althen, 418 F.3d at 1278. This factor has been construed to require that the offered theory has "biological plausibility." See Walther v. Sec'y of Health and Human Servs., 485 F.3d 1146, 1147 (Fed. Cir. 2007) (finding no error in the special master's requirement that petitioner prove biological plausibility); Pafford, 451 F.3d at 1356 (stating that petitioner must prove that the vaccine(s) at issue can cause the injury alleged and the actual symptoms alleged).

The offered theory must be reliable as well. See Knudsen, 35 F.3d at 548; see also Pafford, 451 F.3d at 1355-1356 (requiring that "petitioner . . . provide a reputable medical theory causally connecting the vaccination and the injury" to satisfy the test set forth in Althen) (emphasis added). A special master's evaluation of the reliability of the offered theory is informed by the broad standards set forth in Daubert, 509 U.S. at 594; Terran, 195 F.3d at 1316 (affirming use of Daubert in vaccine cases "as a tool or framework for conducting the inquiry into the reliability of the evidence").

The Supreme Court in Daubert noted that scientific knowledge "connotes more than subjective belief or unsupported speculation." Daubert, 509 U.S. at 590. Rather, some application of the scientific method must have been employed to validate an expert's opinion. Id. (requiring "a grounding in the methods and procedures of science"). An expert's "testimony must be supported by appropriate validation . . . based on what is known." Id. Factors relevant to evaluating an expert's theory may include, but are not limited to:

> [W]hether the theory or technique employed by the expert is generally accepted in the scientific community; whether it's been subjected to peer

> review and publication; whether it can be and has been tested; and whether the known potential rate of error is acceptable.

Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1316 (9th Cir. 1995) (decision on remand) (emphasis added).

In determining the reliability of a novel proposition, the Supreme Court has offered the following guidance to lower courts:

> [S]ubmission to the scrutiny of the scientific community is a component of "good science," in part because it increases the likelihood that substantive flaws in methodology will be detected. The fact of publication (or lack thereof) in a peer reviewed journal thus will be a relevant, though not dispositive, consideration in assessing the scientific validity of a particular technique or methodology on which an opinion is premised.

Daubert, 509 U.S. at 593-594.

Neither medical nor scientific certainty is required. Knudsen, 35 F.3d at 548-549.

2. The Second Althen Factor: A Logical Sequence of Cause and Effect

Petitioners satisfy the second Althen factor by presenting a "logical sequence of cause and effect" between the vaccinations and the vaccinee's condition. Althen, 418 F.3d at 1278. The Federal Circuit has instructed that a persuasive medical theory offers "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury." Knudsen, 35 F.3d at 548 (citations omitted); Grant, 956 F.2d at 1148 (same); Hines v. Sec'y of Health and Human Servs., 940 F.2d 1518, 1525 (Fed. Cir. 1991) (citations omitted) (same).

The proposed "logical sequence" must be supported by "reputable medical or scientific explanation" or medical opinion. Althen, 418 F.3d at 1278; Grant, 956 F.2d at 1148 (may show a "logical sequence of cause and effect" through "scientific studies or expert medical testimony"). Consideration must be given to the opinions offered by a vaccinee's treating physicians. Capizzano, 440 F.3d at 1326. Medical records, particularly those rendered contemporaneously to the onset of the alleged injury, receive "favored" consideration. Id. See also Cucuras v. Sec'y of Health and Human Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993) (recognizing that in circumstances where the later offered fact witness testimony conflicts with contemporaneously prepared medical

records, the "[m]edical records, in general, warrant consideration as trustworthy evidence").

Special masters are guided by these considerations when evaluating the support for the logic of a proposed "sequence of cause and effect." Althen, 418 F.3d at 1278.

3. The Third Althen Factor: A Proximate Temporal Relationship

Petitioners satisfy the third Althen factor by showing a proximate temporal relationship between "vaccination and injury." Althen, 418 F.3d at 1278. See also Hines, 940 F.2d at 1525 (considering the temporal relationship between the inoculation and the onset of the injury). Without more, a simple showing that an injury occurred after the vaccination is not enough. See Pafford, 451 F.3d at 1358 (observing that "without some evidence of temporal linkage, the vaccination might receive blame for events that occur weeks, months, or years outside of the time in which scientific or epidemiological evidence would expect an onset of harm"); Grant, 956 F.2d at 1148 (recognizing that a vaccination is not the cause of every event that follows within a period of time after the receipt of the vaccine). Rather, the presented evidence must support a finding that the onset of the injury occurred within a medically acceptable time frame. See Pafford, 451 F.3d at 1358.

III. The Components of Petitioners' Second Theory of General Causation

The general causation theory that petitioners have advanced in the three test cases has the following key components. Petitioners assert that the affected child received the recommended pediatric schedule of thimerosal-containing vaccines during the first two years of life. See Mead Ps' Brief at 12. The child has no family history of autism spectrum disorders and has no evidence of any genetic anomalies. Id. at 13. Additionally, the child has not suffered a prenatal or postnatal exposure to any other substances known to cause or suspected of causing autism. Id. Nor has the child suffered a prenatal or postnatal trauma associated with the development of autistic symptoms. Id.

During the first year of life, the child developed normally, meeting most or all of the key developmental milestones. Id. at 12. But, exposure to thimerosal-containing vaccines led to the accumulation of inorganic mercury in the child's brain. Id. The continued presence of inorganic mercury in the child's brain triggered a local neuroinflammatory process. Id. That neuroinflammatory process affected the developing brain in two ways. Id. First, it created an "an environment of oxidative stress in the brain" that produced "a complex cycle of impaired and disrupted chemical processes" that interfered with brain function, but did not cause "gross neurotoxicity" or "neuronal death."

Id. at 12-13. Second, the triggered inflammatory process led to "an overabundance of glutamate," the primary excitatory neurochemical in the brain. Id. at 12. Petitioners contend that the excess glutamate in the brain led to a persistent state of "overexcitation" or "overarousal" and also to a compensatory expression of autistic symptoms. Id. The impaired and disrupted brain function that resulted from the neuroinflammation induced by the thimerosal-containing vaccines also caused developmental regression in the child. Id. at 13. Described as regressive autism, this developmental regression is characterized by the "loss of previously acquired skills" in the three development domains of communication, social skills (including social reciprocity), and behavior. See id. at 13.

Before turning attention to each of the components of petitioners' proposed theory of general causation, the undersigned first addresses petitioners' claimed injury, autism spectrum disorder. The undersigned specifically addresses what an autism spectrum disorder is, what are the different diagnostic categories that comprise the spectrum of disorders, what are the diagnostic criteria for autism, and what are some of the commonly observed characteristics or features in autistic individuals.

A. Autism Spectrum Disorders

The spectrum of neurodevelopmental disorders that involve impairments in the three core areas of socialization, communication, and behavior is referred to alternately as pervasive developmental disorders (PDDs), autism spectrum disorders (ASDs), or autism.[23] See RMRL 123 at 70 (2000 DSM-IV text excerpts[24]); see also PMRL 264 at 469 (2000 Filipek article[25]); Mead R's Ex. MM at 7 (Dr. Fombonne's report). The impairments that are characteristic of autism are qualitative in nature. Mead Tr. at 3250. Respondent's expert pediatric psychiatrist, Dr. Rutter, explained that the impairments in autism do not concern either the degree of or the delayed timing of the affected individual's functioning but rather an "abnormality in type" of functioning. Id. at 3250-3251.

Although the disorder now termed autism "has been recognized" and described for "hundreds of years," it did not receive its name until 1943. Mead R's Ex. MM at 7; see

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[23] The undersigned uses the terms ASDs or autism interchangeably in this ruling.

[24] DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition, Text Revision (DSM-IV-TR). American Psychiatric Association, Washington, D.C., pp. 69-84 (2000).

[25] P. A. Filipek, et al., Practice parameter: Screening and diagnosis of autism: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society, Neurology 55(4): 468-479 (2000).

also Mead Tr. at 3716. At that time, Leo Kanner, M.D., a pediatric psychiatrist at Johns Hopkins Hospital in Baltimore, Maryland, used the term in a paper he issued reporting his observations of 11 children with "significant social and language deficits and impairment of imaginative play." Mead R's Ex. MM at 7; see also Mead Tr. at 3250.

The autistic spectrum is comprised of five disorders: (1) Rett's Disorder; (2) Childhood Disintegrative Disorder (CDD) or Heller's Disease; (3) Autistic Disorder or Classic Autism; (4) Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS); and (5) Asperger's Disorder. RMRL 123 at 69 (2000 DSM-IV text excerpts); PMRL 264 at 470. The differences among the five diagnostic categories are briefly described in turn.

1. Distinctions Among the ASD Categories

The first of the ASD categories, Rett's disorder, has been diagnosed principally in females and is understood to be triggered by a genetic defect. See RMRL 123 at 74, 76-77 (2000 DSM-IV text excerpts); see also Mead Tr. at 2597-2599 (Dr. Rust). Features of this disorder include a characteristic pattern of head growth deceleration, loss of previously acquired purposeful hand skills, and the appearance of poorly coordinated gait or trunk movements. Id. at 74. Another developmental aspect of the disorder is the acquisition of language followed by a loss of words. Mead Tr. at 2598-2599.

The second of the ASD categories, CDD, has a distinctive pattern of severe developmental regression in multiple areas of functioning following at least two years of normal development. RMRL 123 at 74, 77-79 (2000 DSM-IV text excerpts). The disorder is usually associated with severe mental retardation. Id. at 78.

In cases of autistic disorder–the third of the ASD categories–the developmental abnormalities typically are noted within the first year of life. RMRL 123 at 74 (2000 DSM-IV text excerpts). This diagnosis is also appropriate when information about early development is not available or when it is not possible to document the required period of normal development. Id. This disorder is more prevalent in males. See id.

A diagnosis of PDD-NOS–the fourth of the ASD categories–is proper when there is a severe and pervasive impairment in the development of reciprocal social interaction associated with an impairment in either verbal or nonverbal communication skills or with the presence of stereotyped behavior, interests, and activities, but the criteria are not met for another specific ASD. RMRL 123 at 84 (2000 DSM-IV text excerpts). This category includes "atypical" presentations of autism that may involve either onset at a late age, atypical symptomatology, or diagnostically "subthreshold" symptomatology, or a combination of all three of these features. Id.

The fifth ASD category, Asperger's Disorder, is characterized primarily by a "severe and sustained impairment" in social skills. RMRL 123 at 80 (2000 DSM-IV text excerpts). Restricted and repetitive patterns of behavior are also present. Id. Notably, persons with Asperger's Disorder show no clinically significant delays or differences in language acquisition but "subtle aspects of social communication" may be affected, such as the "typical give-and-take in conversation." Id. Mental retardation is not usually observed in cases of Asperger's Disorder, but symptoms of overactivity and inattention are frequently present. Id. at 81. Indeed, it is not uncommon for individuals to have received a diagnosis of Attention Deficit/Hyperactivity Disorder prior to receiving a diagnosis of Asperger's Disorder. Id.

As presently comprised, the autism spectrum contains five different diagnostic categories. But, there is increasing evidence that the distinctions among the diagnostic categories "merely represent variations in intensity of the same core underlying deficits." Mead R's Ex. MM at 10.

2. Criteria for an ASD Diagnosis

To meet the diagnostic criteria for an ASD, qualitative impairments in the three core areas of social interaction, communication, and behavior must become apparent within the first three years of the child's life.[26] See RMRL 123 at 70-71, 73 (2000 DSM-IV text excerpts); Mead Tr. at 3253 (Dr. Rutter); Mead R's Ex. MM at 11. Among the objective instruments used to diagnose ASDs are the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS).[27] See Transcript of Dwyer Hearing (Dwyer Tr.) at 223 (Dr. Leventhal). The ADI-R is a "long semi-structured interview" in which an examiner asks a child's caregivers to describe the specific contexts in which the child has been observed and to describe the types of behaviors and facial expressions that the child exhibits. See Mead Tr. at 3549-50 (respondent's expert, Dr. Lord, one of the authors of this diagnostic instrument). The ADOS requires that a clinician perform a standard set of activities with a child (or an adult referred for examination) for approximately 45 minutes and record standardized observations; this instrument is a shorter companion to the ADI-R. Mead Tr. at 3550-3551 (Dr. Lord, also one of the authors of this diagnostic instrument). Both instruments are used around the world in clinical and research settings. Mead Tr. at 3550-3552 (Dr. Lord). And there is "a high degree of consensus among world experts on the definition [of

[26] Persons affected with CDD, one of the five categories of ASDs, may lose language skills or manifest changes in behavior later than the first three years of life. RMRL 123 at 79.

[27] Dr. Leventhal was one of the authors of the ADOS. Dwyer Tr. at 217 (Dr. Leventhal).

autism] and the procedures required to diagnose and assess subjects with Autistic Disorder." Mead R's Ex. MM at 10.

The particular manifestations of an ASD vary greatly. RMRL 123 at 70 (2000 DSM-IV text excerpts). A few illustrative examples of impairments in each of the three core areas are briefly described below.

In the area of reciprocal social interaction, there may be marked abnormalities in the use of nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to communicate. Id. at 70; see also Mead Tr. at 2363-2364 (Dr. Rust addressing the observed difficulties that autistic persons have decoding the facial and gestural expressiveness of others). Additionally, there may be little interest in establishing friendships or there may be a lack of understanding of the conventions of social interaction. RMRL 123 at 70.

In the area of communication, there may be marked impairments in both verbal and nonverbal skills. Id. Spoken language development may be delayed or absent. Id. Individuals who do speak may use language repetitively or idiosyncratically. Id. Also, comprehension of language may be impaired such that simple questions or directions are not understood. Id. at 70-71.

In the area of behavior, affected individuals may have restricted, repetitive, and stereotyped interests or activities that are abnormal either in intensity or focus. Id. at 71. Such individuals may have a rigid adherence to routines or rituals or exhibit a persistent preoccupation with parts of objects or a narrow interest in, for example, dates or phone numbers. Id.

Typically, parents recognize the developmental abnormalities when the children are 18 to 24 months of age. Mead Tr. at 3259; PMRL 264 at 469 (2000 Filipek article). The manifestations of autism may be identified as early as the end of the first year of life by a diagnostic specialist trained to evaluate home videos that may include first birthday parties. See Mead R's Ex. MM at 12.

3. Characteristics or Features Commonly Observed in Autistic Individuals

In most cases of autism, there is an associated diagnosis of mental retardation that can range from mild to profound. RMRL 123 at 71 (2000 DSM-IV text excerpts); see also Dwyer Tr. at 229 (Dr. Leventhal). In addition, children with autism are prone to develop seizures at some time during their lives. Mead Tr. at 3241, 3258; Mead R's Ex. GG at 6; PMRL 264 at 474 (2000 Filipek article).

Also reported as common in autistic individuals, particularly during the preschool years, are motor stereotypies[28] that may include hand or finger mannerisms, body rocking, toe walking, or unusual posturing. PMRL 264 at 473 (2000 Filipek article); see also Mead R's Trial Ex. 8 at 10. Another feature noted to be prevalent in autistic children is a sensory peculiarity that may manifest as a particular sensitivity to: (1) the temperature of served food (whether hot or cold); (2) the texture of served food or the clothing worn; and (3) the touching of the head (a phenomenon referred to as head shyness). See Mead Tr. at 2383, 2400, 2461; Mead R's Trial Ex. 8 at 44. Alternatively, this sensory peculiarity may manifest as an unusual pain tolerance. See Mead Tr. at 2463.

In approximately 20 to 50 percent of cases, physical abnormalities exist that are indicative of atypical brain development; such anomalies may include small feet and large hands or an enlarged head circumference (macrocephaly).[29] See Mead R's Ex. MM at 16-17, 22; Mead R's Ex. GG at 6; PMRL 108 at 418 (2005 Herbert article[30]) (a review article noting "a strong trend toward bigger brains in autism"); PMRL 264 at 473 (2000 Filipek article); Mead Tr. at 3052 (Dr. Rodier placing estimates as high as 50 percent of autistic individual have dysmorphic features of some type); id. at 2835-2838 (Dr. Kemper referring to studies showing that there is rapid brain growth in the first few months of life in autistic brains).

Another observed physical abnormality may include posteriorly rotated ears. See Mead R's Trial Ex. 11 at 14 (picture of child with low-set, posteriorly rotated ears). As respondent's expert teratologist Dr. Rodier explained during her testimony, an embryo forms ears (sitting on their sides near the neck of the embryo) during the eighth week after conception, and as the embryo grows older, typically developing ears rotate from the sideways position to an upright position that is related to the eyes. See Mead Tr. at 3029; Mead R's Trial Ex. 11 at 13. Ears that sit low and have a posteriorly rotated orientation after a child's birth are indicative of an insult to development that occurred in the embryo. Mead Tr. at 3029-3030.

An additional dysmorphic feature that occurs in autistic children is wide-set eyes or eyes that are positioned "just a little too far apart" (a condition also known as

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[28] Stereotypies are persistent repetitions of senseless acts or words. See Dorland's at 1759.

[29] One of the characteristic features in autistic individuals is a normal head circumference at birth but an abnormal increase in head circumference during the preschool years. Mead Tr. at 3415.

[30] M. R. Herbert, Large brains in autism: the challenge of pervasive abnormality, Neuroscientist 11(5): 417-440 (Oct. 2005).

hypertelorism). Mead Tr. at 3030. Dr. Rodier explained that the human face (and some animals' faces) develops from the middle part of the face first and then "the rest of it comes to join the middle." Id.; see also Mead R's Trial Ex. 11 at 15 (picture of developing face at 54 days, with the eyes at the far sides of the face). Comparing the wide-set orientation of the eyes on the face of a developing embryo at 54 days after conception with a picture of the wide-set eyes of two little boys who developed autism as a result of their prenatal exposure to valproic acid, Dr. Rodier observed that such small physical malformations are not just associated with genetic syndromes but are exemplary of the prenatal environmental exposures that can cause autism. Id. at 3030-3031; see also Mead R's Trial Ex. 11 at 15-16.

B. The Neuroanatomy of the Brain

Studies of autistic brains also show certain neuroanatomical features that are indicative of an early prenatal onset of autism. Mead R's Ex. MM at 23. Before identifying those features, the undersigned offers first a brief description of the structure of the brain that may assist in understanding the differences in structure and composition of brains that have been taken from autistic individuals (after autopsy) and examined. In addition, the following description of the structure of the brain may assist in understanding the aspects of petitioners' theory that pertain to mercury's effect on the brain.

1. Structure of the Brain

The brain is comprised of three main structures: the cerebrum (forebrain), the cerebellum (the hindbrain), and the brainstem (the midbrain). See http://www.brainexplorer.org/brain_atlas/brainatlas_index.shtml. The cerebrum is the largest part of the human brain and is associated with higher brain function such as thought and action. Id. Sitting in the hindbrain and below the cerebrum is the cerebellum. Id. The cerebellum is the part of the brain that is responsible for regulating and coordinating complex voluntary muscular movement (motor coordination) as well as maintaining posture and balance. Id. This part of the brain is connected to the base of the brain (known as the brainstem). The brainstem is that portion of the brain (stalk-like in appearance) that connects the forebrain and the spinal cord. Id. The brainstem contains the midbrain and operates as a relay station, permitting nerve impulses to pass between the brain and the spinal cord. Id.

Covering the cerebrum of the brain is the cerebral cortex, known as the gray matter of the brain. The cerebral cortex has pronounced bulges and deep folds that produce a wrinkled appearance. The cerebral cortex is a multi-layered structure composed of closely packed nerve cells. Nerve cells or neurons are the cells that conduct the transfer of signals throughout the nervous system. See Dorland's at 1256. Synapses are the sites at which

signals or impulses are transmitted–usually by a chemical neurotransmitter–from one neuron to another. Dorland's at 1806; see also Mead Tr. at 796 (Dr. Kinsbourne).

Beneath the outermost synaptic layer of the cerebellar cortex is the Purkinje layer comprised of large neurons (Purkinje cells) that release the chemical neurotransmitter GABA.[31] Dorland's at 1260, 1806. The neurotransmitter GABA inhibits (or reduces) the transmission of nerve impulses and thus permits the regulation and coordination of motor movements. See id. at 1260.

Lying below the layer of Purkinje cells is the receptive layer of the cerebellar cortex that is comprised of "enormous numbers of small neurons" in white tissue known as the white matter of the brain. See http://www.brainexplorer.org/brain_atlas/brainatlas_index.shtml. Projecting from the small neurons in the receptive layer of the cerebral cortex are long white nerve fibers (axons) that develop and lengthen during early brain development to form the long connections that carry signals, along prescribed routes, to the synaptic layer of the cerebral cortex. See http://www.britannica.com/EBchecked/topic/484088/Purkinje-cell.; see also Mead Tr. at 2548-2550 (Dr. Rust); Mead R's Trial Ex. 8 at 77 (slide illustrating an axonal connection). The axonal connections in the synaptic layer excite the dendrites (that form the receptive surface) of the Purkinje cells that, in turn, project axons to the portion of the brain nestled within the cerebral cortex (described below as the limbic system). See http://www.britannica.com/EBchecked/topic/484088/Purkinje-cell; see also Dorland's at 488. Most of the actual information processing in the brain takes place in the cerebral cortex.

The cerebral cortex is divided into two hemispheres, left and right, and each hemisphere is divided into four lobes. The four lobes are: (1) the frontal (which has a top, front position in the cerebellar brain); (2) parietal (which has a top, middle position in the cerebellar brain); (3) occipital (which sits in the back of the cerebellar brain); and (4) temporal (which sits in the bottom position in the cerebellar brain). The frontal lobe is associated with reasoning, planning, and problem solving. The parietal lobe is associated with movement, orientation, and processing sensory information from the body. The occipital lobe is associated with visual processing. The temporal lobe is associated with hearing, memory, emotion, and language. Many of the functions of the four lobes occur in both hemispheres.

Buried beneath the cerebral cortex and lying above the brain stem is the limbic system. See Mead R's Trial Ex. 10 at 2 (slide showing the limbic lobe of the brain). Also

[31] GABA is the abbreviation for gamma-aminobutyric acid. See http://www.britannica.com/EBchecked/topic/484088/Purkinje-cell.

referred to as the "emotional brain," the limbic system includes the thalamus, hypothalamus, amygdala, and hippocampus. The thalamus manages sensory perception and motor functions. See Mead Tr. at 2833 (Dr. Kemper stating that the limbic system has key components that are involved in motion). The hypothalamus is associated with circadian rhythms[32] and the autonomic nervous system.[33] The amygdala is involved in the processing of emotion, particularly fear, and the hippocampus is important for memory functions. See Mead Tr. at 2418 (Dr. Rust); see also id. at 2831 (Dr. Kemper).

Lying over and to the sides of the limbic system and tightly connected to the cerebral cortex above it are the basal ganglia. These brain structures are responsible for repetitive behaviors, rewarding experiences, and focusing attention. See Mead Tr. at 1986 (Dr. Mailman).

With this simple structural and functional review of the brain, the undersigned now addresses the structural features that appear to be characteristic of autistic brains.

2. Structure and Composition of the Autistic Brain

Nearly two dozen brains taken from persons diagnosed with autism have been made available for study through brain banks that the federal government has established around the country.[34] Mead Tr. at 2796, 2864 (Dr. Kemper). Of the brains that have been studied, the subjects have ranged in age from four to 50 years old. Id. at 2800. The reports from different labs examining different brains of different ages have shown consistent findings in certain areas of the brain. Id. at 2799-2801, 2803. The findings in the brains of autistic individuals appear to be developmental abnormalities–based on the known timeline of developmental events in the human brain–that occurred during gestation and, after birth, resulted in abnormal brain growth during the early years of life. See Mead Tr. at 2805-2807; see also Mead R's Trial Ex. 10 at 4. No difference in morphology has been detected between the brains of autistic subjects with or without regression. Id. at 2801 (Dr. Kemper

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[32] Circadian rhythms "pertain to a period of about 24 hours; applied especially to the rhythmic repetition of certain phenomena in living organisms at about the same tome each day." Dorland's at 367. The sleep cycle is the most well-known circadian rhythm. See id.

[33] The autonomic nervous system governs the involuntary movement of muscles (including the cardiac muscles) and glands. See Dorland's at 182, 1841.

[34] The function of the brain banks is to receive brains from organ donors, to process the brains in a uniform manner, and then to make the brains available to investigators for research purposes. Mead Tr. at 2796 (Dr. Kemper).

addressing the findings in the 2005 Vargas article[35]); see also PMRL 69 at 71 (2005 Vargas article) (observing particular changes in the neuroglial cells in the brains of the autistic subjects but "no differences in [the noted cellular changes] as a function of age or clinical profile including history of developmental regression or mental retardation in the autistic patients").

On examination, autistic brains have abnormally small and closely packed neurons in the limbic system. Mead R's Ex. MM at 23 (Dr. Fombonne's report); see also Mead Tr. at 2411 (Dr. Rust). Dr. Kemper, respondent's expert neuropathologist, testified that an examination of tissue taken from autistic brains under a microscope shows that the neurons have failed to migrate from the germinal zone in the brain (that is, "the zone that makes neurons") to the other zones in the brain–as occurs in normal development. Mead Tr. at 2807-2809; see also Mead Resp. Trial Ex. 10 at 5 (slide identifying the normal route of neuronal migration in the brain). Instead, the neurons "were arrested in their zone of development" or along the migratory path to other zones. Mead Tr. at 2809, 2823-2824; Mead R's Trial Ex. 10 at 6, 13-14 (for purposes of comparison, a slide showing normal neuronal migration toward the cerebral cortex and slides showing arrested neuronal development in the germinal zone or arrested neuronal migration in examined autistic brains). Not only are the neurons packed too densely, but also there are too many of them. Mead Tr. at 2412 (Dr. Rust); see also Mead Tr. at 2810-2811 (Dr. Kemper pointing to an abnormal lining up and layering of neurons in the inferior olive[36]). This structural configuration is thought to result in "too many local connections in certain cellular layers" of the brain and not enough "long arc connections" between one small area of the brain and other areas of the brain. Id. at 2412; see also Mead R's Trial Ex. 8 at 24 (trial slide showing the connections forming the brain architecture in the cortical and subcortical layers). The abnormality in the architecture of the autistic brain appears to be in the number of the neuronal connections–both local (too many) and long (too few)–rather than any impairment that is inherent in the neuronal connections themselves because the functions that are affected by impaired neuronal connections (namely, the peripheral nerves, vision, and hearing) are undisturbed in the autistic individual. See Mead Tr. at 2420-2421; Mead R's Trial Ex. 8 at 27; see also Mead R's Trial Ex. 10 at 12-13 (slides illustrating the discussed disturbance in the connectivity of the neuronal circuitry in the cerebellum of the autistic brain); id. at 19-20 (slides showing that the cells in the hippocampus of an autistic brain were more densely packed than were the cells in the hippocampus of a normal brain).

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[35] D. Vargas, et al., Neuroglial activation and neuroinflammation in the brain of patients with autism, Ann. Neurol. 57(1):67-81 (2005).

[36] The inferior olive is a part of the brain that sends sensory information to the cerebellum. See Dorland's at 1306.

Additionally, malformations have been reported in the cerebral cortex. Mead R's Ex. MM at 23. In autistic brains, there is an increase in the density of the outer cortical radiate white matter that occurs as the cortex develops during gestation. Mead Tr. at 2420 (Dr. Rust); id. at 2827 (Dr. Kemper), 2830-2831 (Dr. Kemper addressing published reports of the increased number of–or "too many"–neurons in the white matter of autistic brains); Mead Resp. Trial Ex. 10 at 15-18 (slides showing malformations that occur during the development of the cortex, between weeks 16 and 20 of gestation). This anomalous brain feature can be observed by new brain imaging techniques (known as functional magnetic resonance spectroscopy) that show areas of bridging around the brain with fibers that are too small and are reflective of the overly-dense local neuronal connections that have developed in the autistic brain. See Mead Tr. at 2420-2421, 2557-2560; see also Mead R's Trial Ex. 8 at 37 (trial slide showing an observable difference between an autistic brain and a control brain as the two subjects perform the same activity).

Another consistent finding–and the most commonly reported finding–in the cerebellum of the autistic brain is a decrease in the number of Purkinje cells.[37] See Mead Tr. at 2812, 2815; see also Mead R's Trial Ex. 10 at 9 (slide showing the decreased number of Purkinje cells observed in autistic brains). The Purkinje cells are described as the "boss cell[s] of the cerebellar cortex" because these neuronal cells are GABAergic (meaning they excrete the chemical neurotransmitter GABA that has certain key inhibitory functions). Id. at 2812, 2882 (Dr. Kemper); see also Dorland's at 1260.

The loss of Purkinje cells is accompanied by a loss of granule cells. Mead Tr. at 2812-2814. Granule cells are diminutive star-shaped neuronal cells that form the thick granular layer of the cerebellum. See Dorland's at 321; see also http://medical-dictionary.thefreedictionary.com/granule+cell. Dr. Kemper testified that from the literature addressing development, it is well known that when Purkinje cells are lost early in development, the correlative cohort of granule cells also decreases. Mead Tr. at 2814.

A depletion in the number of Purkinje cells has been detected in autistic brains without a concomitant loss of neurons in the inferior olive of the brain–even though the neuronal connections between Purkinje cells and the neurons in the inferior olive are very close. Mead R's Ex. MM at 23 (Dr. Fombonne); see also Mead Tr. at 2804 (Dr. Kemper). Neurons from the inferior olive–which is located in the brain stem of the brain–project into the cerebellum of the brain and specifically up to the Purkinje cells. See Mead Tr. at 2816,

[37] A single Purkinje cell has approximately 175,000 synapses and 350,000 inputs. Mead Tr. at 2426 (Dr. Rust); see also Mead R's Trial Ex. 8 at 33. Purkinje cells are now understood to have an important role in language development. See Mead Tr. at 2417-2418 (Dr. Rust).

2818; see also Mead R's Trial Ex. 10 at 10 (slide showing the climbing neuronal fibers from the inferior olive to the Purkinje cells). The particular finding in the autistic brain of depleted Purkinje cells but no correlative loss of the olivary neurons indicates–based on what is understood about the development of the brain structure–that the injury causing the destruction of the Purkinje cells occurred before the 28th week of gestation, the point in time when the close neuronal connections are established.[38] Mead R's Ex. MM at 23 (Dr. Fombonne); see also Mead Tr. at 2817 (Dr. Kemper); Mead R's Trial Ex. 10 at 10-11 (slides showing the climbing neuronal fibers from the inferior olive to the Purkinje cells). This understanding is further informed by the scientific knowledge that a loss of Purkinje cells that occurs after birth leads to the loss of inferior olivary neurons. Mead Tr. at 2817-2818.

Also found in brains examined from autistic patients are an excessive number of minicolumns that connect the various parts of the brain. Id. at 2838; see also Mead Tr. at 3268-3269, 3334-3335, 3338 (Dr. Rutter stating that imaging of autistic brains shows a systems abnormality–rather than a localized brain area abnormality–marked by either an overgrowth of interconnections [or failure of the normal process of pruning interconnections] between different parts of the brain that do not function properly); PMRL 104 at 590-593 (2005 Courchesne article[39]) (pointing to evidence that early, improper development of the neural microcircuitry–particularly, the minicolumns in the

[38] Respondent's teratologist Dr. Rodier also helpfully referred to a slide containing Purkinje cells that could be examined easily without the aid of a microscope as histologic evidence that autism begins earlier in time than petitioners' theory of vaccine-related causation suggests. See Mead Tr. at 3027-3028; Mead R's Trial Ex. 11 at 12. Pointing to two large gray cells, each with a very bright pinpoint of a nucleus, Dr. Rodier explained that axons from the neighboring cells formed what she described as "baskets" around the Purkinje cells. Id. She stated that if the cells had died shortly before the histological sample had been taken, the "baskets" would be expected to have been left empty, as an indication of acquired Purkinje cell loss. Id. at 3028; see also PMRL 220 at 899 (A. Bailey et al., A clinicopathological study of autism, Brain 121(Pt 5):889-905 (1998) noting the detected differences in the autopsied brains taken from mentally retarded subjects with autism and control subjects). Instead, research conducted by Dr. Kemper, one of respondent's testifying experts and others, indicates that–based on what is known about the time period during which Purkinje cells develop a relationship with other structures in the brain–the Purkinje cells either did not develop or were lost prenatally (before week 30 of the pregnancy). See Mead Tr. at 3028 (Dr. Rodier); see also id. at 2812-2820, 2834-2835 (Dr. Kemper); Mead R's Ex. U at 3 (Dr. Kemper's report).

[39] E. Courchesne et al., Autism at the beginning: microstructural and growth abnormalities underlying the cognitive and behavioral phenotype of autism, Dev. Psychopathol. 17(3):577-597 (2005).

brains of autistic subjects–prevents the formation of the circuits that are "essential for higher order social, emotional, language, speech, and cognitive functions"). This finding further suggests that an early, prenatal pathological process is involved in autism because minicolumns are generated within the first 40 days of gestation in the primate species. Mead R's Ex. MM at 23-24.

Another abnormality found in the brains of autistic patients occurs in the facial nucleus which is the part of the brain that controls the muscles of facial expression that affect, for example, the ability to smile or to close one's eyes. In a study conducted by respondent's expert teratologist Dr. Rodier comparing the facial nucleus of a control case to that of an autistic subject, there were approximately 4,000 motor neurons in the facial nucleus of the control case compared to only 400 motor neurons in the facial nucleus of the autistic subject. Mead Tr. at 3024-3026; see also Mead R's Trial Ex. 11 at 11 (showing a slide taken from RMRL 403 at 254 (the 2006 Rodier article[40])). As telling evidence that the missing aspect of the facial nucleus in the autistic subject never existed (rather than was formed and then died), Dr. Rodier pointed to slides taken from the 2006 Rodier article showing that in the control case, the neuronal fibers that connect the facial nucleus to other parts of the brain "respect the boundaries of [structures] like [the] facial nucleus" and follow a path that permits the facial nucleus to be surrounded by the neuronal fibers. Mead Tr. at 3026. But in the autistic brain, the neuronal fibers "are just running willy-nilly through th[e] area" of the facial nucleus, a structural pattern that suggests that the facial nucleus–which forms between the fourth and fifth week after conception–was not present when the neuronal fibers formed their tracks. Id. at 3026-3027.

In addition to certain structural abnormalities found in the autistic brain, the finding of certain proteins in the neonatal blood of children with autism or mental retardation without autism points to prenatal anomalies in children with autism or intellectual impairments. R's Ex. MM at 24. Also, the levels of at least one of the variously detected proteins in neonatal blood exceeded the levels in control children. Id.

Although a number of the findings in the neuropathology of autistic subjects suggests that the injury has "a very early origin," none of the findings to date correlates with the specific pattern of symptoms that informs a diagnosis of autism. Mead Tr. at 3041-3042. Yet, what is well-known in neuroscience generally is that very early occurring (prenatal) injuries that produce lesions in the nervous system often result in a later regression because as the brain matures, it cannot access the more advanced part of the nervous system that was ablated by the earlier injury. See id. at 3031-3032, 3057.

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[40] P. Rodier, et al., Embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei, J. Comp. Neurol. 370(2):247-261 (1996).

It is also well-known in neuroscience that a regression or even autistic-like symptoms can be provoked by a later-occurring, postnatal injury that occurs in those parts of the brain that influence autistic behavior, but the injury must be a "very, very severe" brain damaging event that specifically affects the areas of the brain that studies have shown are involved in autism. See id. at 3045, 3058-3059. In contradistinction to such catastrophic brain injuries that create lesions or "big holes" in the brain, autism is a disorder widely believed to result from improperly formed basic brain connections that are established during gestation. Id. at 3060-3061 (Dr. Rodier); see also id. at 2358-2359, 2430-2431 (Dr. Rust describing the autistic disorder as a systems disease–brought about by improper brain development–that causes "systems problems" and not the type of specific functional effects that are caused by toxic insults to or inflammation of a specific part of the brain).

C. Evidence that There is a Strong Genetic Component in the Development of Autism

Certain evidence points to a strong underlying genetic component to ASDs. The evidence of particular interest is the clustering within families of relatives with ASDs and the number of known causes of autism that are genetic.

1. ASDs Appear to Cluster in Families

Ongoing genetic studies of families with at least two relatives who are affected with an ASD have found that the affected relatives tend not to have the same ASD. Mead R's Ex. MM at 10. The risk of autism in such a family is more than 10 times higher than in the general population. Id. at 20. The detected clusters of ASDs within families suggest that the causal mechanisms for the disorders are shared ones and are genetically influenced. Id. at 10, 20; Mead Tr. at 2389, 2395 (Dr. Rust); id. at 3275 (Dr. Rutter).

Also pointing to the strong influence of genetic factors in autism are the results of studies of same-sex twin pairs. The most recent estimates indicate that monozygotic (MZ or identical) twins have approximately a 70 percent concordance rate and dizygotic (DZ or fraternal) twins have a concordance rate of between zero and five percent. Mead R's Ex. MM at 20; see also PMRL 90 at 68 (1995 Bailey article[41]) (rate of autism reported for MZ twins is 69 percent and for DZ twins is zero percent); Mead Tr. at 3272-3274 (Dr. Rutter explaining that the concordance rate in identical twin pairs is "about 60 percent for the full picture of autism" and "about 90 percent for a broader phenotype" with milder

[41] A. Bailey et al., Autism as a strongly genetic disorder: evidence from a British twin study, Psychol. Med. 25(1):63-77 (1995).

manifestations[42]). The twin studies indicate not only that genetic factors are involved in the development of autistic disorders, but also that multiple genes–rather than a single gene–are implicated. Mead R's Ex. MM at 20; see also Mead Tr. at 3275-3276 (Dr. Rutter).

Genetic factors influence both early development and later development.[43] See Mead Tr. at 3288-3290. Interestingly, many of the genes that have been proposed as candidate genes for autism susceptibility are genes controlling early development that are involved in the formation of the brainstem, and the implicated genes during early development are believed to be associated with later appearing autistic symptoms. Mead Tr. at 3045 (Dr. Rodier). The scientific evidence to date indicates that autism is strongly associated with genetic risk factors, and the parties in this case agree that genetic susceptibility is a key determinant in the development of the disorder. See Mead Petitioners' Exhibit (Mead Ps' Ex.) 30 at 7-8 (Dr. Kinsbourne's report); accord Mead R's Ex. MM at 10 (Dr. Fombonne's report).

2. Known Genetic and Prenatal Causes of Autism

Although the particular cause (or causes) of autism remains unknown in most cases, certain genetic factors and prenatal environmental exposures have been identified as the causal factors in approximately 5-10% of the diagnosed cases. See R's Ex. MM at 19; see also Mead Tr. at 2376 (Dr. Rust estimating that genetic causes can be identified in 10 to 15 percent of cases); id. at 851 (Dr. Kinsbourne testifying that in about 10 to 20 percent of

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[42] Symptoms of a broader phenotype of cognitive or social abnormalities have been detected in the non-autistic relatives of autistic individuals. PMRL 90 at 63 (1995 Bailey article). The cognitive abnormalities typically include speech or language deficits, and the social abnormalities generally involve either an emotional or social disability. Id.

[43] As an example, Dr. Rutter pointed to children with "profound congenital nerve deafness" who produce normal vocalizations for approximately the first six months of life and then develop the guttural vocalization characteristic of deaf children. Mead Tr. at 3292. He observed that because "babies all over the world have the same range of phonological skills," Japanese, French, English and American babies "all make much the same sounds . . . up to about the first six months of age." Id. at 3293. He noted that the loss of clear vocalization in congenitally deaf children is attributable entirely to genetic factors and not to environmental ones. Id. at 3292. He explained that as part of the normal developmental process, the input of language becomes important in vocalizations in the middle of the first year of life, and children who were born deaf cannot receive that language input. Id. The loss of clear vocalization constitutes the loss of a skill as part of the child's "biological programming." Id. at 3293.

cases, there is an association between the disorder and a known causative factor). Accordingly, when a diagnosis of autism is made, an investigation of the known genetic or medical causes of the condition may be conducted consistent with the existing guidelines for such an investigation. See PMRL 264 at 472-474 (2000 Filipek article); see also Mead Tr. at 848-851 (Dr. Kinsbourne testifying that the search for the cause of the disorder involves the conduct of a "differential diagnosis," which is the process of identifying and, in turn, ruling out those suspected causes of the disorder[44]).

Among the known genetic disorders associated with autism are tuberous sclerosis,[45] fragile X syndrome,[46] Angelman's syndrome,[47] and isodicentric chromosome 15 q syndrome.[48] See R's Ex. MM at 19. Research now has identified regions on several

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[44] A differential diagnosis involves a "determination of which one of two or more diseases or conditions a patient is suffering from, by systematically comparing and contrasting their clinical findings." Dorland's at 507. A differential diagnosis allows an examining physician to identify the disease or condition for which the patient should be treated. It may follow that a properly identified disorder has known causes that also can inform treatment options.

Dr. Kinsbourne acknowledged during his testimony that, in his preparation of a book chapter on developmental disorders to be included in the new sixth edition of Menkes' Textbook of Child Neurology, he has prepared a list of known associations with autism that does not include thimerosal-containing vaccines. Mead Tr. at 849-850.

[45] This genetic disorder is characterized by the tumor-like protuberances (known as tubers) in the brain, the retina, and various cavities of the body. Dorland's at 1669. The protuberances outside the brain are called tumors. The condition is associated with mental retardation and seizures. Id.

[46] This syndrome is an x-linked syndrome associated with a fragile site on the long arm of the x chromosome. Dorland's at 1818. The condition is associated with mental retardation, a high forehead, and enlarged jaws and ears in males. Id. The same condition is associated with mild mental retardation in females. Id.

[47] This syndrome can be caused by a deletion on chromosome 15 inherited from the mother. When inherited from the father, the same deletion causes Prader-Willi syndrome. Dorland's at 1810.

[48] A particular chromosomal change called an isodicentric chromosome 15 (previously called an inverted duplication 15) can affect growth and development. See http://ghr.nlm.nih.gov/chromosome=15. In some cases, the isodicentric chromosome 15

(continued...)

chromosomes that may contain the genes that predispose an individual to the development of autism. R's Ex. MM at 20-21 (noting that family studies have suggested that genetic susceptibility to autism may involve three to 20 different genes).

Certain prenatal exposures that appear to disrupt early developmental processes also are causally associated with autistic manifestations. Among the prenatal exposures known to lead to the presentation of autistic symptoms is rubella virus.[49] R's Ex. MM at 19. The window of vulnerability for this in utero exposure appears to be during the first 12 weeks of gestation. Id. at 22; see also Mead Tr. at 3019 (Dr. Rodier identifying the period of time "before the ninth week after conception" as the critical time period within which rubella exposure can cause autistic-like symptoms); see also Mead R's Trial Ex. 11 at 9 (slide identifying rubella as an environmental exposure known to increase the risk of autism). Although a number of children with congenital rubella showed autistic traits, studies indicate that those symptoms diminished over time. R's Ex. MM at 19. At present, congenital rubella does not account for more than a handful of cases of autism due to systematic vaccination against rubella. Id.

[48](...continued)
is a very small extra chromosome that has no effect on a person's health. Id. That small extra chromosome is made up of genetic material from chromosome 15 that has been abnormally copied. Id. In other cases, the isodicentric chromosome 15 is larger and can result in weak muscle tone (hypotonia), intellectual disability, recurrent seizures (epilepsy), and behavioral problems. Id. This larger form of the chromosomal change has been found in some children with the features of autism or related developmental disorders affecting communication and social interaction. Id. Individuals with this abnormal chromosomal duplication have been discovered to be at increased risk for sudden death. See Dwyer Tr. at 232 (Dr. Leventhal).

[49] Rubella is an acute, usually benign, infectious disease caused by a togavirus. Dorland's at 1644.

Other identified prenatal exposures that appear to increase the risk of autism are the chemicals ethanol,[50] thalidomide,[51] valproic acid,[52] misoprostol,[53] and terbutaline.[54] See R's Ex. MM at 22; Mead Tr. at 234, 3019. The malformations that present in individuals with in utero exposures either to thalidomide or valproic acid "indicate that the developmental interference occurs someplace between 20 to 24 days after conception." R's Ex. MM at 22; see also Mead Tr. at 3019 (Dr. Rodier stating that exposure to thalidomide or valproic acid during the third or fourth week of conception may result in the development of autism); Mead R's Trial Ex. 11 at 9 (slide addressing the timing of the developmental interference caused by the identified prenatal exposures associated with the development of autism). Other studies indicate that exposure to ethanol between the third and fifth week following conception puts a developing fetus at risk for developing autism as does exposure to misoprostol during the sixth week after conception. Mead Tr. at 3019. Each of these in utero exposures is understood to interfere with development during the first trimester of pregnancy. See R's Ex. MM at 22 (noting the risks associated with exposures occurring within the first 12 weeks of gestation); Mead Tr. at 3020.

Notably, of the identified prenatal exposures associated with an increased risk of autism, respondent's experts–and respondent's teratologist Dr. Rodier, in particular–expressed some reservation with respect to terbutaline. See Mead Tr. at 3020-3022. Dr. Rodier explained that her reluctance to identify terbutaline as a positive risk factor stemmed from the limitations of the 2005 Connors study, filed as PMRL 73,[55] that considered the possibility of a causal link between terbutaline exposure and an autistic

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[50] Ethanol or grain alcohol is capable of causing acute intoxication when ingested in excessive amounts. Dorland's at 646.

[51] Thalidomide is a sedative that enjoyed popular use in the 1960s before its use by women during early pregnancy was discovered to cause serious congenital anomalies. Dorland's at 1891; see also Mead Ps' Ex. 19 at 9 (Dr. Aposhian's report).

[52] Valproic acid is used to treat seizures. See Mead Tr. at 3019.

[53] Misoprostol is administered orally to prevent the gastric ulcers that are associated with long-term nonsteroidal, anti-inflammatory drugs. Dorland's at 1161. In addition, it is used orally in combination with another drug to terminate pregnancy. Id.

[54] Terbutaline sulfate is administered to pregnant women to stop preterm labor. Dorland's at 1866. It is also used for treatment of asthma-associated bronchospasms. Id.

[55] S. Connors et al., beta2-adrenergic receptor activation and genetic polymorphisms in autism: data from dizygotic twins, J. Child Neurol. 20(11):876-884 (2005).

outcome. Id. at 3020-3021. The 2005 Connors study was not a population study but rather a genetic study, in which only a small subset of male twins showed a greater rate of concordance between autism and terbutaline exposure. Id. At 3020-3022; see also PMRL 73 at 878-879. Due to the difficulty in determining from the study whether the terbutaline itself contributed to the development of the autism or whether the twins were already autistic before they were exposed to the terbutaline (in an effort to avoid a premature birth), Dr. Rodier declined to include terbutaline among the environmental risk factors for autism that she listed in her submitted report. Mead Tr. at 3020-3022.

In addition to questioning whether a causal link between prenatal terbutaline exposure and autism has been established yet, Dr. Rodier distinguished the prenatal exposure of humans to terbutaline that was addressed in the 2005 Connors article from the postnatal exposure of neonatal rats to terbutaline that was addressed in the 2007 Zerrate article, filed as PMRL 106,[56] and on which petitioners relied as support for the proposition that an exposure "during an early critical period" of postnatal development could result in overstimulation of certain brain cells, cause inflammation, and induce autistic-like manifestations. Compare Mead Tr. at 3023-3024 (Dr. Rodier) with Mead Ps' Trial Ex. 2 at 101 (Dr. Aposhian's trial slide) and Mead Ps' Brief at 40. She made clear that the effects of the postnatal exposure of the neonatal rats to terbutaline could not be compared to such a postnatal exposure in humans because "rats are born very immature compared to humans." See id. at 3024. Thus, the period of time in which the studied neonatal rats received terbutaline in the 2007 Zerrate article was more properly compared to the late gestation period in humans. See id.

D. Autistic Regression

While most children with ASDs exhibit developmental differences from birth or early in infancy and are described as having "classic" autism, see PMRL 279 at 299 (2006 Richler article[57]), a notable proportion of autistic children are reported to have acquired skills that are subsequently lost between 18 and 24 months of age. Mead Tr. at 3284-3285 (Dr. Rutter), 3558-3559 (Dr. Lord), 3669-3670 (Dr. Fombonne); Mead R's Ex. W at 3 (Dr.

[56] M. Zerrate et al., Neuroinflammation and behavioral abnormalities after neonatal terbutaline treatment in rats: implications for autism, J. Pharmacol. Exp. Ther. 322(1):16-22 (2007).

[57] J. Richler et al., Is there a 'regressive phenotype' of Autism Spectrum Disorder associated with the measles-mumps-rubella vaccine? A CPEA Study, J. Autism Dev. Disord. 36(3):299-316 (2006).

Lord's report); Dwyer Tr. at 256; PMRL 22 at 313 (2005 Luyster article[58]); PMRL 279 at 299 (2006 Richler article); PMRL 308 at 296 (1998 Kobayashi article[59]). This phenomenon is referred to by the autism community as a regression in autism. PMRL 329 at 560 (1997 Tuchman article [60]); PMRL 343 at 1216 (1991 Tuchman article[61]); see also Mead Tr. at 3284 (Dr. Rutter explaining that the term "regressive autism" was first introduced with vaccine litigation but the phenomenon had been observed for "many, many years").

Not a new phenomenon, regression in autism was first described in the 1940s. Mead Tr. at 3559 (Dr. Lord), 3284 (Dr. Rutter pointing out that "[f]or many decades there have been repeated clinical studies which have noted that a proportion of individuals with autism go through a period in which they appear to lose skills that they had previously); see also Mead R's Ex. MM at 33 (Dr. Fombonne pointing to references in early psychiatric literature published in the mid-1960s describing regressive patterns of autism). The most recent studies indicate that the current rate of regression in autism is between 25 to 40 percent. Mead Tr. at 3310 (Dr. Rutter); Mead R's Ex. MM at 34 (Dr. Fombonne's report); accord Mead Ps' Ex. 30 at 5 (Dr. Kinsbourne's report). The rate has remained stable over time. Mead Tr. at 3285, 3674-3675 (Dr. Fombonne); see also RMRL 151 at 6 (2004 Fombonne article[62]); RMRL 243 at 576 (2005 Honda article[63]); RMRL 478 at 393 (2002 Taylor article[64]). Regression has been found to occur in different disorders falling

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[58] R. Luyster et al., Early regression in social communication in autism spectrum disorders: a CPEA Study, Dev. Neuropsychol. 27(3):311-336 (2005).

[59] R. Kobayashi & T. Murata, Setback phenomenon in autism and long-term prognosis, Acta Psychiatr. Scand. 98(4):296-303 (1998).

[60] R. F. Tuchman & I. Rapin, Regression in pervasive developmental disorders: seizures and epileptiform electroencephalogram correlates, Pediatrics 99(4):560-566 (1997).

[61] R. F. Tuchman & I. Rapin, Autistic and dysphasic children. I: Clinical characteristics, Pediatrics 88(6):1211-1218 (1991).

[62] E. Fombonne, et al., Validation of the diagnosis of autism in general practitioner records, BMC Public Health 4:5-13 (2004).

[63] H. Honda, et al., No effect of MMR withdrawal on the incidence of autism: a total population study, J. Child Psychol. Psychiatry 46(6):572-579 (2005).

[64] B. Taylor, et al., Measles, mumps, and rubella vaccination and bowel problems

(continued...)

within the spectrum of autistic disorders, particularly in classic autism that is characterized by a very early presentation and in pervasive developmental disorder-not otherwise specified. Mead Tr. at 3559 (Dr. Lord); see also Mead Tr. at 2608-2609 (Dr. Rust defining "classic" autism as occurring very early developmentally and without an indication of the regression that may manifest later).

1. Assessing Regression

There are no formal diagnostic criteria for regression in autism. See Mead Tr. at 846-847 (Dr. Kinsbourne acknowledging that "[n]obody has a definition of regressive autism"). The phenomenon is described generally as the loss of skills that had been acquired previously. See id.

Regression is most typically assessed by a clinician or researcher through a "very detailed" interview of a child's parents. Mead Tr. at 3560-3561 (Dr. Lord). The interview requires ascertainment of what the child could do, when the child could do it, and how specific the child's skills were. Id. at 3560; see also id. at 3767-3768 (Dr. Fombonne explaining that the formal interview instrument [the revised ADI[65]] used to diagnose autism does not contain a separate subcategory for regressive autism, but a child may be determined to have regressive autism based on the determination that the child had a loss of skills during the course of his development). Additionally, because many children regain a measure of the lost skills, attention is also given to whether the child is still losing skills, whether the child's skills have become relatively stable, and whether the child is regaining skills or acquiring new skills. Id. at 3560-61; see also RMRL 207 at 608 (2003 Goldberg article); Mead R's Ex. MM at 18 (Dr. Fombonne pointing out that studies have shown consistently that although autistic symptoms persist during an individual's life span, "marked improvements can sometimes be seen"). Respondent's expert Dr. Lord, a clinical psychologist, testified that in an ongoing study of toddlers, one of several major autism research projects with which she is currently involved, the researchers have found that the majority of children who develop autism lose social skills. See Mead Tr. at 3544-45, 3548, 3561-62. She added that if regression is defined by the loss of social skills, a marked loss of certain social skills (including making eye contact and engaging in social interaction) is documentable in "almost all children with autism" between the first and second years of life. Id. at 3562.

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[64](...continued)
or developmental regression in children with autism: population study, BMJ 324(7334):393-396 (2002).

[65] This instrument is referenced as the "ADI" in transcript testimony cited.

2. Features of Regression

The most commonly described manifestation of regression is loss of language. RMRL 364 at 463 (2005 Ozonoff article[66]). The lost communication may be a total loss of language or the loss of a few words. Id. The loss of age-appropriate gestural or imitative communication may also signal a regression in the communication domain. Id.

Losses in the behavioral domain may also be indicative of an occurring regression. Id. Among the behaviors that may be lost are the ability to point, reciprocal smiling, eye contact, anticipatory reaching to be held, and self-care abilities such as eating, dressing or toileting. Id.

Autistic children who experience a regression in skills typically do not lose their motor skills. Mead Tr. at 3565. Similarly, autistic children in general usually do not lose motor skills. Id. Rather, detailed studies show that the chief component of regression is the loss of social communication. Id. Although language or word loss has been the most reliably reported characteristic of regression, researchers have found that the loss of social skills is "in the long run, more characteristic[]" of autistic regression. Id. at 3566.

Regression in autism is understood to follow a predictable, albeit not uniform, pattern. Mead Tr. at 3562. The pattern seems to be characterized first, by a child's acquisition of skills and then, by a slowing down in the acquisition of skills. Id. at 3562. That slowing down is accompanied by a lack of progress and, over a period of time, the acquired skills disappear. For example, the child who has acquired a few words does not acquire new ones for a period of time, and then the acquired words begin to appear less frequently. See id. at 3563; see also RMRL 207 at 608 (2003 Goldberg article[67]) (observing that "some children may acquire a few words by 12–15 months of age and then plateau in expressive language use before the loss of all words"). The child may also become less engaged socially and begin to develop odd behaviors or fascinations. Mead Tr. at 3563. At the time that the child is losing some skills, the child is gaining others. Id. at 3564.

While this pattern or trajectory of regression in autistic children is common, the timing of the process may shift in individual children–occurring at 12 months in some and at 15 months in others–but typically within a six to eight month period of time. Mead Tr. at 3564. Additionally, the scope of the regression that occurs in autistic children varies

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[66] S. Ozonoff et al., Parental report of the early development of children with regressive autism: the delays plus-regression phenotype, Autism 9(5):461-486 (2005).

[67] W. Goldberg, et al., Language and other regression: assessment and timing, J. Autism Dev. Disord. 33(6): 607-16 (2003).

greatly because the subset of skills that a child may lose during regression is limited by the skill set that the child previously acquired. Id. at 3564-3565.

Petitioners' expert Dr. Kinsbourne, a pediatric neurologist, noted in his report that the condition of regressive autism is distinguishable from several known medical conditions that feature regression from normal to autistic functioning. Mead Ps' Ex. 30 at 4 (Dr. Kinsbourne's report). These known medical conditions include Rett's Syndrome, Landau-Kleffner's Syndrome, and Heller's Disease (Childhood Disintegrative Disorder-CDD), and, in each of the conditions, the regression is marked by the loss of previously attained developmental skills. Id.

Rett's Syndrome is limited to females and has additional identifying characteristics that include a specific genetic mutation.[68] See id. The condition is distinguishable from regressive autism because it does not remit as regressive autism has been known to do. Id.

The regression in Landau-Kleffner's Syndrome is typically ushered in by seizures. Id. The early appearance of seizures distinguishes this condition from that of regressive autism, a condition in which seizures usually appear later in the course of the disease. Id.

Additionally, because Landau-Kleffner's Syndrome and, by definition, Heller's disease or CDD, "are not expected to present until after three years of age," the two conditions are distinguishable from regressive autism. Id. at 4-5. The regression that occurs in regressive autism begins in the second year of life. Id. at 4.

Petitioners assert that when the known causative factors of a child's autistic regression are ruled out through a thorough review of the relevant medical history, a reasonable differential diagnosis would then consider other potential causes that might

[68] See RMRL 10 at 187 (R. E. Amir et al., Rett syndrome is caused by mutations in X-linked MeCP2, encoding methyl-CpG-binding protein 2, Nat. Genet. 23(2):185-188 (1999)) (researchers noting that to their knowledge, Rett's syndrome "is the first human disease to be caused by mutations in a gene encoding a . . . factor that has a role in the epigenetic regulation of gene expression"). Factors that are epigenetic affect genetic expression but do not alter genetic structure. See Stedman's Medical Dictionary at 654-655 (28th ed. 2006). See also PMRL 128 at 1261 (M. D. Shahbazian and H. Y. Zoghbi, Rett syndrome and MeCP2: linking epigenetics and neuronal function, Am. J. Hum. Genet. 71(6):1259-1272 (2002) (authors stating that "[d]ata from many laboratories have demonstrated that mutations in [the] MECP2 [gene] are the primary cause" of Rett's syndrome).

have contributed to the regression.[69] See Mead Ps' Ex. 30 at 5 (Dr. Kinsbourne's report). Petitioners argue that among the other potential causes to be considered are environmental factors, including thimerosal-containing vaccines. Id. at 8-9

Rejecting petitioners' claim that environmental factors must be considered once known causative factors of regressive autism are ruled out, respondent's expert Dr. Lord, who has studied regression in autism since the early 1990s, observed in her expert report:

> A major advance in the last 10 years [in the study of regressive autism] has been the recognition that the occurrence of a loss in skills or behavior does not necessarily imply that a child had completely normal development prior to that change. . . . [R]esearchers have become aware . . . of the need to separate the documentation of a loss of skills or change in behavior from whether the child's progress preceding that change was truly normal.

Mead R's Ex. W at 3 (Dr. Lord's report); see also Mead Tr. at 3570-3571 (Dr. Lord stating that "research studies in the last 10 years [indicate] that most children who have losses showed deficits prior to that loss"); RMRL 207 at 608 (2003 Goldberg article) (noting that "[r]ecent findings" suggest that some autistic children may have abnormalities in certain areas of development before they begin to lose skills). Dr. Lord emphasized that whether a child has a skill loss and whether a child has developmental differences are different questions–even if the questions are related ones. Mead Tr. at 3570-3571.

Researchers have found that when parents were asked specifically about their infant's acquisition of different social and communication skills, their responses have pointed to delays in the social and communication domains that preceded the subsequently

[69] An important step in the process of performing a differential diagnosis is ruling in the potential cause of the condition, and if the potential causative agent cannot in fact cause the injury, expert testimony regarding a differential diagnosis that includes that potential causative agent is not helpful. See In re Prempro Products Liability Litigation, 586 F.3d 547, 566 (8th Cir. 2009) (finding testimony properly admitted from an expert that had "sufficiently established that hormones were necessary to the development of [plaintiff's] tumors and [then] conducted her differential diagnosis from th[at] starting point"); Hocraffer v. Sec'y of Health and Human Servs., 63 Fed. Cl. 765, 777 n. 15 (2005) (describing differential diagnosis as a standard scientific technique, with widespread acceptance in the medical community, used to identify the cause of a medical problem by eliminating the likely causes until the most probable is isolated); Heinzelman v. Sec'y of Health and Human Servs., No. 07-01V, 2008 WL 5479123, *5 (Fed. Cl. Spec. Mstr. Dec. 11, 2008) (stating that "without a determination that the potential causative agent actually can cause the injury, differential diagnosis is not a reliable method for determining causation").

reported regression in the child's skills. See Mead R's Ex. W at 4; RMRL 364 at 474 (2005 Ozonoff article). Moreover, research has revealed that the phenomenon of regression or the loss of skills must be distinguished from the phenomenon of stagnation or developmental plateaus, which phenomenon is characterized by a child's failure to gain new skills or progress as expected. RMRL 364 at 463 (2005 Ozonoff article).

In addition, research has suggested that, typically, regression occurs gradually. RMRL 364 at 463 (2005 Ozonoff article). But, in a minority of cases, the onset appears to be sudden. Id.; see also Mead Tr. at 3364-3365 (Dr. Rutter).

At hearing, petitioners' expert, Dr. Kinsbourne, asserted that in cases of regressive autism caused by vaccines, the symptoms of regression occur suddenly. See Mead Tr. at 901-902. Another of petitioners' experts, Dr. Mumper, also testified that "regressive autism" is characterized by the "sudden" onset of symptoms. See Mead Tr. at 1489.

However, respondent's expert, Dr. Lord, a licensed clinical psychologist who has diagnosed nearly 4,000 children with autism and has been researching regression in autism since the early 1980s, testified that describing regression as either a gradual or a precipitous process does not adequately describe the "moving target" of regression. See Mead Tr. at 3542, 3547, 3566. She explained that how regression is viewed–whether as a gradual or as a precipitous process, turns, in part, on what standards are applied to evaluate a regression. See id. at 3566. The higher the threshold required for both skills acquired and for skills lost, the smaller the number of observed regressions. Id. at 3566-3567.

Moreover, the research does not show that regression is characterized routinely by a clear decline in or loss of skills. Id. at 3567; see also id. at 783-784 (Dr. Kinsbourne observing that what constitutes regression in autism is "not always clear-cut" and regression can present on "a continuum"). For example, while most children who lose words regain language, the duration between the loss of language and the return of language varies significantly among autistic children. Id. at 3567 (Dr. Lord). Additionally, while children with autism generally improve by "force of development," the degree of improvement can differ widely. Id. at 3568-3569; see also Mead R's Ex. MM at 18 (Dr. Fombonne noting that follow-up studies of autistic individuals have shown consistently that, although autistic symptoms persist over a life span, marked improvement can occur in individuals with good language and cognitive skills). As Dr. Lord made plain in her testimony, regression in autism does not have a fixed presentation.

Dr. Lord further observed that prior to the first use of the term "regressive autism" in connection with the work of Dr. Andrew Wakefield and the MMR vaccine,[70] regression

[70] As addressed more extensively in the undersigned's decision in Hazlehurst, (continued...)

was viewed simply as one of the variables researchers considered when "looking at early development." See id. at 3578-3579; see also Dwyer Tr. at 224 (Dr. Leventhal testifying that he first heard the term in the 1990s in connection with the work performed by Dr. Andrew Wakefield). Dr. Lord added that the "term 'clearly regressive autism[,]'" a phrase used by petitioners' epidemiologist Dr. Greenland in this case, has neither been heard of nor discussed in the published literature addressing regression in autism. Mead Tr. at 3571.

One of the explanations offered for regression or the loss of skills is an impairment in the brain's signaling process that becomes apparent over the course of the brain's development. See id. at 2602-2603 (Dr. Rust). The signaling process of interest is responsible for turning on or off certain genes that permit more sophisticated brain functions to come on-line over time to replace less sophisticated brain functions that go off-line over time. See id. at 2603. Impairments in this signaling process prevent the gene switching that is necessary to form the more elaborate brain connections that support more sophisticated brain functions. See id. The triggers that lead to impairments in the signaling process appear to be of an internal origin rather than an external one. See id. at 2604.

The second theory of general causation brought by petitioners involved in the omnibus autism proceedings–including the Meads–pertains only to children with a "regressive form" of autism. See Mead Ps' Brief at 13-14, 50; Mead Ps' Ex. 30 at 3 (Dr. Kinsbourne's report); see Mead Tr. at 72 (Dr. Greenland describing this form of autism as "clearly regressive"). The theory does not apply to children with what has been called early onset or classic autism. See Mead Ps' Ex. 30 at 4 (Dr. Kinsbourne's report). The limited application of petitioners' theory reflects petitioners' view that the cause of regressive autism differs from the cause of autism in general. See Mead Ps' Ex. 30 at 4

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[70](...continued)
2009 WL 332306, Dr. Wakefield and several of his colleagues were the principal proponents of the hypothesis that the receipt of the MMR vaccine results in the development of autism spectrum disorders and gastrointestinal problems in certain children. See id. at *87. The techniques used by Dr. Wakefield and his colleagues to implicate the measles vaccine in the development of inflammatory bowel disease were criticized as flawed. See id. Eventually, Dr. Wakefield's hypothesis was dismissed by the scientific community following the publication of a series of methodologically sound studies by a number of groups in the late 1990s unable to replicate the alleged findings of Dr. Wakefield. See id. at *86. But, the hypothesis he put forth precipitated litigation in the United Kingdom examining the causal relationship, if any, between the MMR vaccine and autism. See id. The United Kingdom litigation preceded similar litigation here in the United States.

(Dr. Kinsbourne's report). The undersigned turns now to address the issue of whether "clearly regressive autism" is a distinct phenotype of autism.

E. Petitioners' Claim that Regressive Autism is a Distinct Phenotype of Autism

Petitioners assert in their post-hearing briefing that they "do not seek to create a new diagnostic category for their conditions, no[r] do they endeavor to designate it as a diagnostically distinct syndrome or disorder." Mead Ps' Brief at 51. Rather, petitioners contend that they have put forth evidence "that they experienced an onset of symptoms and pattern of development" described in the medical literature as autistic regression and that the expression of their symptoms is consistent with their theory of causation. Mead Ps' Brief at 50-51. Although petitioners maintain that it is not their position that regressive autism is a separate phenotype of autistic spectrum disorders, what is important to petitioners' theory of causation is a finding–as urged by petitioners' experts Drs. Kinsbourne and Mumper–that regressive autism is a distinguishable condition from early onset or classic autism because regressive autism is characterized by ostensibly normal development prior to the onset of notable changes in behavior and the loss of previously acquired skills.

Respondent's experts pointed to various studies that show no clear distinction between the autism with regression and autism without regression. Respondent's experts contend that regressive autism does not constitute a distinct phenotype of the autistic condition.

At hearing, respondent's expert, Dr. Lord, who was instrumental in the development of the standardized diagnostic instruments for autism and has researched regression in autism for nearly 30 years, see Mead Tr. at 3544, 3547, spoke directly to the issue of whether regressive autism is a distinct phenotype of autism. She addressed her work as the principal investigator on the 2006 Richler study of 351 children with ASDs and 31 typically developing children. Mead Tr. at 3573; PMRL 279 at 303. As she explained, the purpose of the study was to investigate whether there existed a phenotype of "clear regressive unit type of autism" and, if so, whether the phenotype had any relationship to the MMR vaccination. Mead Tr. at 3574. The investigators "started with the hypothesis" that early onset autistic children were different from regressive autistic children, and the investigators wanted to learn "how [the children] were different." Id. at 3575. The investigators examined the group of children in whom researchers had expected to find evidence of a distinct phenotype of regressive autism, if such a phenotype were to exist. Id. at 3578. Dr. Lord stated that a phenotype "implies that there are a cluster of behaviors that are associated with each other. And that there is something

unique about that cluster of behaviors."[71] Id. at 3587; see also id. at 3672, 3684 (Dr. Fombonne explaining that syndromes or phenotypes in psychiatry are validated by clusters of behaviors that are "meaningfully different" and can be correlated to particular differences–such as a biological marker, certain family history, or a different treatment response. If the proposed phenotype cannot be measured, it cannot be investigated.).

The investigators who conducted the 2006 Richler study used existing data from different research projects around the country that were undertaken using the same methods "to diagnose autism and to describe the children with autism." Mead Tr. at 3574 (Dr. Lord). Follow-up interviews were conducted of the previously studied children. Id. The investigators defined regression as "having a loss of words," and asked "very systematic questions about loss of social [skills]." Id. at 3575. The investigators also compared various aspects of development in autistic children prior to their losses with typically developing children. Id. Other factors, such as gender, birth order, ethnicity, and the existence of gastrointestinal symptoms, were examined in the children who had losses "to see if there was something special about those kids." Id. Dr. Lord testified that over the course of the study, only "minor differences in . . . outcome" were detected–specifically, in the children with regression, a slightly lower verbal intelligence quotient ("about 10 points") and a slightly higher frequency of parental reports of diarrhea and constipation. Id. at 3575-3576. The investigators did not find any "clustering of the characteristics " that had been suggested by some to be the defining elements of a regressive subtype of autism. Id. at 3577-78; see also id. at 3587-3588, 3594-3595 (Dr. Lord describing regression in autism as a "striking phenomenon" and "remarkable . . . to watch" but not a "yes-or-no phenomenon" and not a distinct phenotype within the spectrum of autistic disorders). The investigators determined that "[w]hile there was evidence of group differences between children with and without regression, these differences were not associated with particular patterns of timing of vaccination."[72] See PMRL 279 at 315. Nonetheless, the investigators concluded that the evidence overall did not support a finding that the regressive form of autism was vaccine-induced. Id.

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[71] A phenotype is defined as "the entire physical, biochemical, and physiological makeup of an individual as determined both genetically and environmentally, as opposed to genotype [(meaning the "genetic constitution" of the individual)]." Dorland's Illustrated Medical Dictionary 764, 1421 (30th ed. 2003). Inherent in the definition of a "phenotype" is the combined effect of particular genetic and environmental influences on an individual.

[72] Among the detected differences in the children with regression were: (1) stronger skills prior to loss; (2) greater abnormality immediately following skill loss; (3) the involvement of gastrointestinal symptoms; and (4) poorer outcomes. Id.

The 2006 Richler study focused on the role of the MMR vaccine in the development of regressive autism and found no association. See PMRL 279 at 310, 313-314; Mead Tr. at 3598. Although studies are ongoing that focus on whether thimerosal-containing vaccines contribute to the development of regression in autism, Dr. Lord was not aware of any published studies on that subject at the time of the hearing. See Mead Tr. at 3598.

Dr. Lord testified that most studies have found no difference in the clinical outcomes between children with early onset autism and children with autism who have exhibited regression. Id. at 3580; see also id. at 2468 (pediatric neurologist Dr. Rust, another of respondent's expert's, describing his experience in treating autistic children over time and finding no difference in the clinical presentation of children with classic autism and children with regressive autism); Dwyer Tr. at 224-225 (Dr. Leventhal stating that researchers have not been able to show distinctions that would support a finding that regression in autism is indicative of a separate phenotype of the disorder); accord Mead Tr. at 909 (Dr. Kinsbourne testifying that "once the regression has occurred, the person is in an autistic state[, and] [t]he similarities are more than the differences"). Dr. Lord stated that from the longitudinal study that she is conducting now of children who have been identified–either by their parents or by their pediatricians–as at-risk for developing autism,[73] there is information emerging that "much more complicated changes in development [are occurring] than we thought. And . . . [the] things that we used to think only happened in kids who had regressions are actually happening in almost everybody who has autism." Id. at 3580-3582. Different skills are changing at different times, and while some skills deteriorate for a period of time, the skills gradually begin to improve in a number of the studied children. Id. at 3581-82. By way of example, Dr. Lord noted that almost all of the children in her ongoing longitudinal study exhibit some loss in eye contact between the age of 12 months and 24 months. Mead Tr. at 3581. But the children who were not making eye contact at 12 months are not the most autistic children at age three. Id. at 3582. Research is showing the lack of any clear patterns of development in autistic children, whether described as cases of regression or cases of nonregression, that permit a division of the children based on what caused the autistic condition. Id. at 3583.

The clinical presentation of children with classic autism and children with regressive autism is indistinguishable after a period of time, and individuals with autistic features (whether classic or regressive in initial presentation) generally show improvement over time. See Mead Tr. at 2451-2460, 2512-2513 (Dr. Rust); accord id. at 781 (Dr. Kinsbourne noting that "most studies have not found very important differences in the

[73] Among the factors of concern to the parents or the pediatricians of the children who have been referred for inclusion in the longitudinal study are: (1) having an autistic sibling or (2) suffering seizures during the first year of life. Mead Tr. at 3580-81.

outcome between children whose autism gradually emerges and becomes more and more clear, which is the usual situation, and children who regress into such a state"). The improvement occurs without any of the experimental treatments–such as intravenous immunoglobulin (IVIG), nutritional supplements, secretin, chelation, fermented vegetables, earthworm eggs, charcoal capsules, and eskimo oil–for which there has been no reliable showing of efficacy or how the treatments alter the biological process that leads to the development of autism.[74] See Mead Tr. at 2451-2460, 2512-2513 (Dr. Rust).

Dr. Lord asserted at hearing that drawing a distinction between "congenital" or "classical" autism and regressive autism, as Dr. Kinsbourne has in his expert opinion, creates a "false dichotomy." Id. at 3584-3585. She explained that because autism is a disorder affecting development, it cannot be diagnosed until a child's developmental course can be observed and, thus, the disorder cannot be diagnosed in newborns. Id. Dr. Lord cautioned against making "simple inferences" regarding causation based primarily on the later emergence of the disorder. She pointed out that many different disorders, including Huntington's disease,[75] schizophrenia, and sickle-cell anemia, have onsets that occur later but are genetically-influenced. Id. at 3584.

1. Summary of Findings

The weight of the evidence considered in this case fails to point to a cluster of associated behaviors in children described as having regressive autism that is clearly distinguishable from that observed in autistic children in general. Careful studies of children described as having early onset autism and children described as having regressive autism have not shown plainly different patterns of development between the two groups. Nor are the clinical outcomes observed between the groups markedly different. In the view of the undersigned, the lack of a clear distinction between the two

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[74] Respondent's experts expressed open skepticism regarding reports of improvement that follow certain autism treatments, first pointing out that there is no published evidence that chelation therapy is effective in the treatment of autism. Mead Tr. at 3703 (Dr. Fombonne). In addition, as demonstrated in three separate randomized clinical trials comparing the effects of secretin treatments to the effects of a placebo treatment, secretin treatments have been shown to have no efficacy in the treatment of autism. Id. at 3703 (Dr. Fombonne); see also id. at 3342 (Dr. Rutter).

[75] Huntington's disease is a genetic disorder that is characterized by mental deterioration and chronic progressive spastic movements (known as chorea). See Dorland's at 357. Although the age of the affected individual at onset is variable, the onset of the disease usually occurs in the fourth decade of life and death occurs within 15 years of onset. Id.

groups of children militates against a finding that regressive autism is a distinctive phenotype within the spectrum of autistic disorders.

F. Epidemiologic Studies Have Examined Whether There is an Association between Childhood Vaccines and the Development of Autism

Epidemiology is the study of disease distribution in human populations and of the factors that influence that distribution. Mead R's Ex. MM at 24 (Dr. Fombonne's report); Mead Tr. at 3088-3089 (Dr. Goodman defining epidemiology as "the science of patterns . . . of disease in populations and . . . the risk factors for those patterns"). Historically, epidemiologic evidence has assisted the medical sciences community in "look[ing] at environmental causes of disease[s]." Mead Tr. at 3297. Epidemiologists use several methods to measure the occurrence of disease, principally: (1) incidence rates; (2) prevalence rates; and (3) ecologic studies. Mead R's Ex. MM at 24-25.

Incidence rates refer to the number of new cases of a disease (expressed as the numerator) occurring over a specified period of time in those at risk of developing the disease in the population (expressed as the denominator, and measured in person x years). Id. at 24; Mead Tr. at 3814 (Dr. Fombonne explaining that "incidence involves the passage of time . . . [a]nd in this [time] interval[,] you count the number of new cases of disease in the particular population" that was predefined at the start of the study). Cumulative incidence is the proportion of those who were free of the disease at the beginning of the observation period and then developed the disease during that period. Mead R's Ex. MM at 24. Measures of incidence estimate the morbidity associated with a particular disease, the possible changes over time, and the risk factors underlying the disease status. Id. This type of study is referred to as a cohort study, one of two types of controlled epidemiologic studies.[76] See Mead Ps' Ex.18 at 8-9 (Dr. Greenland's report). By design, a cohort study examines and compares how many new cases of a disease occurred in a group of subjects who were exposed to a particular risk factor of interest with how many new cases of a disease occurred in a control group who were not exposed to the same risk factor. See Mead Tr. at 3626 (Dr. Fombonne). Cohort studies have compared autism incidence among vaccinated children (the index group) to the incidence of autism among unvaccinated children (the control group). See Mead Ps' Ex. 18 at 9. Relying on prospective observational data, cohort studies are one of the strongest epidemiologic study designs. Mead Tr. at 3625 (Dr. Fombonne).

[76] The other type of controlled study is a case-control study. A controlled epidemiologic study compares two groups of subjects–one with the disease in question and the other without it–and retrospectively examines the exposure of the two groups to selected risk factors of interest to assess whether an association exists. See Mead Tr. at 3627.

Prevalence rates are measures that reflect the proportion of subjects in a given population who, at that point in time, suffer from the disease. Mead Ps' Trial Ex. 1 at 9 (Dr. Greenland's slides); Mead Tr. at 3634, 3813 (Dr. Fombonne describing prevalence as "a photograph of a particular population at a particular point in time"). Prevalence rates are determined by surveying a cross-section of subjects without the passage of time. Mead R's Ex. MM at 24 (Dr. Fombonne's report). Most epidemiologic studies of autism have been prevalence, rather than incidence, studies. Id. These controlled studies are also referred to as case-control studies. See Mead Ps' Ex. 18 at 8-9 (Dr. Greenland's report). In these studies, vaccination frequency among autistic children (the index or case group) is compared to vaccination frequency among normal children (the control group). Id. at 9. By design, these case-control studies look retrospectively to identify the exposures that increased the risk of disease occurrence. See Mead Tr. at 3627-3628 (Dr. Fombonne).

Controlled studies permit comparisons that allow for inferences to be made regarding the presence or absence of an association. See Mead Ps' Ex. 18 at 9. Controlled studies are distinguishable from ecologic studies.

Ecologic studies compare the rates of the disorder and the rates of the exposure at a population level without ascertaining the association between the disease and the exposure at the individual level. Mead R's Ex. MM at 24-25 (Dr. Fombonne's report); see also Mead Tr. at 92 (Dr. Fombonne). By examining trends in the disease rates in different places or over time in populations with different exposure prevalence, these studies lack data specifically linking the exposure of interest–here, mercury-containing vaccines–to the disease in an individual–here, autism. Mead Ps' Ex. 18 at 9 (Dr. Greenland's report). Because these studies examine trends in the aggregate rather than examining disease onset in exposed individuals, ecological studies are afforded less evidentiary weight in the medical community than controlled studies are. Mead Tr. at 3629. Ecologic studies have been used to evaluate risk of autism in relation to various vaccines. Mead R's Ex. MM at 24-25 (Dr. Fombonne's report).

The prevalence rate for ASDs is estimated to be 60-70/10,000. See Mead R's Ex. MM at 25; Mead Tr. at 3636, 3708; Mead R's Trial Ex. 12 at 6 (Dr. Fombonne's slides). Based on recent surveys by the Centers for Disease Control of eight-year-olds in the United States, one child in 150 children has an ASD. Mead Tr. at 3720. The most prevalent of the ASDs are autistic disorder and pervasive developmental disorder-not otherwise specified. See Mead Tr. at 3710. Cases of Asperger's disorder are more "elusive" and cases of childhood disintegrative disorder are "extremely rare." See id. at 3711-3712. Studies of successive birth cohorts[77] of children born from 1972 to 1985 and of children born from 1987 to 1998 have examined whether the prevalence rate reflects a

[77] An epidemiologic study of a birth cohort is an observational study conducted over a period of time of individuals born in the same year. See Dorland's at 386.

true increase in the incidence rate of autism (or an epidemic) and have led to a belief that the increase in reported rates of autism is due to the broadening of the case definition for autism (changes in diagnostic criteria) and better case ascertainment or detection (changes in diagnostic practices). See id. at 3716; Mead R's Ex. MM at 25-26,32; Mead Tr. at 3281-3283 (Dr. Rutter, who was involved in the formulation of both the diagnostic code for diseases and the classification code for diseases known respectively as the DSM-IV and the ICD-10, describing the broadening of the diagnostic concept of autism to include individuals with normal intelligence). The impact of changes in the practice of diagnostic substitution–that is, assigning an ASD diagnosis to a child who was likely to have received, under former diagnostic practices, a non-ASD diagnosis of either mental retardation or language disorder–cannot be ignored. Mead R's Ex. MM at 27-28. The available epidemiologic evidence has failed to detect a true upward trend in rates of ASDs. Id. at 32; see also Mead Tr. at 3280 (Dr. Rutter stating that "[w]hat is generally agreed is that the diagnosis of autism has risen spectacularly" but whether the noted rise in diagnoses correlates to a "true increase" in the occurrence of autism has not been determined).

1. The Epidemiologic Evidence has Failed to Show An Association between Thimerosal-Containing Vaccines and Autism

Various epidemiologic studies have investigated specifically whether there is a causal association between thimerosal-containing vaccines and the development of autism. The studies show no association between thimerosal-containing vaccines and the development of autistic spectrum disorders.[78]

[78] Although studies conducted by Dr. Mark Geier and his son purport to find an association between thimerosal-containing vaccines and autism, their studies have been criticized consistently by various reviewers, including petitioners' own expert epidemiologist, as methodologically deficient. See Mead Tr. at 122-123 (Dr. Greenland's testimony); accord id. at 3664-3668 (Dr. Fombonne's testimony); Mead R's Ex. O at 10 (Dr. Goodman's report); see also Mead Tr. at 3386-3394, 3423-3424 (Dr. Rutter characterizing the 2008 Young study–that was conducted in part by Dr. Geier and his son and was filed in this case as PMRL 665–as a poorly designed study for the following reasons: (1) the researchers used a "strange" study design that is both a cohort study [a controlled study] and a time/trend analysis of the available database information [an ecological study]; and (2) the researchers included emotional disturbance as one of the neurodevelopmental disorders observed following exposure to thimerosal-containing vaccines even though emotional disorders are not included in any of the official psychiatric classification systems for neurodevelopmental disorders). The undersigned has reviewed carefully the presented studies conducted by the Geiers and has considered

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The undersigned briefly describes the different epidemiologic studies that have examined this issue. As reported in the 2003 Hviid article,[79] a Danish cohort study of 467,000 children compared the incidence of autism in a group of children who had no exposure to thimerosal-containing vaccines and the incidence of autism in a group of children who had such exposure. PMRL 238. The researchers found no increased risk in the subjects with thimerosal exposure. Id. Similarly, a cohort study in the United States of 124,170 children in two health maintenance organizations [HMOs] compared the neurodevelopmental outcomes, including autism, in children with differing levels of exposure to thimerosal through vaccinations and found no clear association between exposure and outcome. PMRL 247 at 1042-1044 (2003 Verstraeten article[80]); see also

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[78](...continued)
the criticisms leveled against the Geiers' studies. Persuaded that the studies are flawed methodologically in critical respects, the undersigned, without addressing the studies in extensive detail here, declines to accord any evidentiary weight to the studies. The undersigned notes that other researchers have been unable to verify the validity of the Geiers' statistical analysis on a number of occasions and a number of courts have expressed concerns about the reliability of their work. See IOM, Immunization Safety Review: Vaccines and Autism (Washington, DC: National Academies Press (2004)) at 55-62, 65 (calling their work unintelligible); see also Graham v. Wyeth Laboratories, 906 F.2d 1399, 1418 (10th Cir.1990) (the magnitude of Dr. Geier's calculation error deemed sufficient to warrant a new trial); Doe v. Ortho-Clinical Diagnostics, 440 F. Supp.2d 465, 474 (M.D.N.C. 2006) (Dr. Geier's testimony excluded on grounds that it included "hypothesis and speculation."); Redroot v. B.F. Ascher & Co., 2007 U.S. Dist. LEXIS 40002 (N.D. Cal. June 1, 2007) (finding Dr. Geier's testimony "not reliable" and excluding him as an expert); Pease v. American Cyanamid Co., 795 F. Supp. 755, 760-61 (D. Md.1992) (trial court granted summary judgment, noting inconsistencies in Dr. Geier's opinion); Jones v. Lederle Laboratories, American Cyanamid Co., 785 F. Supp. 1123, 1126 (E.D. N.Y.1992) (stating that "the court was unimpressed with the qualifications, veracity, and bona fides" of Dr. Geier); and Militrano v. Lederle Laboratories, American Cyanamid Co., 3 Misc.3d, 523, 537-38, 769 N.Y.S.2d 839 (N.Y. Sup. Ct. 2003) (describing Dr. Geier's affidavit as "conclusory and scattershot" and "undermined by many of the materials submitted in support of it"); Snyder v. Sec'y of Health and Human Servs., No. 01-162V, 2009 WL 332044 n.204 (Fed. Cl. Spec. Mstr. Feb. 12, 2009) (noting repeated criticism of the Geiers' analytical methods).

[79] A. Hviid et al., Association Between Thimerosal-Containing Vaccines and Autism, Journal of American Medical Association 290(13): 1763-1766 (2003).

[80] T. Verstraeten et al., Safety of Thimerosal-Containing Vaccines: A Two-Phased Study of Computerized Health Maintenance Organization Databases, Pediatrics 112(5):
(continued...)

RMRL 18 (2006 Austin article[81]) (a reanalysis of the data sets examined in the Verstraeten study). Other researchers reported in the 2004 Andrews article[82] the results of a cohort study that examined the thimerosal exposure by vaccination and the neurodevelopmental problems in 107,152 children, including 2,500 low-birth weight (pre-term) infants, as documented in the electronic medical database maintained in the United Kingdom. PMRL 4. The researchers found no relationship between the received vaccine doses and the development of autism. Id.

As reported in the 2003 Madsen article,[83] researchers conducted an ecological study looking at the effect of discontinuing the use of thimerosal in vaccines in 1992 in Denmark and found that autism rates continued to increase after the removal of thimerosal from vaccines. PMRL 239. The researchers drew the conclusion that their data did not support a finding of a correlation between thimerosal content in vaccines and the incidence of autism. Id. Another ecological study, the results of which were reported in the 2003 Stehr-Green article,[84] similarly showed increasing rates of autism in California, Denmark, and Sweden even though the use of thimerosal had been discontinued in Denmark and Sweden. PMRL 230 at 106. The researchers conducting that study concluded that no correlation existed between thimerosal exposure and autism rates. Id. The following year, the results of an English cohort study of the children born to the 13,000 pregnant women

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[80](...continued)
1039-1049 (2003).

[81] H. Austin & C. Lally, A Re-analysis of the Vaccine Safety Datalink (VSD) Project Conducted by the Centers for Disease Control and Prevention Pertaining to Safety Issues Related to Thimerosal-Containing Vaccines (2006). This document was filed into the Omnibus Autism Docket as Exhibit 91.

[82] N. Andrews et al., Thimerosal Exposure in Infants and Developmental Disorders: A Retrospective Cohort Study in the United Kingdom Does Not Support a Causal Association, Pediatrics 114(3): 584-591 (2004).

[83] K. M. Madsen et al., Thimerosal and the Occurrence of Autism: Negative Ecological Evidence From Danish Population-Based Data, Pediatrics 112(3): 604-606 (2003).

[84] P. Stehr-Green et al., Autism and Thimerosal-Containing Vaccines: Lack of Consistent Evidence for an Association, American Journal of Preventive Medicine 25(2): 101-106 (2003).

recruited for the study were reported in the 2004 Heron article.[85] PMRL 14. The researchers found no association between vaccination exposure and special needs in children. Id. at 583. Subsequently, as addressed in the 2006 Fombonne article, filed as RMRL 167,[86] researchers conducting an ecological study that examined trends in autism rates and different vaccination exposures of children–over a time period during which the immunization schedule in the province of Quebec changed–failed to find a correlation between the variables of autism and vaccination.[87] PMRL 40. More recently, researchers reported in the 2008 Schechter article[88] the results of an ecological study examining trends in the database maintained by California's Department of Developmental Services to see whether referrals for state services declined after the use of thimerosal in vaccines was discontinued. RMRL 439. Finding that the number of referrals for services did not drop but rather increased, the researchers concluded that the study did not support a connection between thimerosal-containing vaccines and developmental problems. Id.

Another study of note is a case-control study based on information contained in the large electronic medical database kept in the United Kingdom. PMRL 245 (2003 Jick article[89]). One of the researchers that conducted that study noted in a letter to the editor of the New England Journal of Medicine that the researchers found no evidence of an increased risk of autism following a three-dose series of thimerosal-containing DPT vaccinations. See PMRL 92 at 1 (2004 Jick letter[90]). The same researcher observed that

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[85] J. Heron et al., Thimerosal Exposure in Infants and Developmental Disorders: A Prospective Cohort Study in the United Kingdom Does Not Support a Causal Association, Pediatrics 114(3):577-583 (2004).

[86] E. Fombonne, Past and Future Perspectives on Autism Epidemiology, in Understanding Autism: From Basic Neuroscience to Treatment 25-48 (S. Moldin & J. Rubenstein, eds., CRC Press, Taylor & Francis Group) (2006).

[87] The changes occurred in 1996 and included the discontinuance of the use of thimerosal in the vaccines and the addition of a second dose of MMR at 18 months of age (to follow the first dose of MMR administered at 12 months of age). PMRL 40 at e139.

[88] R. Schechter and J. Grether, Continuing increases in autism reported to California's developmental services system: mercury in retrograde, Arch Gen Psychiatry. 65(1):19-24 (2008).

[89] H. Jick & J. Kaye, Epidemiology and Possible Causes of Autism, Pharmacotherapy 23(12): 1524-1530 (2003).

[90] H. Jick and J. Kaye, Autism and DPT vaccination in the United Kingdom

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the finding "provide[d] further support for the view that exposure to mercury in vaccines is not the cause of the rising incidence" of autism diagnoses over the past decade. See id. at 2. Although that finding reported in the 2003 Jick article was consistent with the results of another study finding "no evidence of an increased risk of autism or other developmental problems related to exposure to thimerosal in vaccines," the undersigned gives little weight to the 2003 Jick article because the researchers–who disclosed in the letter to the editor that they had served as consultants to legal counsel for a vaccine manufacturer involved in litigation involving allegations of vaccine-related harm–may have conducted the study for litigative purposes.

Respondent's expert, Dr. Rutter, a pediatric psychiatrist who has looked specifically at the interplay between genetics and the environment in autistic persons, noted that "the best studies all have limitations." Mead Tr. at 3300. Having examined the limitations of the studies addressed here, he opined that taken as a whole, the studies were all "unsupportive of a causal association." Id. at 3300-3305.

Dr. Rutter acknowledged that epidemiologic evidence does exist that "high doses of mercury are toxic to the brain and cause [brain] damage" and "there is some suggestive evidence there may be slight cognitive sequelae with . . . intermediate levels" of mercury exposure.[91] Mead Tr. at 3295-3296. But, Dr. Rutter made clear that none of the

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[90](...continued)
N. Engl. J. Med. 350(26): 2722-2723 (2004).

[91] The studies of high dose exposure to which Dr. Rutter referred are the epidemiologic studies in the Seychelles Islands, in the Faroe Islands, and in New Zealand. See PMRL 241 at 1692 (G. J. Myers et al., Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study, Lancet 361:1686-1692 (2003) (a longitudinal assessment of a group of children in the Seychelles Islands examined at six, 19, 29, and 66 months of age and then at 9 years of age showed "no detectable adverse effects in a population consuming large quantities of a wide variety of ocean fish")); PMRL 180 at 302-304 (P. Grandjean et al., Methylmercury Exposure Biomarkers as Indicators of Neurotoxicity in Children Aged 7 Years, American Journal of Epidemiology 150(3):301-305 (1999) (children born in the Faroe Islands having significant prenatal methylmercury exposure from their mothers' ingested whale meat were administered neuropsychological tests at seven years of age that showed some diminution in visuospatial memory performance)); PMRL 215 at 72 (T. Kjellstrom et al., Physical and mental development of children with prenatal exposure to mercury from fish. Stage II: Interviews and psychological tests at age 6, National Swedish Environmental Protection Board, Report 3642. Solna, Sweden (1989) (a follow-up study of children with high prenatal methylmercury exposure through maternal fish

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epidemiologic studies identifies autism as an outcome of high dose mercury exposure or even an intermediate level dose exposure. Id. at 3296. Moreover, in his opinion, there is an absence of reliable evidence that chronic low-dose exposure to thimerosal vaccine causes regressive autism. Id.

Petitioners concede through their expert, Dr. Greenland, that the epidemiologic literature to date has not detected an association of mercury-containing vaccines with autism in general or autistic-spectrum disorders. Mead Ps' Ex. 18 at 1 (Dr. Greenland's report); see also Mead Tr. at 122. Petitioners assert, however, that the epidemiologic literature "has not ruled out the possibility" that mercury-containing vaccines are associated with a specific "type of autism, [in particular,] the regressive form." Mead Ps' Ex. 18 at 1. See also Mead Ps' Trial Ex. 1 at 2 (Dr. Greenland's slides); Mead Tr. at 70 (Dr. Greenland). Petitioners argue that "[t]he inability of the literature to reject this possibility is largely due to the limited number of autism cases of the regressive type, and the failure of published controlled epidemiologic studies to date to separate regressive autism from other types." Mead Ps' Ex. 18 at 1. The premise of petitioners' argument is that regressive autism is a distinct form of autism, and by failing to "isolate" the regressive form of autism from other disorders on the autism spectrum, the conducted studies lack the specificity to detect an association, if any exists. See id.; see also Mead Tr. at 76 (Dr. Greenland testifying that if any association between thimerosal-containing vaccines and clearly regressive autism exists, it has been "submerged" in all the available epidemiologic studies).

2. Petitioners Claim that the Epidemiologic Studies Conducted to Date Lack Sufficient Specificity to Detect an Association, If One Were to Exist

Petitioners' expert epidemiologist, Dr. Greenland, stated that the ability to detect an association between a particular exposure and the disease of interest turns on the specificity of the association. See Mead Tr. at 77; Mead Ps' Ex. 18 at 4 (Dr. Greenland's report) (stating that "[i]f an exposure . . . is associated with a disease category, an exposure will likely exhibit different associations with the different disease types within the broad category [of diseases, such as cancer]"). He explained:

> [S]pecificity of an association means that an exposure has little or no association with the majority of [the disease] types in a disease category, but [has] some association with one or a few of those

[91](...continued)
consumption that found "a tendency for the group with [a] mean pregnancy hair mercury level above 6 mg/kg to perform less well in the psychological tests than children with lower mercury exposures")).

> [disease] types. If a highly specific association is present, failure to separate the [disease] types can severely dilute the association of the exposure with the disease category to the point that it can become undetectable.

See Mead Tr. at 77.

Dr. Greenland classified cases of regressive autism that occur without ostensible early developmental abnormalities as "clearly regressive cases," a descriptive phrase he acknowledged creating "for lack of a better term." Id. at 77. He reasoned that "such cases would be a minority of regressive cases and thus a small minority of all cases of autism, so even if something called regressive cases is common, but certainly not the majority of cases, then clearly regressive cases would become quite uncommon." Id. at 77-78. Using the estimate of clearly regressive cases of autism contained in the report prepared by respondent's expert Dr. Fombonne, a pediatric psychiatrist who testified at hearing about the characteristics of regression in autism and about the epidemiologic studies that have failed to find an association between vaccines and autistic regression, Dr. Greenland stated that approximately six percent of all autism cases are clearly regressive ones. Id. at 78; Mead Ps' Trial Ex. 1 at 12; see also Mead R's Ex. MM at 14 (Dr. Fombonne's report) (acknowledging that it "is perhaps the case in a small subset of children with regressive autism" that development prior to the onset of regression was "absolutely normal"). Deferring to Dr. Fombonne's expertise in diagnosing ASDs, Dr. Greenland construes the figure of six percent, taken from Dr. Fombonne's report, as the upper limit of the clearly regressive type of autism cases. See Mead Tr. at 79-80; Mead Ps' Trial Ex. 1 at 12 (Dr. Greenland's slides).

The premise for Dr. Greenland's testimony is his determination–purportedly based on Dr. Fombonne's testimony–that about six percent of all autism cases are "clearly regressive." Mead Tr. at 79-80. Because the premise is important to Dr. Greenland's opinion, it merits closer examination.

Dr. Fombonne did assert that regression in autism is sufficiently common to be detected in epidemiologic studies because approximately 20 percent of autism cases involve regression. See Mead Tr. at 78 (Dr. Greenland)(referring to Dr. Fombonne's report); Mead R's Ex. MM at 33-34 (Dr. Fombonne's report). In a study of children with regressive autism, 72 percent were found not to have been developing normally before the regression occurred–a finding that was consistent with studies that have shown that most children with regressive autism display subtle developmental abnormalities long before the regression occurs. Mead R's Ex. MM at 14. Although Dr. Greenland admitted that he had no expertise in autism or regressive autism, he construed Dr. Fombonne's expert report–stating that studies have shown that recognizable abnormalities existed prior to regression in 72 percent of the reported cases of regressive autism–to indicate that 28

percent of the 20 percent (or roughly six percent) of the estimated total cases of regressive autism involve "clearly regressive" autism. See Mead Tr. at 78, 126. Dr. Fombonne observed that "abnormal development can be documented in children with 'regressive autism' before the regression occurs even though the parents are unaware of it." Mead R's Ex. MM at 14. Dr. Fombonne added: "Even if a child's development were absolutely normal, as is perhaps the case in a small subset of children with regressive autism, the regressive pattern of behavior does not mean that the cause of the regression is environmental." Id. (internal reference omitted). Dr. Fombonne reasoned that "[t]here are many genetic diseases that manifest only after a period of normal development, followed by a loss of function or regression." Id. Contrary to Dr. Greenland's characterization, Dr. Fombonne did not identify any "clearly regressive" cases of autism. Rather, Dr. Fombonne merely allowed for the possibility that ostensibly normal development preceded the onset of regression in a small subset of children with regressive autism, a distinction that calls into question the validity of Dr. Greenland's premise that approximately six percent of the total cases of regressive autism involve "clearly" regressive autism.

Based on the premise that the clearly regressive form of autism constitutes a small percentage of autism cases in general, Dr. Greenland speculated that–if exposure to thimerosal-containing vaccines is associated only with the clearly regressive form of autism–the increased risk of developing the clearly regressive form of autism through exposure to thimerosal-containing vaccines still would elude detection by epidemiologic studies. See Mead Tr. at 79-81. Dr. Greenland explained that "[e]pidemiology is simply too crude a tool to be able to detect increases in risk of [the] order" involved with the clearly regressive form of autism.[92] Id. at 81. He also observed that the detection of any association between thimerosal-containing vaccines and the clearly regressive form of autism becomes even more difficult in studies that have considered more than classic cases of autism–including, for example, cases from the spectrum of autistic disorders or, even more broadly, cases involving developmental disorders in general. Id.

[92] Assuming no exposure to thimerosal-containing vaccines, Dr. Greenland indicated that six cases of 100 would be expected to be of the clearly regressive form. Mead Tr. at 80. Further assuming that exposure to thimerosal-containing vaccines is associated only with the clearly regressive form of autism and that with such vaccine exposure, the number of cases of clearly regressive autism doubles, Dr. Greenland explained that the increase in risk would yield an "excess of six cases over the original six. . . . [which] would result in a total of 100 plus six cases or 106 cases." Id. at 80-81. "This six percent increase [would] translate[] [in]to a risk ratio of only 106 over 100 or 1.06." Id. at 80-81; Mead Ps' Trial Ex. 1 at 12-13 (Dr. Greenland's slides). Risk ratios that are close to 1.0 are not deemed to be statistically significant. See Mead Tr. at 83-84 (Dr. Greenland). Only when the risk ratio is 2.0 or greater is the exposure of interest thought to have "led to an increase in the risk of the outcome." Id. at 3627 (Dr. Fombonne).

Dr. Greenland asserted that small increases of risk that yield small risk ratios cannot be reliably distinguished from a risk ratio of 1.0 by ordinary epidemiologic studies. See Mead Ps' Ex. 18 at 6 (Dr. Greenland's report). A risk ratio of 1.0 is reported in studies as a demonstration of no association between the exposure and the disease of interest. See Mead Tr. at 83-84; Mead Ps' Ex. 18 at 11; see also Mead Tr. at 3100 (Dr. Goodman explaining that a risk ratio of 1.0 indicates that the risk associated with a particular exposure is "equal in [the] two groups"–specifically, the control and study groups–and, thus, the exposure is of "zero effect"); Mead Tr. at 3626-3627 (Dr. Fombonne explaining that "a risk ratio [of] . . . one . . . means the [disease] incidence is not affected by the exposure"). Dr. Greenland asserted that the proper interpretation of this risk ratio "is not a demonstration of no association," but rather a "[f]ailure to detect an association." See Mead Tr. at 83-84. According to Dr. Greenland, the distinction is an important one because the "[f]ailure to detect an association" allows as "one among many possibilities" that no association exists. See id. at 84. But it does not foreclose the possibility of an association and, thus, permits petitioners' claim to remain a viable one. See id.

Dr. Greenland added that any evaluation of the statistical strength of a study must consider not only the statistical significance or non-significance of the reported risk ratio, but also the reported confidence intervals. See Mead Tr. at 84-87. The confidence intervals establish a range of values (specifically, the upper and lower limits of the values) deemed to reflect the same relative risk as the determined risk ratio. See id. Dr. Greenland testified that because the confidence intervals give a broader range to the risk ratio to account for random errors, the statistical significance or non-significance of the reported risk ratio can becomes less certain. See id. at 85-86, 97; see also Mead R's Ex. O at 7 (Dr. Goodman's report) (concurring that "the 'confidence intervals' around the summary risk estimates" demonstrate the statistical imprecision associated with such estimates of risk); Mead Tr. at 3098-3101 (Dr. Goodman explaining that the confidence interval establishes the range of uncertainty within which an estimated exposure risk is expected to fall) .

Having pointed out the technical limitations of epidemiologic studies, Dr. Greenland stated that:

> [w]hat one needs to understand very carefully about epidemiologic studies and statistical studies of that sort is that they leave open a broad range of uncertainty. They're simply not within their power.
>
> Those studies do not have the ability in a scientific sense to rule out these other options or possibilities.

Mead Tr. at 85. Dr. Greenland observed that in his review of the epidemiologic studies of thimerosal-containing vaccines and neurodevelopmental disorders on which respondent's experts relied in their reports, he did not find "any published, peer reviewed, controlled epidemiologic stud[ies]" that looked for an association between thimerosal-containing vaccines and clearly regressive autism in particular. Dr. Greenland addressed, in turn, the key epidemiologic studies cited by respondent's experts.[93] See id. at 87-105.

Unpersuaded that the cited series of studies provides evidence that there is no association between thimerosal-containing vaccines and clearly regressive autism, he stated:

> I'm not convinced . . . [by] [t]he epidemiologic evidence . . . for the dilution reason that I've given[.] [And] if I take into account all of the uncertainties associated with these studies, both the statistical error, the summary confidence interval that I would get combining these studies and then take into account the dose differences and what's not understood about the dose

[93] Addressing the 2003 Hviid study, PMRL 238, Dr. Greenland indicated that the 95 percent confidence interval limits reported in that study "would allow for [the finding of a] substantial association with clearly regressive autism." Mead Tr. at 88; Mead Ps' Trial Ex. 1 at 24. He further stated that because the children in the Danish study "have roughly half the total mercury exposure in early childhood from the vaccines as in the American vaccination schedules, . . . the study should be expected to exhibit a weaker association than would an American study if there were such an association." Mead Tr. at 89; Mead Ps' Trial Ex. 1 at 26.

Dr. Greenland's criticisms of the 2003 Hviid study were the same for the 2004 Andrews study, PMRL 4, and the 2004 Jick study, PMRL 92. Mead Tr. at 89-90; Mead Ps' Trial Ex. 1 at 27-28. Dr. Greenland observed that the 2004 Heron study reported no analysis for autism, Mead Tr. at 89-90, and he noted that the first author of the 2003 Verstraeten study, PMRL 247, concluded that "an association between thimerosal and neurological outcomes could neither be confirmed nor refuted," Mead Tr. at 90.

Dr. Greenland stated that the two ecological studies of time trends in autism, namely the 2003 Madsen study, PMRL 239, and the 2003 Stehr-Green study, PMRL 230, were not able to detect "a specific association of [thimerosal-containing vaccines] with clearly regressive autism" because such an association, if one exists, "would be submerged by the large background trends reported." Mead Ps' Trial Ex. 1 at 17, 32. Similarly, because the 2009 Fombonne study analyzed pervasive developmental disorders, a broader category of disorders that includes classic and regressive autism, see PMRL 761, Dr. Greenland reasoned that the results of the study were similarly diluted. Mead Tr. at 93.

> differences, th[en] I could not possibly rule out the kind of small risk ratio overall that we saw before arising from a relatively large risk ratio for clearly regressive autism.

Id. at 90-91. In Dr. Greenland's view, the epidemiologic data allowed for the theoretical possibility that an association exists between thimerosal-containing vaccines and autism spectrum disorders even though, to date, that data has shown no such association. See id. at 121-122. His opinion that there could be an elevated risk associated with thimerosal exposure pertained to persons with the clearly regressive form of autism only, see id. at 124-126, and his opinion was premised on the theoretical possibility that the clearly regressive form of autism is a distinct and rare subgroup of autism, see id. at 129-130.

Dr. Greenland conceded that he has no expertise with autism or with regressive autism. Id. at 126. In addressing regressive autism, he relied on the definition of regressive autism supplied in the filed literature, and he relied "on other experts" for evidence that the regressive form of autism is biologically distinct from other cases of autism. Id. at 126-128. Moreover, Dr. Greenland acknowledged on cross-examination that if the number of identified autism cases is–as petitioners in this case assert–attributable to a true increase in the occurrence of the disorder (described by some as an epidemic) rather than to changes in diagnostic practices, the epidemiologic studies do not support the hypothesis that the epidemic is caused by thimerosal-containing vaccines, presumably because the alleged epidemic has continued even though vaccines no longer contain thimerosal. Id. at 124. Dr. Greenland also made clear that although it is his opinion that the epidemiologic studies have not disproved the hypothesis that thimerosal-containing vaccines cause clearly regressive autism, it is "[d]efinitely not" his opinion that the studies have proved the hypothesis. Id. at 133-134.

An important underpinning to petitioners' position is a finding that regressive autism is a distinct phenotype on the spectrum of autistic disorders. Respondent's expert epidemiologist, Dr. Goodman,[94] pointed out, however, that "[d]istinctions based on disease phenotype ([such as,] regressive autism) are only meaningful if that phenotype is shown to be associated with a different causal pathway, or has a fundamentally different biology than other phenotypes." R's Ex. O at 8 (Dr. Goodman's report). Accordingly, Dr. Goodman asserted that analogizing different types of cancer to autism phenotypes, as

[94] Dr. Goodman practiced as a board-certified pediatrician before joining the faculty of Johns Hopkins School of Medicine in the Department of Oncology, with joint appointments in epidemiology and biostatistics. Mead Tr. at 3066.

Dr. Greenland did, is inappropriate because

> different types of cancer affect recognizably different organs, tissues, and cells that, in consequence, have well-characterized and dramatically different phenotypes, biology, prognoses, and treatments. These types of biological distinctions in cancer are not known to apply to autism phenotypes, and no scientific evidence is offered for the speculation that they might.

Mead R's Ex. O at 7; see also Mead Tr. at 3105-3108 (Dr. Goodman stating that the different risk factors, different disease courses, and different treatments that exist for different forms of cancer have not been shown, at this point in time, to exist "in the autism realm"); id. at 3679 (Dr. Fombonne stating that researchers do not conduct studies to search for "very rare phenotypes . . . [u]nless we have some preliminary evidence that there might be such a subgroup").

Dr. Goodman agreed with Dr. Greenland that an individual epidemiologic study, when examined in isolation, would not eliminate the possibility that an elevated risk exists in a small subgroup. Mead R's Ex. O at 8. But, he explained, when a meta-analysis is performed to combine quantitatively the results from the separate studies, "the collective precision of all the studies taken together is greater than any of the studies taken alone."[95] Id. Dr. Goodman noted that the similarity in the findings of "[m]any studies, designed in different ways, in different populations, and using different approaches" is instructive. Id. at 9-10, 14; Mead Tr. at 3095; see also Mead Tr. at 3386 (Dr. Rutter explaining that when a varied range of study designs and strategies–each with particular strengths and weaknesses–"come up with a broadly similar answer," greater confidence can be placed in the conclusion reached as more likely than not to be "solid"); id. at 3661-3662 (Dr. Fombonne stating that although each study has its own limitations, the consistency of the findings "across different populations with different study designs" provides "robust" support for rejecting the hypothesis put forward in this case).

Dr. Goodman added that epidemiologic studies cannot be viewed "in purely statistical terms" but must also be guided by biologic understanding. Mead R's Ex. O at 5; see also Mead Tr. at 3091-3092, 3113-3115. He observed that as a member of the Immunization Safety Review Committee of the Institute of Medicine (IOM) that prepared

[95] Dr. Goodman elaborated at hearing that meta-analysis has two parts: quantitative and qualitative. Mead Tr. at 3108-3109. The qualitative aspect of meta-analysis focuses on the results of a series of studies done in different ways. Id. The quantitative aspect of meta-analysis combines the studies that have upper confidence interval limits that are only slightly above 1.0 to get a more precise confidence interval. Id. at 3109.

the 2004 IOM Report that expressly considered whether a causal relationship existed between thimerosal and autism,[96] he has reviewed a range of evidence, including epidemiologic studies and "an array of laboratory animal clinical-type studies . . . related to the [presented] hypothesis." Mead Tr. at 3084. Dr. Goodman explained that the Immunization Safety Review Committee of the IOM had conducted an assessment of the scientific plausibility of a causal relationship between the thimerosal preservative in vaccines and neurodevelopmental problems in response to emerging immunization safety concerns based on evidence suggesting "that exposure to . . . mercurial compounds c[ould] affect the nervous system." Mead Tr. at 3076, 3083; see also RMRL 254 at 2 (2001 IOM report[97]); RMRL 255 at 11 (2004 IOM report[98]). Based on a series of issued reports, the IOM concluded that there was no causal association and that the hypothesis had little

[96] Congress created the National Academy of Sciences by An Act of Incorporation in 1863 to advise the federal government on scientific and technical matters. See An Act to Incorporate the National Academy of Sciences, ch. 111, 12 Stat. 806 (1863), codified as amended, 36 U.S.C. § 150303 (1998). Under the charter of the National Academy of Sciences, the Institute of Medicine (IOM) was established in 1970 to serve as an advisor to the nation on health issues. See www.iom.edu (last visited on 2/26/10); see also RMRL 254 (IOM 2004 Report). When enacting the Vaccine Act in 1986, Congress further charged the IOM with conducting studies to explore whether any causal relationships might exist between vaccines and injuries. See 42 U.S.C. § 300aa-1 note. See also RMRL 254 (IOM 2004 Report).

[97] Institute of Medicine, Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders, Washington, D.C. (National Academies Press 2001).

[98] Institute of Medicine, Immunization Safety Review: Vaccines and Autism, Washington, D.C. (National Academies Press 2004).

scientific merit.[99] See RMRL 254 at 66 (2001 IOM Report) (concluding first "that the evidence [was] inadequate to accept or reject a causal relationship between exposure to thimerosal from childhood vaccines and the [neurodevelopmental disorders] of autism, ADHD, and speech or language delay); RMRL 255 at 1 (2004 IOM Report) (then concluding that the body of epidemiologic evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism). Dr. Goodman observed at hearing that "a combination of the strength of the epidemiologic evidence [finding no causal association] and the absence of any laboratory or mechanistic evidence that would controvert that conclusion" led to the IOM's reported determination that "the evidence favors rejection" of the hypothesis. Mead Tr. at 3085, 3095-3096.

Dr. Goodman stated that before an inference could be made that a causal relationship exists, the strength of the epidemiologic evidence and the strength of the biologic evidence must be assessed. See Mead Tr. at 3093, 3126-3128, 3141. Referring to the epidemiologic evidence as "counting evidence," Dr. Goodman noted that "the weaker the counting evidence [that nonetheless must] . . . be beyond the play of chance, the stronger the underlying biologic theory has to be." Id. at 3093. Dr. Goodman, as well as respondent's experts Drs. Fombonne and Rutter, asserted that the totality of the current epidemiologic evidence strongly supports the conclusion that there is no causal association

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[99] In the 2001 report, the Immunization Safety Review Committee used the phrase "biological plausibility" to indicate that the hypothesis "did [not] violate any known biologic[al] or physical principles." See Mead Tr. at 3080-3081; RMRL 254 at 56 (2001 IOM Report). Although intended to convey only that the hypothesis was not a biological impossibility, the phrase in the issued report was interpreted by many as suggesting that the hypothesis was likely or probable. Mead Tr. at 3081. Because that was not the manner in which the committee intended to use the phrase, the committee became much more precise in subsequent reports about how it was evaluating the biological evidence. Id.

The committee identified three categories into which a proposed biological mechanism could fall: (1) theoretical; (2) experimental; and (3) demonstrated. Id. at 3081-3082. The theoretical category applied to a mechanism that was biologically plausible and was presented "as a possibility worthy of exploration." Id. The experimental category applied to aspects of the mechanism that presented a portion of the causal pathway that had been demonstrated "in the laboratory or in other clinical experiments" and, thus, allowed an evaluation of whether the mechanistic evidence was weak or strong. Id. at 3082. The third category of demonstrated or proven applied where there was an actual showing in a human being that a particular exposure caused a certain outcome–as in the case of a re-challenge. Id. A re-challenge is demonstrated when the same outcome is reproduced in a person each time that person is exposed to the same vaccine. Id.

between the mercury component in childhood vaccines and the development of autistic disorders.

3. Summary of Findings

Although petitioners agree that to date, the epidemiologic evidence has failed to show any association between thimerosal-containing vaccines and autistic spectrum disorders, petitioners assert that the conducted epidemiologic studies lack the sensitivity to detect a correlation between thimerosal-containing vaccinations and regressive autism. Petitioners' position presumes that regressive autism is a phenotype of autism that is distinct from early onset or classic autism, rests on a theoretical statistical possibility, and relies on the limitations that are inherent in each of the individual epidemiologic studies. However, studies of the developmental patterns in children described as having early onset autism and in children described as having regressive autism militate against a finding that regression in autism constitutes a separate phenotype of autistic disorder. The likelihood of the theoretical statistical possibility on which petitioners rely is diminished when, consistent with sound analytical principles, the results of the epidemiologic studies conducted at different times in different populations and with different study designs are viewed as a whole and are found to reach consistent conclusions. Petitioners' assertions that a clearly regressive form of autism exists as a separate phenotype of autistic disorder and that current epidemiologic studies do not preclude the finding of a causal association between thimerosal-containing vaccines and the clearly regressive form of autism are highly speculative possibilities that are difficult to credit in the absence of affirmative evidentiary support and in the presence of a mounting body of evidence to the contrary. Although the epidemiologic evidence is not determinative, it is instructive.

G. Petitioners' Proposed Biological Mechanism of Harm

The undersigned turns next to examine petitioners' proposed theory of harm caused by thimerosal-containing vaccines. Thimerosal is the mercury-containing preservative formerly found in vaccines commonly administered to children. Information about the different forms of mercury and the principal sources of human exposure to mercury is important to an understanding and evaluation of petitioners' theory. Information about what happens to mercury once it enters the body and then reaches the brain, and information about what effect mercury has once it is in the brain is also important. Additionally, in evaluating petitioners' proposed theory of harm, consideration must be given to petitioners' claim that certain persons are hypersusceptible to mercury due to an innate inability to excrete it. The undersigned now addresses each of these subjects and examines first the thimerosal component in the vaccines at issue.

1. The Thimerosal Component in Pediatric Vaccines

Thimerosal contains 49.6% mercury by weight. See RMRL 254 at 27 (2001 Report of the Institute of Medicine). Thimerosal is comprised of ethylmercury, which is an organic form of mercury, and thiosalicylate, a sulfur and salt compound. See id. at 19. After vaccination, thimerosal dissociates into ethylmercury.

In accordance with Food and Drug Administration (FDA) regulations that require the use of preservatives in multi-dose vials of vaccines to prevent fungal and bacterial contamination, thimerosal was added as a preservative to certain recommended pediatric vaccines–specifically the vaccines administered to protect against diphtheria, tetanus, pertussis, Haemophilus influenzae type b (Hib), and hepatitis B. Id. at 27. The other recommended pediatric vaccines–specifically the live viral vaccines administered to protect against measles, mumps, rubella, varicella (chickenpox) and polio–never contained thimerosal as an additive. Id.

In the late 1990s, the FDA conducted an evaluation of the health risks posed to children and other sensitive populations through exposure to mercury. See PMRL 171 at 1147, 1151-1152 (2001 Ball article[100]). The evaluation included an assessment of the exposure dose at which toxicity occurs. Id. The FDA observed that depending on the immunization schedule, vaccine formulation, and infant weight, cumulative exposure of infants to mercury from thimerosal during the first six months of life might exceed EPA guidelines for exposure to methylmercury, a form of organic mercury different from ethylmercury (the form of mercury into which thimerosal dissociates after vaccination). See id. The EPA guidelines, however, conservatively incorporate as much as a 10-fold safety factor. Such guidelines were meant to be a starting point for the evaluation of mercury exposure and were not intended to be viewed as the absolute upper limit of exposure above which toxicity could be expected to occur.

The limits of exposure to methylmercury were developed by various governmental agencies, including the Environmental Protection Agency (EPA), the Agency for Toxic Substances and Disease Registry (ATSDR), the FDA, and the World Health Organization (WHO), and several of the guidelines for methylmercury exposure were informed by studies of the fetal outcomes after in utero exposures to maternally-ingested, methylmercury-contaminated food. PMRL 171 at 1151-1152. The FDA used the EPA's guidelines for exposure to methylmercury to evaluate the health risks posed by ethylmercury exposure in children because no EPA guidelines existed for ethylmercury. Based on its evaluation, the FDA concluded that the doses of thimerosal in vaccines

[100] L. K. Ball et al., An assessment of thimerosal use in childhood vaccines, Pediatrics 107:1147-1154 (2001).

administered to children in accordance with the prescribed immunization schedule "revealed no evidence of harm." Id. at 1153. Other than rare reports of allergic reactions, no other harmful effects were noted. See PMRL 223 at 1737 (2002 Pichichero article[101]).

As a precautionary measure, however, the American Academy of Pediatrics and the United States Public Health Service issued a joint public health statement in July 1999, recommending that the use of thimerosal as a preservative in childhood vaccinations be discontinued. See PMRL 171 at 1152; RMRL 254 at 30 (2001 Institute of Medicine Report). Vaccine manufacturers responded by discontinuing the use of thimerosal as a preservative in most childhood vaccines currently administered in the United States.[102] See PMRL 171 at 1147; RMRL 254 at 30.

Prior to the removal of thimerosal from most pediatric vaccines, the FDA estimated that during the first six months of life, children could receive a cumulative dose of ethylmercury from vaccines as high as 187.5 µg. RMRL 254 at 28-29. The FDA further estimated that during the first two years of life, children could receive a cumulative dose of ethylmercury from vaccines as high as 237.5 µg. Id. The amount of ethylmercury contained in a pediatric dose of vaccine for anti-microbial purposes typically ranged from 12.5 to 25 µg. Id. at 29.

Before addressing further what happens to the thimerosal component in the body following a vaccine injection, the undersigned briefly addresses the different forms of mercury and the factors that determine the toxicity of mercury.[103]

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[101] M. E. Pichichero et al., Mercury concentrations and metabolism in infants receiving vaccines containing thimerosal: a descriptive study, Lancet 360: 1737-1741 (2002).

[102] Trace amounts of thimerosal left from the manufacturing process (<0.5 µg Hg per dose) remained in vaccines produced after the 1999 recommendation to discontinue the use of thimerosal in vaccines. RMRL 254 at 30 (2001 Institute of Medicine Report). Additionally, previously produced lots of thimerosal-containing vaccines remained available. Id. Currently, the use of thimerosal as a preservative continues only in multi-dose vials of the influenza vaccine that may be administered to children. Id. Single dose vials of influenza vaccine, however, do not contain thimerosal.

[103] As Dr. Aposhian notes in his filed expert report, a much fuller discussion of the toxicological properties of mercury was set forth in the test case proceedings on petitioners' first theory of general causation. See Hazlehurst, 2009 WL 332306 at **43-64. Because special masters may use their "accumulated expertise" to understand the evidence presented in a case, see Lampe v. Sec'y of Health and Human Servs., 219 F.3d

(continued...)

a. The Different Chemical Forms of Mercury

The chemical symbol for mercury is Hg. PMRL 35 at 610 (2006 Clarkson article[104]). Mercury is a heavy metal that can present in the following three forms: (1) elemental metal,[105] (2) inorganic salts, and (3) organic compounds.[106] See PMRL 223 at 1737. Nearly all inorganic and organic chemical compounds of mercury are comprised of mercuric mercury, which is the mercuric ion that is created when two electrons are removed from an atom of mercury. PMRL 35 at 611. Based on its prevalence in mercurial compounds, mercuric mercury "plays a key role in the toxicology of most forms of mercury." Id.

b. The Principal Sources of Human Exposure to Mercury that are not Industrial or Occupational Sources

Compounds containing inorganic mercury have had a long history of medicinal use as a laxative and as an infant teething powder. PMRL 35 at 613. While inorganic mercury is no longer commonly used for medicinal purposes, its use appears to continue as the active ingredient in skin bleaching creams still available in a number of Third World countries. Id.

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[103](...continued)
1357, 1362 (Fed. Cir. 2000) (quoting Hodges v. Sec'y of Health and Humans Servs., 9 F.3d 958, 961 (Fed. Cir. 1993)), the undersigned limits her discussion of the toxicological properties of mercury in this case to the aspects that are most relevant to petitioners' second theory of general causation.

[104] T. Clarkson and L. Magos, The toxicology of mercury and its chemical compounds, Crit. Rev. Toxicol. 36(8):609-662 (2006).

[105] Elemental mercury is an inorganic form of mercury that can occur in the form of liquid or gas. Mead Tr. at 155 (Dr. Aposhian). It is often classified independently of other forms of inorganic mercury based on its different toxicological properties. Id. at 156. Of note, mercury is the only metal that is a liquid at ambient temperatures. PMRL 35 at 610. In its liquid form, it is volatile and releases easily the gaseous form of mercury usually referred to as mercury vapor. As a vapor in ambient air, mercury is quite stable. Id.

[106] Mercury compounds are classified as organic when they contain carbon. PMRL 35 at 611.

Of the organic mercury compounds, methylmercury is the most common form in the environment. RMRL 6 at 2 (1999 ATSDR Mercury Profile[107]). This form of mercury accumulates in fish and shellfish.[108] Id. at 10. Until the 1970s, the organomercurials–particularly, methylmercury and ethylmercury–were used in agriculture as antifungal agents in seed grain. PMRL 35 at 612. Additionally, the ethylmercury-containing compound thimerosal found use in the topical antiseptics known as merthiolate or mercurochrome. See Mead Tr. at 465.

The chief sources of mercury exposure for humans at present are through dental amalgams (containing elemental mercury) and the consumption of fish (containing methylmercury). Id. at 152-154, 460-461; see also PMRL 228 at 15 (2000 National Research Council report[109]). In addition, and of concern to petitioners here, vaccinations were a source of ethylmercury exposure for children during the period between the 1970s and the end of 1999. See Mead Tr. at 153.

Of these sources of mercury exposure, the amount of exposure estimated to come from the average American's consumption of fish in one year is 11,000 μg. See Mead R's Trial Ex. 4 at 9 (Dr. Brent's slides). The average exposure of an infant to mercury from breast feeding is estimated to be 280 μg during the first six months of life. Id. The cumulative exposure to ethylmercury from vaccines could reach 237.5 μg during the first two years of life. See RMRL 254 at 28-29.

Whether human exposure to mercury is toxic depends on a number of factors, including: (1) the form of mercury to which an individual is exposed; (2) the amount (or dosage) to which an individual is exposed; (3) the route of entry into the body; and (4) the individual's age at the time of exposure. See PMRL 223 at 1737; see also Mead Tr. at 143-144 (Dr. Aposhian). Importantly, certain doses of exposure correlate to certain observed or measured responses in an individual; this toxicological concept is referred to as the dose/response relationship. See RMRL 6 at 15, 141. Study of the dose/response relationship assists in determining what adverse effects are produced at what exposure doses. For many substances, including methylmercury, an exposure does not provoke a

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[107] Agency for Toxic Substances and Disease Registry, Toxicological Profile for Mercury (1999).

[108] This form of mercury also may be found in chicken in the United States that are fed with feed containing pulverized fish products. Mead Tr. at 152 (Dr. Aposhian).

[109] Committee on the Toxicological Effects of Methylmercury, Board on Environmental Studies and Toxicology, National Research Council, Toxicological Effects of Methylmercury (2000).

response until a threshold exposure dosage has been reached. See Mead Tr. at 1800, 1820 (Dr. Brent). A toxic level of mercury exposure produces a characteristic set of signs and neurological symptoms. See PMRL 35 at 632.

During the test case proceedings on petitioners' first theory of general causation, petitioners relied, in part, on the neurotoxic effects of ethylmercury, an organic form of mercury, as part of the biological mechanism contributing to the development of autism in genetically susceptible children. See Hazlehurst, 2009 WL 332306 at **50-60. In the trio of test cases on petitioners' second theory of general causation, of which this case is one, petitioners have focused on the neurotoxic effects of de-ethylated mercury, an inorganic form of mercury, as part of the biological mechanism contributing to the development of autism in genetically susceptible children. Of particular importance to petitioners' theory of causation presented here is the neurotoxic role of the inorganic mercury deposited in the brains of those individuals who develop regression in autism.[110] See Mead Tr. at 362-363,

[110] Prior to examining the scientific underpinnings of petitioners' claim, the undersigned again notes that the use of the term "theory" under the Vaccine Act is distinguishable from its use as it relates to the scientific method. The term "theory" has a "very precise meaning[]" in the context of the scientific method. Mead Tr. at 1979 (Dr. Mailman). Dr. Mailman addressed the echelon of scientific ideas, explaining:

> [E]ssentially a hypothesis is an idea that one has about why something occurs or what might be a result of a certain phenomenon. . . . [O]ne of the creative parts of science is how to generate hypothesis.
>
> However, the scientific method demands something that's not generally appreciated, and that is one should seek to disprove one's own ideas, not to prove them . . . . [D]isproving an idea is to test it rigorously and look for ways to show that the idea is wrong.
>
> . . . [I]f one does that over and over again, and [one] fail[s] to disprove a hypothesis, that hypothesis then gathers additional weight and eventually if that's done by multiple investigators and done critically, one then develops what is called a theory, so a theory is actually a much higher level idea than a hypothesis.
>
> . . . [A] theory really means an idea that has been investigated relatively rigorously and is generally believed to be true, not something that one speculates about. Ultimately, if a theory is tested again continuously and it's never found to be false, one may actually turn it into a law.

(continued...)

467 (Dr. Aposhian). Before evaluating petitioners' claim that thimerosal-containing vaccines had neurotoxic effects that led to the development of autism in certain hypersusceptible children, the undersigned reviews the route that thimerosal follows in the body once injected.

2. Exposure to Organomercurial Compounds Can Lead to the Deposition of Inorganic Mercury in the Brain

As indicated earlier, the principal source of organomercurial human exposure is fish consumption (for methylmercury exposure) and thimerosal-containing vaccines (for ethylmercury exposure). With respect to the organomercurial compound of particular interest in this case, petitioners assert and respondent agrees that once a thimerosal-containing vaccine is injected, the thimerosal component dissociates in the bloodstream of the body yielding ethylmercury, an organic form of mercury, and thiosalicylate, a sulfur and salt compound. Compare Mead Tr. at 173-174 (Dr. Aposhian) with Mead Tr. at 1803 (Dr. Brent).

Studies have shown that, once in the body, the two organomercurials–ethylmercury (from thimerosal-containing vaccines) and methylmercury (from fish consumption)–are distributed throughout the bloodstream. PMRL 35 at 646. The half-life of ethylmercury, however, is much shorter than the half-life of methylmercury, which has been studied much more extensively than ethylmercury.[111] See PMRL 223 at 1740 (2002 Pichichero article). The half-life of ethylmercury in the bloodstream is estimated to be less than 10

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[110](...continued)

Id. at 1979-1980.

> Dr. Mailman urged mindfulness of this echelon of scientific ideas when evaluating the scientific strength of a presented idea. Id. at 1980; see also id. at 4315 (Dr. Johnson observing that a hypothesis is "at the lowest level" of the scientific echelon). Dr. Mailman noted that when scientific and clinical experiments are conducted in areas that are relevant to public health, careful adherence to the scientific method as well as "cautious presentation and interpretation of [the] data" is imperative to "prevent expensive and spurious perturbation of the public and scientific consciousness." Id. at 1983 (quoting Mead R's Trial Ex. 5 at 10).

[111] Half-life is "the time required for one half of a quantity of a substance to be eliminated from a system when the substance is eliminated at a rate proportional to its concentration." Dorland's at 810.

days. See id. The half-life of methylmercury in the bloodstream is estimated to be between 40 to 50 days (having identified a range of 20 to 70 days and in some subjects, up to 80 days). Id.; see also PMRL 60 at 226. Of the two organomercurials, ethylmercury clears the bloodstream most quickly.

Once in the bloodstream, ethylmercury appears to target the brain and the kidneys. PMRL 35 at 647. The better studied organomercurial, methylmercury, also appears to target the central nervous system, which includes the brain, and the kidneys–with the route of administration (whether by intramuscular injection or by oral administration) influencing the distribution of the mercury within the brain and kidney tissues. Id.; PMRL 296 at 188 (2004 Harry article[112]) (study of neonatal mice). The investigators conducting the 2004 Harry study found that the intramuscular injections resulted in "significantly lower" mercury concentrations in the tissues of interest than did oral administration. PMRL 296 at 188.

Most of the elimination of these two organic forms of mercury from the body occurs through fecal elimination rather than through urinary excretion. PMRL 35 at 646-647. Urine, however, appears to be a useful indicator of the mercury burden borne by the kidneys because urinary mercury "derives directly from mercury deposited in kidney tissue." Id. at 618.

The organomercurials that remain in the body have some ability to penetrate the blood-brain barrier that protects the brain. While studies indicate that methylmercury may enter the brain either by diffusion across the blood-brain barrier or by active transport of a methylmercury-cysteine complex,[113] ethylmercury does not form a cysteine complex that permits its active transport into the brain. See PMRL 296 at 184 (2004 Harry article); Mead Ps' Trial Ex. 2 at 55 (Dr. Aposhian's trial slides). Rather, ethylmercury is thought to enter the brain more slowly by diffusion across the blood-brain barrier. Id. The limited means by which ethylmercury may enter the brain may explain, in part, why of the sources of mercury deposits in the brain examined in the 2004 Harry study, the greatest percentage of retained mercury in the brain came not from ethylmercury or thimerosal but from methylmercury. See Mead Tr. at 1806-1807, 1882; see also PMRL 296 at 188 (2004 Harry article); PMRL 26 at 1018-1019 (2005 Burbacher article[114]) (study of infant

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[112] G. Harry, et al., Mercury concentrations in brain and kidney following ethylmercury, methylmercury and thimerosal administration to neonatal mice, Toxicol. Lett. 154(3):183-189 (2004).

[113] Cysteine is a sulfur-containing amino acid. See Mead Tr. at 504.

[114] T. Burbacher et al., Comparison of blood and brain mercury levels in infant

(continued...)

monkeys similarly finding that, of the sources of mercury deposits in the brain, more methylmercury was deposited in the brain than ethylmercury).

Once in the brain, both ethylmercury and methylmercury dissociate into inorganic mercury. See Mead Tr. at 157-158 (Dr. Aposhian describing "endogenous inorganic mercury production in the body"). Ethylmercury converts to inorganic mercury in the brain much more rapidly than does methylmercury, see Mead Tr. at 210; see Mead Ps' Trial Ex. 2 at 72; PMRL 35 at 624 (noting that ethylmercury's conversion to inorganic mercury is more rapid in the body than is methylmercury's conversion); accord id. at 1874 (Dr. Brent noting the same). Once ethylmercury enters the brain, its half-life is estimated to be 14 days, or twice the half-life of ethylmercury in the bloodstream. PMRL 35 at 646 (2006 Clarkson article[115]). Similarly, the half-life of methylmercury in the brain is longer than in the bloodstream. See PMRL 60 at 226 (1994 Vahter article[116]). The half-life of methylmercury in the brain approaches 60 days. PMRL 35 at 646 (finding, on average, that the half-life of methylmercury in the brain is 58 days); Mead Tr. at 166-167 (Dr. Aposhian stating that the half-life of methylmercury in the brain is somewhere between 30 and 50 days).

Research has shown that when administered at the same doses (referred to as equimolar doses), methylmercury is more neurotoxic–as evidenced by disordered coordination–than is ethylmercury. Mead Tr. at 1969 (citing 1985 Magos article, filed as PMRL 175 at 265,[117] in which the investigators observed that "[t]he brain accumulates less [mercury] and the kidneys[, as the primary organs for mercury elimination, accumulate] more mercury from ethylmercury than from methylmercury treatment"). On administration, methylmercury has been estimated to be about 20 to 30 percent "more neurotoxic" than ethylmercury. See Mead Tr. at 1969. Notwithstanding the source of the mercury that is converted to inorganic mercury in the brain, however, the deposited

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[114](...continued)
monkeys exposed to methylmercury or vaccines containing thimerosal, Environ. Health Perspect. 113: 1015-1021 (2005).

[115] T. Clarkson & L. Magos, The toxicology of mercury and its chemical compounds, Crit. Rev. Toxicol. 36(8):609-662 (2006).

[116] M. Vahter et al., Speciation of mercury in the primate blood and brain following long-term exposure to methyl mercury, Toxicology Appl. Pharmacology, 124: 221-229 (1994).

[117] L. Magos et al., The comparative toxicology of ethyl- and methylmercury, Archives of Toxicology 57:260-267 (1985).

amounts of mercury are "extremely small" and thus are measured in parts per billion. Mead Tr. at 1804.

Inorganic mercury does not penetrate the blood-brain barrier easily and, when found in the brain, its presence is attributable primarily to the breakdown of the organomercurials–whether ethylmercury or methylmercury–that have traversed the blood-brain barrier. See PMRL 35 at 628. Once deposited in the brain, inorganic mercury remains for a period of years. Id.; see also Mead Tr. at 1812 (Dr. Brent).

While research indicates that organic mercury levels decrease in the body once the source of exposure is removed, the level of inorganic mercury does not decrement as quickly. See PMRL 35 at 647. Various studies conducted by a particular group of researchers on the brains of mercury-exposed monkeys have proved instrumental in providing the scientific community with pertinent information regarding the disposition of mercury that reaches the brain.

a. The "Monkey Studies"

As reported in the 1994 Vahter article, a study conducted on adult monkeys–that had received daily doses of very high levels of methylmercury in apple juice for periods of either 6, 12, or 18 months–indicated that the levels of organic mercury decreased in both the bloodstream and the brain "exponentially" once the exposure ended, but the level of inorganic mercury accumulated in the brain. See PMRL 60 at 223-224 (1994 Vahter article); see also Mead Tr. at 162 (Dr. Aposhian noting that, after four months of mercury exposure, the blood inorganic mercury in the monkeys was 7% of total blood mercury and six months after the mercury exposure had stopped, 74% of the total brain mercury in the monkeys was inorganic mercury[118]). The researchers concluded that the accumulation of inorganic mercury in the brain was attributable, in part, to the demethylation of methylmercury in the brain and, in part, to the limited ability of inorganic mercury to penetrate the blood-brain barrier (whether exiting or entering the brain). PMRL 60 at 227; Mead Tr. at 164; see also PMRL 64 at 279 (1995 Vahter article[119]) (noting that the monkey study showed "a pronounced, but slow, accumulation" of inorganic mercury in the brain following long-term exposure to methylmercury). The researchers surmised that the half-

[118] A measure of total mercury is the measure of organic mercury and inorganic mercury. See Mead Tr. at 163.

[119] M. Vahter, et al., Demethylation of methyl mercury in different brain sites of Macaca fascicularis monkeys during long-term subclinical methyl mercury exposure, Toxicol. Appl. Pharmacol. 134(2):273-284 (1995).

life of inorganic mercury that had accumulated in the brain could be years.[120] See PMRL 60 at 225; see also PMRL 26 at 1020 (noting that the half-life of inorganic mercury in the monkey brain has ranged from 227 to 540 days); Mead Tr. at 165. Although petitioners relied on this study to show that accumulated inorganic mercury can remain in the brain for a protracted period of time, respondent's expert Dr. Brent asserted that the study had limited relevance in this case because the study involved the administration of significant doses of methylmercury–an organomercurial with different toxicokinetics from ethylmercury, the mercury component of interest in thimerosal-containing vaccines–and because the studied animals were found to be "totally normal" behaviorally notwithstanding the reported death of some of the animals' astrocytic brain cells and concomitant microglial activation to clean up the astrocytic cells that had died. See Mead Tr. at 1891-1892, 1896-1897 (noting that "there was so much mercury in the brain that it was toxic to astrocytes, and . . . the microglia were activated to clean up the astrocytes").

A subsequently conducted study, referred to here as the 2005 Burbacher study and filed as PMRL 26, examined infant monkeys that had received either intramuscular injections of thimerosal-containing vaccines or oral doses of methylmercury at 7, 14 and 21 days of life respectively. PMRL 26 at 1016. The selected immunization schedule was intended to "sort of replicate what happens in a human," but was "much more compressed . . . because a monkey's brain develops a little faster." See Mead Tr. at 1807; see also id. at 1866-1867. In contradistinction to the 1994 Vahter study in which high doses of methylmercury were administered to the subject animals (adult monkeys) daily, the researchers in the 2005 Burbacher study administered low doses of mercury to the subject infant monkeys intermittently. See id. at 1871-1872. Nonetheless, the dosing schedule in the 2005 Burbacher study still was almost three times more than what a child would receive in his first four vaccinations, to ensure that the animal subjects had received enough mercury above the threshold detection level for the researchers to measure the mercury distribution. Id. at 1808-1809 (citing a 2004 oral presentation to the IOM filed as RMRL 436[121]); see also id. at 1867-1868. Based on the data gathered during the study, the researchers predicted that little accumulation of organic mercury would occur in the bloodstream of children receiving thimerosal-containing vaccines, but that an

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[120] Instead of the term "half-life," the researchers use the term "half-time." Half-time is the time required for one half of a quantity of a substance to be eliminated from a system when the substance is eliminated at a rate proportional to its concentration. Dorland's at 810. The terms may be used interchangeably.

[121] P. Sager, Thimerosal exposure from vaccines and ethylmercury accumulation in non-human primates. Oral presentation to the Immunization Safety Review Committee Meeting 9: Vaccines and Autism. February 9, 2004.

accumulation of inorganic mercury would occur in the brains of the children. PMRL 26 at 1020.

The investigators who performed the 2005 Burbacher study reported, quantitatively, that the ethylmercury deposited in the infant monkeys' brains was "a little over 10 parts per billion" after the monkeys were exposed to an immunization schedule of nearly three times more thimerosal than what a child would receive by intramuscular injection of vaccines.[122] See Mead Tr. at 1810-1812 (referencing figure 7 of the 2005 Burbacher study); see also PMRL 26 at 1019. Although a portion of the ethylmercury deposited in the infant monkeys' brains was converted to inorganic mercury, "a good deal" of the deposited ethylmercury appears to have exited the brain. See Mead Tr. at 1810-1812 (referencing figure 7 of the 2005 Burbacher study); see also PMRL 26 at 1019. Contrastingly, the methylmercury deposited in the infant monkeys' brains from the given oral doses was "about 100 parts per billion," or 10 times higher than the ethylmercury deposited from the administered thimerosal injections. See Mead Tr. at 1813; PMRL 26 at 1018.

b. Ascertaining Typical Mercury Content in the Brain and the Effect of Mercury Content in the Brain from Autopsied Brains

Because an actual measure of the mercury content in the brain of a living human being is not possible, see Mead Tr. at 185, researchers have relied on examinations of autopsied brains for information about the mercury content in the brains of humans. A study of autopsied brains taken from subjects who had resided in Greenland and died after a lifetime of fish consumption showed that a significant deposit of inorganic mercury remained in the brains. See Mead Tr. at 201-202; see also PMRL 603 (1999 Pedersen article[123]). Much of that inorganic mercury was located in the glial cells of the brain. Id. at 201-202. Glial (or neuroglial) cells form the structure of nervous tissue. Dorland's at 1254. They form a fine web that appears to play a role in maintaining the proper neuronal environment for cellular communication. See id. at 1254, 1689 (myelin).

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[122] The measure used in Figure 7 of the 2005 Burbacher study was nanograms per gram. PMRL 26 at 1019. Nanograms per gram and parts per billion are equivalent measures. See Mead Tr. at 1810-1811 (Dr. Brent).

[123] M. Pedersen et al., Mercury accumulations in brains from populations exposed to high and low dietary levels of methyl mercury: Concentration, chemical form and distribution of mercury in brain samples from autopsies, Int. J. Circumpolar Health 58(2):96-107 (1999).

Dr. Aposhian asserted that studies have demonstrated that inorganic mercury is more potent than organic mercury in inhibiting certain brain activity. See Mead Tr. at 169-170 (citing PMRL 750[124]). The inhibitory effects occur when mercury compounds bind to and are transported by sulfur- or thiol-containing compounds. See Mead Tr. at 170-172, 174-175 (Dr. Aposhian). These compounds are synthesized in nerve cell bodies and are transported to synaptic terminals. Mead Tr. at 170. From there, the compounds are distributed to the main organs and tissues of the body where certain subcellular processes are inhibited. See id. In addition to describing the inhibitory effects associated with inorganic mercury, Dr. Aposhian testified that the reported finding of inorganic mercury in the brains of the mercury-exposed also has significance for petitioners' claim in this case because inorganic mercury is capable of inducing neuronal necrosis (or the death of neuronal brain cells). Mead Tr. at 205-206 (Dr. Aposhian addressing the findings reported in the 1982 Gallagher article[125] filed as PMRL 588).

Respondent's expert Dr. Brent did not dispute the assertion that inorganic mercury deposits in the brain can cause the death of certain brain cells (in particular, the astrocytes that provide important support functions for the neuronal brain cells about which Dr. Aposhian testified). Mead Tr. at 1888; PMRL 116 at 134 (the 1996 Charleston article[126] discussing the functions of astrocytes). Nor did Dr. Brent dispute the fact that the death of astrocytes causes the activation of other cells for the purpose of "clean[ing] up the debris" caused by the cell death (a process known as microglial activation). Mead Tr. at 1888-1889. Rather, he explained that microglia become activated as phagocytes–which are cells that attack and consume cellular waste–when astrocytes die because microglial activation is a normal response to such astrocytic death. Id. at 1928-1930. To produce such cellular effects, however, the level of inorganic mercury in the brain must exceed the toxicity threshold. Id. at 1888 (Dr. Brent). Dr. Kemper, respondent's expert neuropathologist, observed that in cases of mercury toxicity, there is evidence of destructive lesions in the brain that are indicative of the death of neurons in the visual cortex, the auditory cortex, the motor sensory cortex, and the cerebellum. Mead Tr. at 2840-2841; see also Mead R's Trial Ex. 10 at 26 (Dr. Kemper's trial slide showing the differences between autistic subjects and mercury intoxicated subjects in both the clinical features and the

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[124] C. Carvalho et al., Inhibition of the human thioredoxin system: A molecular mechanism of mercury toxicity, J. Biol. Chem. 283(18):11913-11923 (2008).

[125] P. Gallagher et al., Identity of ultrastructural effects of mercuric chloride and methyl mercury after intracerebral injection, Toxicology 23(2-3):261-266 (1982).

[126] J. Charleston et al., Changes in the number of astrocytes and microglia in the thalamus of the monkey Macaca fascicularis following long-term subclinical methylmercury exposure, Neurotoxicology 17(1):127-138 (1996).

neuropathology). Destructive lesions in the areas of the brain that affect vision, hearing, and motor coordination that are idiosyncratic of mercury toxicity but not of autism illustrate the neuropathological differences between mercury toxicity and autism and militate against a finding that the two conditions are similar.

To put petitioners' claim regarding the significance of finding mercury in the brains of humans into further perspective, respondent's expert Dr. Brent testified about the findings reported in the 1995 Lapham article, filed as RMRL 294.[127] See Mead Tr. at 1818. In that study, researchers compared 32 neonatal autopsied brain specimens obtained from Victoria Hospital in the Seychelles Islands (whose population consumes high amounts of fish) to the 12 infant brain specimens obtained from the Autopsy Service at the University of Rochester Medical Center in New York. RMRL 296 at 690-691. The researchers examined the variations in the mercury levels found in six different regions of the brains obtained from the Seychelles and compared them with the variations in the mercury levels found in the same six regions of the brains obtained from Rochester. Id. at 700. The researchers concluded that although there seemed to be some greater affinity for mercury in the phylogenetically (or evolutionarily) older parts of the brain (that are distinct from the cortical structures affecting the higher level brain functions), the data indicated "a fairly strong concentration-dependent relationship between mercury intake and brain levels." Id. at 702. That is, the level of mercury detected in the brain has a reasonably strong correlation to the amount of mercury one has absorbed following exposure.

Additionally in the 1995 Lapham article, the researchers compared the reported mercury levels detected in the autopsied brains taken from infants in Rochester to the reported mercury levels detected in autopsied brains taken from older infants in Germany and taken from adults in Sweden and found that typical background levels of mercury ranged from two to 30 parts per billion. RMRL 294 at 701 (figure 9). The detected mercury levels in the brains obtained from the Seychelles ranged from 50 to 300 parts per billion, and although the Seychelles brain mercury levels exceeded background mercury levels, the detected mercury levels were still well below the levels at which observable effects of a mercury presence in the brain begin to appear.[128] Id. The researchers noted,

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[127] L. Lapham et al., An analysis of autopsy brain tissue from infants prenatally exposed to methylmercury, Neurotoxicology 16(4):689-704 (1995).

[128] Dr. Brent testified that it is of note that Dr. Thomas Clarkson–a highly respected toxicologist and one of respondent's retained experts in this case–was one of the authors of the 1995 Lapham article, had been the lead investigator of prenatal methylmercury exposure in the Seychelles Islands, and had found no evidence of an increased prevalence of autism in more than 30 years of detailed pediatric and

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for example, that the observable effect of biochemical changes has been reported to occur with brain mercury levels of 1,500 parts per billion, and degenerative changes and brains that are diminished in size have been reported for brain mercury levels that range from 2,500 to 9,000 parts per billion. Id. (Interpolating from Figure 9 on page 701); see also Mead Tr. at 3295 (Dr. Rutter observing that it is well-known that exposure to high doses of mercury is neurotoxic). By comparison, the amount of mercury from thimerosal-containing vaccines estimated to be deposited in the brain is in the range of two to three parts per billion (or nanograms per gram). See Mead Tr. at 1810-1811 (Dr. Brent). Notably, Dr. Aposhian's assertion that the amount of inorganic mercury deposited in the brain from received thimerosal-containing vaccines is sufficient to provoke the neuroinflammatory responses detected in the medical literature and to effect the autistic injury that petitioners have posited is based on flawed calculations and thus, is unavailing. Compare Mead Ps' Ex. 38 (Dr. Aposhian's expert report) (describing the assumptions underlying his calculations based on the cited references) with Mead R's Ex. PP (Dr. Brent's supplemental expert report) (addressing the errors in both Dr. Aposhian's assumptions and calculations that informed his position regarding the sufficiency of the inorganic brain mercury deposits–from thimerosal-containing vaccines–to cause produce the effects alleged by petitioners).

Respondent's expert, Dr. Brent, observed that the mercury exposure of the Seychelles population (and the corresponding elevated body mercury levels detected in the population) are similar to what researchers have found in another heavy fish-eating population in the Faroe Islands. See Mead Tr. at 1821-1822. Notwithstanding the elevated body mercury levels detected in the Faroese that included much higher brain deposits of inorganic mercury than are typically found in the United States population, researchers have found no increased incidence of autism in the Faroese related to the inorganic mercury deposits. See RMRL 130 at 442 (2007 Ellefsen article[129]); see also Mead Tr. at 1822. Nor has there been a study to date that has suggested that autistic individuals have more mercury in their brains than non-autistic individuals. See Mead Tr. at 1823.

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[128](...continued)
neuropsychological tests on large group of children in the Seychelles. See Mead Tr. at 1821 (referencing Dr. Clarkson's expert report filed as Respondent's Exhibit K). Based on respondent's subsequent decision not to call Dr. Clarkson as a witness, respondent withdrew Dr. Clarkson's report. Accordingly, the undersigned does not rely on Dr. Brent's references to Dr. Clarkson's filed report.

[129] A. Ellefsen et al., Autism in the Faroe Islands: an epidemiological study, J. Autism Dev. Disord. 37(3):437-444 (2007).

c. Examining the Adverse Effects of Chronic Low-Dose Exposure to Inorganic Mercury that Remains in the Brain for a Period of Time

While a number of mercury studies have focused on the adverse biological effects caused by high dose mercury exposures, Dr. Aposhian posited that chronic low-dose mercury exposure could cause harm as well because once inorganic mercury accumulates in the brain, it remains there for a long period of time. See Mead Tr. at 207-208; Mead Ps' Trial Ex. 2 at 70. Studies comparing the brain levels of both inorganic and organic mercury compounds–including methylmercury and ethylmercury–that also have examined the neurological and morphological[130] effects of organic mercury, however, suggest that the long-term deposits of inorganic mercury in the brain may play a less toxic role than does the presence of organomercurials in the brain. PMRL 35 at 633. Consistent with these findings, respondent's expert teratologist Dr. Rodier pointed out in her testimony that studies of persons who have been exposed to significant levels of organic mercury, and correspondingly have developed neurological symptoms, show that the neurological problems resolved as the organic mercury cleared from the body even as the inorganic mercury levels in the brain remained very high. Mead Tr. at 3018-3019. In Dr. Rodier's view, these studies "absolutely refute[] the hypothesis that inorganic mercury in the brain causes any symptoms" regardless of whether the detected brain levels of inorganic mercury are high, or, as petitioners assert here, low. See id. at 3017-3018.

Petitioners have not challenged those studies finding that neurological symptoms associated with high-dose organic mercury exposures have diminished once organic mercury has cleared the body notwithstanding the significant level of inorganic mercury remaining in the brain. Dr. Rodier's view that the studies strongly suggest that organic mercury rather than inorganic mercury is the more important contributing factor to neurological impairment is well-supported and is persuasive.

d. The Toxic Effects of Mercury Exposure–Whether an Inorganic or Organic Form of Mercury Exposure–are Distinguishable from the Symptoms That are Characteristic of an ASD

The toxic effects of mercury exposure have been studied, and as noted previously, the toxic effects of methylmercury exposure have been studied more widely than the toxic effects of ethylmercury exposure. Among the observed signs and symptoms of impairment that are consistent with the signs and symptoms of methylmercury poisoning

[130] The morphological effects on the brain are the impacts on the structure of an organ. See Dorland's at 1174.

are paresthesia first and then, in rapid succession, ataxia (uncoordinated movement), dysarthria (poor articulation, specifically, slurred speech due to poor motor control of speech-related muscles), and loss of vision.[131] PMRL 35 at 632; see Mead Tr. at 3013 (Dr. Rodier); see also Mead Tr. at 2437(Dr. Rust addressing the severe visual and hearing deficits as well as severe central nervous system and motor dysfunction that are produced by methylmercury intoxication); R's Mead Trial Ex. 8 at 49. The most common symptoms of ethylmercury poisoning are muscle weakness, loss of appetite, and dizziness. PMRL 232 at 252 (1984 Zhang article[132]); see also Mead Tr. at 3016-3017. In contrast, the clinical symptoms associated with inorganic mercury exposures (usually occurring in chemical plants) have been reported to include swollen and painful fingers and toes, tremors, loose teeth, and an unusual pattern of psychiatric illness. PMRL 588 at 261 (1982 Gallagher article); Mead Tr. at 3012 (describing the symptoms of pink disease or acrodynia, a condition caused by inorganic mercury poisoning); see also Dorland's at 20. Notably, not only are the symptoms of mercury poisoning known by the scientific community to vary according to the form of mercury exposure, but also the symptoms of ethylmercury poisoning, methylmercury toxicity, and toxic inorganic mercury exposure are known to be distinguishable from the impairments that are characteristic of an ASD.[133]

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[131] The pregnant women who ate fish contaminated by the accidental chemical plant discharge of extremely high levels of methylmercury at Minamata Bay, Japan suffered less severe injuries than did their congenitally-exposed children. See Mead Tr. at 2435-2437. The severity of the injuries in the children was attributed to the exceedingly high levels of exposure. Id. at 2436-2437.

[132] J. Zhang, Clinical Observations in Ethyl Mercury Chloride Poisoning, American Journal of Industrial Medicine 5(3): 251-258 (1984).

[133] Another physically distinguishable feature of mercury toxicity and autism is head circumference. Head circumference is reduced in individuals suffering from mercury poisoning, while head circumference in autistic individuals is enlarged. Mead R's Ex. GG at 36 (Dr. Rutter's report); see also Mead Tr. at 3015-3016 (Dr. Rodier addressing the characteristic microcephaly that occurs in children exposed prenatally to methylmercury and the macrocephaly that more commonly occurs in autistic children); id. at 2388-2389 (Dr. Rust discussing the head growth in autistic children that is not accompanied by correlative growth in length or weight); id. at 2840 (Dr. Kemper distinguishing larger autistic brains from brains that are smaller as a result of mercury toxicity).

As described in the 2003 Courchesne article, filed as RMRL 94, there seem to be at least four phases of brain growth in autism: (1) characterized first by a slight undergrowth of the prenatal brain (reflected by birth head circumference, on average, in

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Compare Mead Tr. at 3009-3017 (Dr. Rodier discussing the different symptoms of toxicity associated with the different forms of mercury exposure) with PMRL 262 at 463 (2001 Bernard review article[134]) (in which the authors identify traits that are purported to occur in both the mercury-poisoned population and the autistic population in support of the authors' hypothesis that regressive autism is a form of mercury poisoning–but such identified traits do not meet the diagnostic criteria established by either the DSM-IV or the ICD-10 for autism–and, thus, the review article is not useful to the undersigned).

From the scientific literature, it is well-understood that ethylmercury, the organomercurial into which the thimerosal component of vaccines dissociates after an intramuscular injection into the body, has a short half-life in the bloodstream and is eliminated more quickly from the body than methylmercury, another organomercurial and the chief source of human mercury exposure (through fish consumption). It is also well-understood that ethylmercury can enter the brain–most likely by diffusing slowly across the not easily penetrated blood-brain barrier. The means by which ethylmercury can enter the brain is more limited than the methylmercury. Although ethylmercury clears the body more quickly than methylmercury and enters the brain more slowly than does methylmercury, once the organomercurials reach the brain, ethylmercury de-ethylates into inorganic mercury more quickly than methylmercury demethylates into inorganic mercury. Notwithstanding the source of inorganic mercury deposited in the brain–the form of mercury that petitioners allege can contribute to the development of autism due to its long half life in the brain–the amount of accumulated inorganic mercury typically found in human brains is less than 30 parts per billion, a quantity that is 40 times less than the mercury brain level measured in individuals with observable neurological effects of toxicity. Based on what is known about the limited amount of ethylmercury that is able to reach the brain for conversion to inorganic mercury, it seems unlikely to the undersigned that the amount of ethylmercury available from the formerly prescribed thimerosal-containing vaccines was significant enough to be a substantial contributing factor, as

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[133](...continued)
the 25th percentile); (2) followed by a rapid and large overgrowth in the first year of life; (3) succeeded by a phase between the second and fourth year of life during which the overall growth rate of the brain slows; and (4) by the fourth or fifth year of life, marked by having reached the near maximum brain size (which is similar to what is reached by non-autistic children nearly eight years later). RMRL 94 at 343 (E. Courchesne et al., Evidence of brain overgrowth in the first year of life in autism, JAMA 290(3):337-344 (2003)).

[134] S. Bernard et al., Autism: a novel form of mercury poisoning, Medical Hypotheses 56(4):462-471 (2001).

petitioners have alleged, to cause overt neurological symptoms that are consistent with the development of autism.

Nonetheless, the undersigned turns to address further petitioners' claims regarding the alleged effects of long-term mercury deposits in the brain. Before reaching that discussion, however, the undersigned considers petitioners' claim that there is a certain subgroup of children who are both genetically predisposed to autism and are particularly vulnerable to mercury exposure. This vulnerability results from what Dr. Aposhian describes as "a mercury efflux disorder."

3. Petitioners Claim There is a Certain Subgroup of Children Who are Genetically Predisposed to Autism and are Hypersusceptible to Mercury Exposure due to an Inborn Mercury Efflux Disorder

Petitioners posit, as one of the key elements of their general causation theory, that children with autism process mercury differently than non-autistic children. In support of their position, petitioners assert that children are particularly vulnerable to brain injury caused by chemicals, and the time period of "greatest" vulnerability is during the nine months of pregnancy and the earliest years of life. Mead Tr. at 145-146 (Dr. Aposhian). The brain injury in children caused by chemicals "often produces a range of abnormalities that impair function[ing]" and studies have shown that a premature neonate takes "on the average almost four times longer [than an adult] to get rid of a chemical" from the body. Id. at 146.

Petitioners' toxicology expert, Dr. Aposhian, posited that in children who are genetically hypersusceptible to mercury, the receipt of thimerosal-containing vaccines during a narrow window of neurodevelopmental vulnerability enhances the potential for their development of autism. See id. at 409-415. But, Dr. Aposhian was unable to identify with any particularity what neurodevelopmental window is implicated in petitioners' proposed theory of vaccine causation or when that neurodevelopmental window of vulnerability is most likely to occur. Id. at 414-417 (Dr. Aposhian stating, "[T]o ask anyone what window is going on at this time is almost an impossible question. . . . We have many windows[, and] . . . at the present, we don't know.").

Of the firm opinion, however, that there is a group of children who are especially susceptible to mercury exposure because they lack the mechanism for removing mercury from their cells, Dr. Aposhian described the inability to remove mercury from the body as a mercury efflux disorder. See Mead Tr. at 216. As evidence that metal efflux disorders exist, Dr. Aposhian pointed to the well-documented genetic disorder of Wilson's disease, a condition characterized by the accumulation of copper in the body's tissues, particularly in

the areas of the brain stem and the liver. Id. at 217-218; Stedman's Medical Dictionary at 565-566 (28th ed. 2006). A disorder of copper metabolism, the disease is marked by a decrease in plasma levels of copper and an increase in urinary excretion of copper. Stedman's at 565-566. Features of the disorder include cirrhosis of the liver, degeneration of the basal ganglia (an area of the brain that is involved in motor coordination and cognition), yellowing of the eyes, and neurological manifestations that may include slurred speech, tremors, and an ataxic gait. See id. In the absence of treatment, the condition can cause death "very early in life." Mead Tr. at 217-218. The disease is caused by a genetic mutation in the copper transport gene (known as ATP7B) and is treatable by administering chelating agents that draw the copper from the tissues of the affected persons. See id.; see also Stedman's at 565-566.

Asserting that mercury, like copper, "can concentrate in specific tissues or organs of the body, even if mercury blood levels are found to be in the normal range," Dr. Aposhian pointed to the 1999 Frustaci study filed as PMRL 620.[135] Mead Tr. at 215-216. In that study, researchers sought to investigate the possible pathogenic role that certain trace metallic elements found in the heart play in various forms of cardiac failure. PMRL 620 at 1. The researchers discovered that, as compared to control subjects, subjects with idiopathic cases of cardiomyopathy (a condition of weakened or changed heart muscle structure) had elevated levels of certain metallic elements, including mercury. Id. at 1-2. Dr. Aposhian testified that although the study had nothing to do with autism, it did show "what c[ould] happen with mercury." Mead Tr. at 215.

As added support for the proposition that there is a segment of the population that processes mercury exposures differently, Dr. Aposhian pointed to studies that have compared the concentration of mercury in the blood of infants who received thimerosal-containing vaccines to the blood mercury concentration of infants who received thimerosal-free vaccines. See Mead Tr. at 177-179 (citing the 2002 Pichichero article, filed as PMRL 223, and the 2008 Pichichero article,[136] filed as PMRL 497). He asserted that the variation in the mercury blood levels of the infants that had received thimerosal-containing vaccines showed that the children were processing the thimerosal differently due to genetically determined differences in their metabolisms. See id. at 179. But all of the measured mercury blood levels fell "well within the range of blood concentrations in the general population[, and] [t]here has never been any adverse effect associated with

[135] A. Frustaci et al., Marked Elevation of Myocardial Trace Elements in Idiopathic Dilated Cardiomyopathy Compared with Secondary Dysfunction, Journal of the American College of Cardiology 33(6):1578-1583 (1999).

[136] M. Pichichero et al. Mercury levels in newborns and infants after receipt of thimerosal-containing vaccines, Pediatrics 121(2):e208-214 (2008).

blood mercury concentrations in this range." Mead R's Ex. G. at 32-33 (Dr. Brent's report).

Dr. Aposhian also relied on the findings reported in the 2003 Holmes article, filed as PMRL 237,[137] to support his assertions regarding the difficulty some experience as a result of an innate mercury efflux disorder. Mead Tr. at 219-221. The investigators in the 2003 Holmes article compared the mercury content found in the first hair clippings of children diagnosed with various severities of autism with the mercury content found in the first hair clippings of non-autistic children. The investigators found that the "[a]utistic infants released dramatically lower levels of mercury into hair than control infants." PMRL 237 at 283 (2003 Holmes article). The autistic infants had higher mercury exposures in many, but not all, of the considered exposure categories that included both prenatal exposures (through maternal dental amalgams, maternally-received Rho D immunoglobulin injections,[138] and maternal fish consumption[139]) and postnatal exposures (childhood vaccinations). Id. at 279, 283. The investigators concluded, and petitioners here have argued, that measured mercury levels in the hair clippings of autistic infants that are lower than non-autistic controls suggest that autistic children have difficulty excreting mercury. PMRL 237 at 284 (2003 Holmes article); Mead Ps' Trial Ex. 2 at 85-86 (Dr. Aposhian's trial slides). The 2003 Holmes study has been criticized, however, because the reported mercury level in the hair of the control subjects was approximately 15 times greater than the expected mercury levels in the hair of children in the United States as reported in the large 2004 National Health and Nutrition Examination Study (NHANES study), filed as RMRL 333,[140] while the reported mercury level in the hair of the autistic children was only two times greater than the expected hair mercury levels for children in

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[137] A. Holmes et al., Reduced levels of mercury in first baby haircuts of autistic children, International Journal of Toxicology 22: 277-285 (2003).

[138] Rho D immunoglobulin is administered to Rh-negative mothers to prevent the mother's immune system from recognizing and causing distress to the Rh-positive red blood cells of the fetus. See http://www.britannica.com/EBchecked/topic/1444749/Rho-D-immune-globulin (last visited on 2/4/09). Generally, the therapy is administered in the 28th week of pregnancy (when the therapy is most effective) to Rh-negative mothers who have not developed anti-D antibodies naturally. Id.

[139] Notably, the investigators reported, without showing the underlying data, that "[m]aternal dietary consumption of fish was not significantly associated with autism." PMRL 237 at 283.

[140] M. McDowell et al., Hair mercury levels in U.S. children and women of childbearing age: reference range data from NHANES 1999-2000, Environ. Health Perspect. 112(11):1165-1171 (2004).

the United States. See Mead Tr. at 1838-1839 (Dr. Brent). The absence of any explanation for the grossly elevated mercury levels in the hair of the control subjects "raises . . . concern about the Holmes study." Id. at 1839.

Dr. Aposhian noted that consistent with the findings in the 2003 Holmes article were the early findings reported in the 2003 Hu poster presentation, filed as PMRL 16.[141] See Mead Tr. at 220-221. To test the hypothesis that autistic individuals have difficulty excreting mercury, investigators who prepared the 2003 Hu poster presentation used a scientific technique involving neutron activation analysis to compare selected heavy metal concentrations in hair samples taken from three persons with autism spectrum disorder to selected heavy metal concentrations in hair samples taken from two non-autistic controls. PMRL 16 at 1 (2003 Hu poster presentation). Of the three persons with ASD studied, two subjects were undergoing heavy metal detoxification, the protocol for which required the exclusion of seafood from the diet, and the third autistic subject was on a regular diet that included seafood consumption at least once per week. See id. The two ASD subjects undergoing detoxification had low hair mercury levels, and the third autistic subject had a hair mercury level close to what would be expected in the general population. See Mead Tr. at 1840; Mead R's Trial Ex. 4 at 27 (Dr. Brent's slides). The samples taken from the control subjects showed mercury levels that ranged approximately from 250 to 2,400 parts per billion. Of note, by undergoing "heavy metal detoxification," the autistic subjects were participating in a process designed to provoke the elimination of heavy metals, a factor to be considered in the evaluation of the measured mercury levels in their hair samples. Also of note, the poster presentation was never submitted for publication. Nor is there evidence that it was subjected to a peer-review process. Because uncertainty exists regarding the soundness of the poster presentation and its support for petitioners' proposition that certain autistic children have mercury efflux difficulties, Dr. Aposhian's reliance on the 2003 Hu poster presentation is of limited persuasiveness.

In a subsequent effort by different investigators to examine comparatively the hair and blood mercury levels of autistic and non-autistic children in Hong Kong, the investigators found that the measured hair and blood mercury levels for both autistic children and control children were elevated. See PMRL 275 at 433 (2004 Ip article[142]). "The detected elevated tissue mercury level of [the] autistic children reflected an environmental mercury exposure that also occurred in children with normal development."

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[141] L. Hu et al., Neutron activation analysis of hair samples for the identification of autism, Poster Presentation, Transactions of the American Nuclear Society and European Nuclear Society, International Conference (2003).

[142] P. Ip et al. Mercury exposure in children with autistic spectrum disorder: case-control study, J. Child Neurol. 19(6): 431-434 (2004).

Id. The Ip investigators found that the detected differences in tissue mercury levels between the autistic subjects and the non-autistic subjects lacked statistical significance. Id. The investigators concluded that the data did not support the finding of a relationship between measured hair and blood mercury levels and a diagnosis of ASD in a group of children with a mean age of seven years.[143] See id. at 422-423.

To rebut the findings of the 2004 Ip article, Dr. Aposhian drew attention to the 2007 DeSoto article filed as PMRL 423.[144] See Mead Tr. at 221-222. The authors of the 2007 DeSoto article disagreed with the interpretation of the mercury blood level data given by the investigators on the earlier 2004 Ip article. See PMRL 423 at 1309. Contrary to the Ip investigators, the authors of the 2007 DeSoto study found that the data presented in the 2004 Ip article showed a statistically significant link between blood mercury levels and a diagnosis of autism, and they observed that while the data reanalysis did not prove that vaccines cause autism, the results suggest that an individual's reaction to mercury exposure is likely to be affected by genetics. See PMRL 612 at 465 (2008 Aschner editorial and 2008 DeSoto responsive editorial[145]). The DeSoto authors, however, did not challenge the conclusions regarding the hair data from the 2004 Ip study. See Mead R's Ex. G at 44 (Dr. Brent's report).

As other support for his mercury efflux disorder theory, Dr. Aposhian pointed to the 2007 Adams article that examined the mercury content in the baby teeth of both

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[143] Following the initial publication of the study, concerns were expressed by Dr. Catherine DeSoto "about what appeared to be obvious inconsistencies in the data analysis . . . section of that article." PMRL 654 at 1321 (R. Brumback, Note from Editor-in-Chief About Erratum for Ip et al. Article, Journal of Child Neurol. 22(11):1321-1323 (2007)). An inquiry about the communicated concern and a request for the raw data was issued by the editor of the journal that published the study to the corresponding author of the Ip article. The Ip investigators responded by explaining, "The raw data and statistical analysis had been correct. Unfortunately, we now found that quite a few results in the [published] table were typed wrongly." Id. at 1321. A reanalysis of the raw data by Dr. DeSoto resulted in a different statistical conclusion, id., and Dr. DeSoto subsequently discussed the reanalysis of the Ip data in the 2007 DeSoto article filed in this case as PMRL 423.

[144] M. DeSoto et al., Blood levels of mercury are related to diagnosis of autism: a reanalysis of an important data set, J. Child Neurol. 22(11): 1308-1311 (2007).

[145] M. Aschner, Response to article by Desoto and Hitlan on the relationship between mercury exposure and autism, J. Child Neurol. 23(4): 463 (2008); M. De Soto and R. Hitlan, Concerning blood mercury levels and autism: A need to clarify, J. Child Neurol. 23(4):463-465 (2008).

autistic children and controls. Mead Tr. at 229; Mead Ps' Trial Ex. 2 at 90. The investigators examined baby teeth because teeth, which are formed in utero and during the first few years of life, would "provide a measure of cumulative [mercury] exposure during that critical period of development." PMRL 138 at 1047 (2007 Adams article[146]). The investigators found that the mercury levels measured in the teeth of autistic children were twice the amount measured in the teeth of controls. PMRL 138 at 1048-1049; Mead Tr. at 229. Dr. Aposhian asserted that the finding of a greater retention of mercury in the teeth of autistic children is supportive of the theory that autistic children are unable to excrete mercury. See Mead Tr. at 229, 231, 474-475.

The 2007 Adams study has been criticized, however, as a "small and nonreplicated study" and because the researchers did not control for: (1) gender ratios in both the autistic and control groups to reflect the male predominance of the disorder; and (2) the type of tooth examined because different teeth have different mercury concentrations.[147] Mead Tr. at 1835-1836. Moreover, informed by a much larger tooth study conducted in Norway of the expected mercury level in the primary teeth of the general population, see RMRL 488 at 23 (2000 Tvinnereim article), respondent's expert Dr. Brent stated that the finding in the 2007 Adams article that the mercury levels in the teeth of both the control and autistic subjects were lower than the expected mercury level for primary teeth in the general population was a "concern[]." Mead Tr. at 1837 (Dr. Brent comparing the findings in the 2000 Tvinnereim article with those in the 2004 Adams article). The finding of mercury levels in the primary teeth of both the autistic and control subjects examined in the 2007 Adams study that were lower than the expected mercury levels in the primary teeth of the general population calls into question the validity of the findings of the 2007 Adams study.

As additional support for his theory that certain autistic children have a mercury efflux disorder, Dr. Aposhian cited the 2003 Bradstreet article that detailed the findings of a retrospective study comparing the urinary mercury excretion of 221 children with ASDs to the urinary mercury excretion of 18 non-autistic children after three days of treatment with the oral chelating agent known as DMSA (or meso-2,3-dimercaptosuccinic acid). Mead Tr. at 222-224; PMRL 244 at 76 (2003 Bradstreet article[148]). The investigators

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[146] J. Adams et al., Mercury, lead, and zinc in baby teeth of children with autism versus controls, J. Toxicol. Environ. Health A. 70(12): 1046-1051 (2007).

[147] Molars have higher mercury concentrations than other teeth. Mead Tr. at 1834 (Dr. Brent); see also RMRL 488 at 42 (H. Tvinnereim et al., Heavy metals in human primary teeth: some factors influencing the metal concentrations, Sci. Total Environ. 255: 21-27 (2000)).

[148] J. Bradstreet et al., A case-control study of mercury burden in children with

(continued...)

found that chelated autistic children excreted far more mercury than the control children did. PMRL 244 at 79. Dr. Aposhian explained that because a metal "will have a greater affinity for [the chelating agent] than for the ligand or the protein to which it is attached in the body," a chelating agent will facilitate the urinary excretion of mercury. See Mead Tr. at 222-223. He reasoned that the finding reported in the 2003 Bradstreet article–specifically that the autistic children's urinary mercury excretion exceeded that of the control children–showed that the autistic subjects had a higher body burden of mercury possibly indicative of an efflux disorder. See id. at 223-224.

Dr. Aposhian briefly described how the chelating agent DMSA that was administered to the subjects in the 2003 Bradstreet study operates. Mead Tr. at 440. Although use of DMSA was FDA-approved originally for the removal of lead from children with elevated blood lead levels, Dr. Aposhian explained that the chelating agent has been used "off-label" to remove mercury as well. Id. at 223. He stated that DMSA forms a ring with mercuric mercury, the inorganic form of mercury that petitioners here assert leads to the development of autism when deposited in the brains of certain genetically susceptible children. See id. at 222-223, 440. Dr. Aposhian acknowledged that when DMSA is administered as a chelator, most of the mercury excreted comes from the kidney and not from the brain. Id. at 441-442; accord id. at 1843 (Dr. Brent). He further acknowledged that performed chelation studies have shown that DMSA does not remove mercury from the brain and that chelation therapy has serious risks. Id. at 442-443, 448 (Dr. Aposhian). He maintained, however, that parental belief that chelation therapy is beneficial for their children cannot be ignored. See id. at 444, 447, 449; but see id. at 1845 (Dr. Brent unable to "find a single study in the peer-reviewed medical literature or scientific literature that demonstrates that chelation therapy is beneficial in autism"). And, Dr. Aposhian asserted, the 2003 Bradstreet study indicated that after the administration of DMSA, more mercury was removed from the autistic children than the control children. See id. at 223-224.

Pointed criticism, however, has been leveled against the 2003 Bradstreet study. As Dr. Brent testified, the reported results could not be reproduced using the researchers' own methodology to show that they were statistically significant. Mead Tr. at 1842. Additionally, although the urinary mercury levels of the autistic subjects were "fairly typical of what . . . might [be] expect[ed] for anybody given a chelator whether . . . autistic or not," the results were not interpretable because the pre-chelation urinary mercury levels had not been determined. Id. at 1843. Dr. Brent explained that while "plenty of reference ranges [exist] for what is normal in the population for a non[-]chelated urinary mercury excretion level[,] [t]here are . . . no validated reference ranges for chelated mercury

[148](...continued)
autistic spectrum disorders, Journal of American Physicians and Surgeons 8(3): 76-79 (2003).

levels." Id. at 1850. Accordingly, because the effect of chelation, consistent with its purpose, is to increase the urinary excretion of mercury, the results of any urinary testing for mercury after chelation "are essentially uninterpretable" without a measure of the urinary mercury levels before chelation indicating whether or not levels were within the normal range.[149] See id. at 1850, 1852.

Moreover, a subsequent study, as reported in the 2007 Soden article filed as RMRL 458,[150] could not confirm the 2003 Bradstreet study results. See Mead Tr. at 1844. The investigators found that "DMSA provoked excretion testing did not produce evidence of an excess chelatable body burden among the autistic [study] participants." RMRL 458 at 480. The investigators concluded that "[i]n the absence of a . . . novel mechanism of heavy metal toxicity or an alternate therapeutic action of chelators, the data presented provide[d] no justification for chelation therapy for the [study] participants." Id.

Dr. Aposhian also looked to the 2005 Woods study filed as PMRL 45[151] for evidentiary support of the mercury efflux theory that he put forth. The investigators in the 2005 Woods study found that a segment of the examined population of dental practitioners–reportedly, 15%–experienced changes in the porphyrin metabolism in their kidney cells and their urinary porphyrin excretion pattern after exposure to mercury. Mead Tr. at 213; PMRL 45 at 119. Previously conducted studies of subjects with occupational mercury exposures–that included dental professionals–indicate that these changes occurred "irrespective of [the] intensity of [the mercury] exposure." PMRL 45 at 114. The investigators that conducted the 2005 Woods study described a certain genetic variation (known as a polymorphism[152]) "that appears to specifically modify the effect of mercury on porphyrin metabolism in humans, resulting in [the] excretion of unexpectedly high levels of . . . atypical porphyrin . . . in the urine." Id. at 119. The investigators noted

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[149] Emphasizing this point, Dr. Brent referred to a laboratory result for William Mead's urine metal levels that stated in bold at the bottom of the report, "'Reference ranges are representative of a healthy population under nonchallenge or nonprovoked conditions.'" Mead Tr. at 1851-1852 (quoting Ps' Ex. 15 at 118).

[150] S. Soden et al., 24-hour provoked urine excretion test for heavy metals in children with autism and typically developing controls, a pilot study, Clin. Toxicol. 45(5): 476-481 (2007).

[151] J. Woods et al., The association between genetic polymorphisms of coproporphyrinogen oxidase and an atypical porphyrinogenic response to mercury exposure in humans, Toxicol. Appl. Pharmacol. 206(2): 113-120 (2005).

[152] A polymorphism is a genetic variation that is too common to be maintained merely by a new mutation. See Dorland's at 1481.

that the discovered polymorphism might "represent a genetic predisposition to an altered biological response to [mercury]." Id. Or more particularly, the polymorphism might serve as a biomarker of susceptibility to mercury toxicity. PMRL 199 at 160 (2006 Heyer article[153]). Subsequently, in the 2006 Nataf study, filed as PMRL 65,[154] researchers reported that in a study of 269 children (including 12 control subjects and 257 study subjects that had been diagnosed with various neurodevelopmental disorders), the autistic children demonstrated excess urinary porphyrin levels that were reduced after chelation. PMRL 65 at 104-105. In the view of Dr. Aposhian, these studies showed that there are differences in the ability of various individuals to metabolize mercury and suggested that the affected individuals have a mercury efflux disorder–characterized by the inability to excrete "as much mercury as is normal." See Mead Tr. at 383-384, 392-394. Dr. Aposhian conceded, however, that the form of mercury to which the subjects in the 2005 Woods article were exposed was mercury vapor and not ethylmercury, the form of mercury into which the thimerosal component of vaccines dissociates. See id. at 387.

Dr. Aposhian asserted that the inability to excrete mercury that results from an inborn mercury efflux disorder causes mercury toxicity that, in turn, leads to autism. Mead Tr. at 394-395. He explained that it is the "mercury build[] up in the tissues, and . . . in the brain" that is "one of the causes of autism." Id. at 395. Petitioners' experts, Drs. Aposhian, Deth, and Mumper opined that a certain percentage of children with autism "clearly suffer from mercury toxicity." Mead Tr. at 396. While acknowledging that he is neither a clinician nor a physician, Dr. Aposhian testified that "many of the physicians who treat and diagnose autistic children . . . say that they see very similar signs of . . . mercury toxicity in some of their autistic children." Mead Tr. at 400. When questioned further during cross-examination, Dr. Aposhian stated that in the genetically susceptible population that has a mercury efflux disorder, mercury toxicity also "could" result from eating too much fish. Id. at 401-404 (Dr. Aposhian citing the 2003 Hightower article, filed as PMRL 2554,[155] but admitting that there is no evidence that the subjects of the 2003 Hightower study–whose neurological impairments appeared to resolve when the subjects abstained from eating fish–had mercury efflux difficulties).

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[153] N. Heyer, A cascade analysis of the interaction of mercury and coprophyrinogen oxidase (CPOX) polymorphism on the heme biosynthetic pathway and porphyrin production, Toxicol. Lett. 161: 159-166 (2006).

[154] R. Nataf et al., Porphyrinuria in childhood autistic disorder: implications for environmental toxicity, Toxicol. Appl. Pharmacol. 214: 99-108 (2006).

[155] J. Hightower & D. Moore, Mercury levels in high-end consumers of fish, Environmental Health Perspectives 111(4): 604-608 (2003).

As the preceding discussion illustrates, respondent's experts refuted petitioners' theory of a mercury efflux disorder and challenged the interpretation that petitioners offered for the studies they cited in support of their theory. Moreover, Dr. Brent, respondent's expert medical toxicologist, testified that there is a range of exposure doses, defined by the "dome" portion of a bell-shaped curve, to which a majority of people will respond.[156] See Mead Tr. at 1800-1802; Mead R's Trial Ex. 4 at 5 (Dr. Brent's slides). As indicated by the tails of the bell-shaped curve, there are some people who respond at lower doses and some who respond at higher doses. Mead Tr. at 1801. This range of values reflects the range of naturally-occurring individual variability rather than a particularly susceptible population. Id. What is known toxicologically about a susceptible population is that the "bell-shaped curve for that group of people is shifted . . . way down to lower doses." Id. at 1801-1802. Accordingly, when a hypersusceptible population is determined in fact to exist, the resulting bell-shaped curve has two clearly identifiable "domes" with the smaller of the two (representing the susceptible population) preceding the larger (representing the general population) on an x-axis (measuring the exposure dose needed to trigger a response). See id.; Mead R's Trial Ex. 4 at 6. Respondent's experts asserted that what is known about mercury exposure does not indicate that a hypersusceptibility to mercury exists in certain individuals. Mead Tr. at 3416 (Dr. Rutter); id. at 1802 (Dr. Brent). Respondent's experts further asserted that variability in individual levels of mercury in the blood and in the brain does not require an environmental influence because "huge individual variability" is part of the biology of human beings. Mead Tr. at 3414 (Dr. Rutter); id. at 1801 (Dr. Brent).

a. Summary of Findings

An important aspect of petitioners' general causation theory is that certain individuals have a genetic predisposition to both autism and an inborn difficulty excreting mercury (described as a mercury efflux disorder). Petitioners' position that a mercury efflux disorder exists is premised on several studies, variously involving blood, hair, teeth, and urine samples, that purport to show that there are differences in the way control subjects and autistic individuals process mercury. The difficulty with petitioners' reliance on these studies, however, is two-fold. First, with respect to the hair, teeth and urine sample tests, there are unresolved questions concerning the scientific reliability of the studies. Second, petitioners have pointed–in error–to the naturally-occurring variations in the human response to mercury exposure (that are demonstrable on a bell-shaped curve illustrating the dose-response relationship) as evidence of the scientifically distinguishable phenomenon of hypersusceptibility (a condition that is demonstrable on a distinctively

[156] Almost all people fit within two standard deviations of the dose level at which the greatest number of exposed persons manifest a response. See Mead Tr. at 1801; Mead R's Trial Ex. 4 at 5 (Dr. Brent's slides). This dose level is found at the apex of the bell-curve and is the mid-point between the two standard deviations. See id.

"two-humped" bell-shaped curve illustrating the dose-response relationship). The support offered for the mercury efflux disorder component of petitioners' theory lacks the scientific reliability that, in the view of the undersigned, would make the proposition more likely than not.

The undersigned turns now to consider further petitioners' claims regarding the alleged neurotoxic effects of the long-term mercury brain deposits that contribute to development of autism.

H. Examining Further the Alleged Neurotoxic Effects of Long-Term Inorganic Mercury Deposits in the Brain

Petitioners assert that the accumulation of mercury in the brain can lead to neuroinflammation and posit that neuroinflammation has been implicated in the etiology of autism. See Mead Ps' Brief at 24-38. Petitioners argue that neuroinflammation disrupts proper neuronal functioning in the brain and also can create a harmful condition of oxidative stress. Id. at 38-55. Petitioners contend that these particular effects of neuroinflammation impair normal brain function and lead to the behaviors that are observed in autistic individuals. See id. at 55.

Respondent challenges petitioners' proposed theory of vaccine-related causation as "hypothetical," "speculative," and "scientifically unsound." Mead Respondent's Post-Hearing Brief (Mead R's Response) at 17-18. Describing the hypothesis presented as "complex and awkward," respondent's expert neurologist Dr. Rust asserted that the hypothesis was based on "meager data" that either was not representative of the papers from which the data were extracted or reflected "some distortion" of the data. Mead Tr. at 2465. He added that the proposed hypothesis does not address or incorporate what is widely known about the regulation of that aspect of the nervous system contemplated in petitioners' general causation theory. Id. at 2465-2466.

The undersigned turns now to address, in turn, the components of the neurotoxicity aspect of petitioners' theory.

1. Petitioners' Claim that the Accumulation of Inorganic Mercury in the Brain Leads to Neuroinflammation

A critical underpinning to the neurotoxicity aspect of petitioners' theory is the reported finding of neuroinflammation in brains that have been examined after mercury exposure. In support of petitioners' claim that the accumulation of inorganic mercury in the brain leads to subcellular effects that can contribute to the development of autism,

petitioners rely heavily on the multiple articles described earlier in this decision as the "monkey studies." The earlier cited articles address the results of a study of the brain levels of mercury in monkeys following long-term exposures to methylmercury. See Section III(G)(2)(a) (discussing the "Monkey Studies") above. In the 1996 Charleston article, filed as PMRL 116, the same core group of researchers who also authored the 1994 Vahter article examined the brains of the sacrificed study animals for mercury deposits. See PMRL 116 at 128-129. At the time of sacrifice, the mercury-exposed study animals showed no abnormalities in behavior or motor skills. Id. at 130; see also Mead Tr. at 1932 (Dr. Brent, respondent's medical toxicologist, noting that the "monkeys were all clinically normal" even though the administered doses of mercury were "far, far in excess" of any dose to which a human being reasonably would be exposed); id. at 2593 (Dr. Rust testifying that although the monkeys were given "very large [doses of organic mercury] . . . very repetitively over a long interval," there was no evidence of clinical deterioration prior to the animals' sacrifice). The effects of the long-term methylmercury exposure were subclinical, and the "most responsive cell type" within the central nervous system to that exposure was the microglia. PMRL 116 at 132; see also PMRL 32 at 326 (1995 Charleston article[157]). Following the mercury exposure, the microglia increased in number and changed in shape. See Mead Tr. at 2584-2585. The results of the study showed a preferential accumulation of inorganic mercury in the astrocytes and microglia and a slower rate of accumulation of inorganic mercury in the neurons. PMRL 32 at 329-330. The researchers observed that the lack of any change–whether an increase or decrease–in the number of neurons did not mean that the cells were "completely unaffected" by the methylmercury exposure because subcellular changes have been found to occur after mercury exposure. PMRL 116 at 133. But, "the histological staining of the neurons in th[e] study did not reveal any significant chronic or acute damage to the neurons." Id. Moreover, the researchers observed that "[w]idespread loss of astrocytes c[ould] be expected to disrupt the composite ability of the astrocytes to carry out their supporting function for neurons, and ultimately their loss would be expected to impact the overall function of the central nervous system." Id. at 134. The researchers subsequently stated in the 2005 Burbacher study that "[i]t is important to note that 'an active neuroinflammatory process' has been demonstrated in brains of autistic patients, including a marked activation of microglia." PMRL 26 at 1020 (the 2005 Burbacher article) (quoting the 2005 Vargas paper that was filed as PMRL 69[158]). Relying on this series of observations and statements by the researchers who conducted the monkey brain studies, petitioners assert that the

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[157] J. Charleston et al., Autometallographic determination of inorganic mercury distribution in the cortex of the calcarine sulcus of the monkey Macaca fascicularis following long-term subclinical exposure to methylmercury and mercuric chloride, Toxicol. Appl. Pharmacol. 132(2):325-333 (1995).

[158] D. Vargas et al., Neuroglial activation and neuroinflammation in the brain of patients with autism, Ann. Neurol. 57(1):67-81 (2005).

inorganic mercury that is deposited in the brains of children after receipt of thimerosal-containing vaccinations leads to neuroinflammation and the subcellular effect of that process is a dysfunction that contributes to the state of overexcitation that manifests as autistic behavior.

As the researchers noted in the 1996 Charleston article, however, no significant chronic or acute damage to the neurons in the monkeys' brains had been detected following the methylmercury exposure. PMRL 116 at 133. Dr. Brent noted that typically not much inorganic mercury is seen in the neurons. Mead Tr. at 1919. But, he explained, because the adult monkeys in the study received 3,500 micrograms a day of methylmercury (nearly one-third of the annual human exposure to methylmercury in the United States through fish consumption),[159] the neurons of the monkeys' brains would have been expected to have a more appreciable presence of mercury. See id.

The difficulty with this particular aspect of petitioners' theory is that the subcellular changes that have been observed in the brains of those who have been exposed to mercury generally have involved substantially higher dosages of mercury exposure than are present in the thimerosal-containing vaccines at issue. Moreover, the subcellular changes that were detected in the brains of those with elevated levels of mercury exposure were not accompanied by any noticeable changes in behavior. The failure to detect any behavioral changes in those purposely exposed to mercury levels sufficient to cause subcellular changes renders petitioners' claim that such subcellular changes can lead to the manifestation of autistic symptoms less than likely.

The undersigned now considers petitioners' claim that over time, inorganic mercury deposits in the brain disrupt sulfur metabolism at the subcellular level, set into motion a process that impairs normal brain function, and lead to the development of autism.

2. Petitioners' Claim that Inorganic Mercury Deposits in the Brain Cause Subcellular Effects that Disrupt Sulfur Metabolism and Lead to Improper Brain Function

[159] The dose of methylmercury administered to the monkeys was 50 micrograms per kilogram of body weight per day. Mead Tr. at 1933-1936. With body weights roughly equivalent to a 70 kilogram person, the monkeys received about 3,500 micrograms of methylmercury daily, a dosage well in excess of what is received through thimerosal-containing vaccines. Id. at 1936. After three days of such exposure, the monkeys received well in excess of the average annual methylmercury exposure in the United States through diet. Id.

Petitioners' expert pharmacologist Dr. Deth set forth petitioners' theory regarding how mercury deposits in the brain produce subcellular effects that disrupt proper brain function. As a threshold matter, Dr. Deth explained that mercury and sulfur are well-suited chemically to form a strong chemical bond (and a compound known as a mercaptan) that is not easy to break. See Mead Tr. at 500-501; see also Mead Ps' Trial Ex. 3 at 3 (Dr. Deth's trial slides). The "non-specific" ability of mercury to bind to sulfur-containing compounds (that are also known as thiols[160]) permits the disruption of sulfur metabolism that is critical for many different life forms. Id. at 502; accord id. at 2699 (Dr. Jones testifying that "[s]ulfur is the fifth most abundant element in biological systems [and] [p]retty much all of life depends upon sulfur"). It is this feature–specifically, the ability to disrupt the sulfur metabolism of bacteria and fungi–that precipitated the use of thimerosal (which is a combination of ethylmercury and a sulfur carrier) as a preservative in vaccines. Id. at 502-503. In addition, it is this feature–the disruption of sulfur metabolism–that is at work, in the opinion of Dr. Deth, in the brains of certain autistic individuals who have received thimerosal-containing vaccines. See id. at 505, 3958-3959; see also Mead Ps' Trial Ex. 3 at 2 (trial slide of flow chart showing path from the administration of thimerosal to the deposition of inorganic mercury in the brain to the disruption of sulfur metabolism process).

The most important of the mercury-induced disruptions to sulfur metabolism that Dr. Deth identified in autistic persons who have received thimerosal-containing vaccinations are: (1) the disruption in the oxygen environment in cells, which leads to oxidative stress; and (2) the disruption of the methylation process that has a critical role in the regulation of gene expression and is a particularly significant process during the developmental period when genes are either turned on or off. See id. at 513-518; see also Mead Ps' Trial Ex. 3 at 5, 6 (Dr. Deth's trial slides). Dr. Deth testified that a disruption in sulfur metabolism, leading to oxidative stress, necessarily results in reduced methylation activity affecting more than 150 methyl transfer reactions.[161] Mead Tr. at 516, 518; see also Mead Ps' Trial Ex. 3 at 6. Dr. Deth further testified that oxidative stress and the inhibition of the methylation process both lead to a loss of cellular function that stops short of cell death. Id. at 522-523, 610-611, 3973. Dr. Deth asserted that the cellular dysfunction triggered by both oxidative stress and an impaired methylation process is relevant to petitioners' theory here because such cellular dysfunction has been associated

[160] A thiol-containing compound is a compound that contain a sulfhydryl, a chemical group comprised of sulfur and hydrogen that can both enter into and come out of different chemical combinations without being changed (a property that permits a thiol or sulfhydryl to be characterized chemically as a radical). Mead Tr. at 171-172, 175 (Dr. Aposhian); see also Dorland's at 1562, 1903.

[161] Transfer of a methyl group involves the transfer of a carbon-containing chemical group. Dorland's at 1145; Mead Tr. at 515 (Dr. Deth).

with the neuroinflammation observed in the autopsied brains of autistic persons. Id. at 570-571, 3959-3960; see also Mead Ps' Ex. 3 at 4 (Dr. Deth's trial slides).

Examining Dr. Deth's theory in greater detail, the undersigned turns first to address the chemical bond between mercury and thiols that can have an impact on sulfur metabolism in the body.

a. The Bond between Mercury and Thiols

Once ethylmercury dissociates in the blood stream from the sulfur component in thimerosal, it may reach the brain, there de-ethylate, and then become inorganic mercury. In its inorganic form, mercury is capable of binding to two thiols or sulfur groups. See Mead Tr. at 499 (Dr. Deth).

Three thiols that are important to the process of sulfur metabolism are: (1) homocysteine; (2) cysteine; and (3) glutathione. Id. at 504-505. The amino acid homocysteine is a precursor to the amino acid cysteine, and the amino acid cysteine is crucial for making the antioxidant, glutathione. Id. Glutathione is a small peptide (comprised of three amino acids, namely glutamate, cysteine, and glycine) that is found in every cell in the body–including the neurons, astrocytes, and microglia in the brain–in a concentration of up to about 10 millimolar.[162] Id. at 507 (Dr. Deth), 2705 (Dr. Jones); see also Mead Ps' Trial Ex. 3 at 3. Glutathione has "a very important role in metabolism," and three major detoxification functions. Mead Tr. at 2699, 2701 (Dr. Jones).

The three major detoxification functions of glutathione are described briefly here. See Mead Resp. Trial Ex. 9 at 3 (Dr. Jones' trial slides). First, glutathione is the most important anti-carcinogenic chemical in the human body. Id. at 2702. Second, it is an antioxidant that prevents both the cell dysfunction and the risk of cell death that can occur when there is too much oxygen in the cellular environment, a condition alternatively referred to as oxidative stress. See Mead Tr. at 507 (Dr. Deth), 2702 (Dr. Jones). Dr.

[162] To put this concentration of glutathione into perspective, the undersigned notes that one millimolar is one thousandth of a molar. One micromolar is one millionth of a molar, and one nanomolar is one billionth of a molar. By comparison, the undersigned points out that the amount of mercury estimated to be deposited in the brain from thimerosal-containing vaccines is in the range of a few nanograms per gram (or parts per billion). Although the measures for these two substances are different (concentration for glutathione and weight for mercury), the order of magnitude of difference between the amount of glutathione in the body and the amount of inorganic mercury estimated to be deposited in the brain after receipt of thimerosal-containing vaccines is significant and demonstrates that the amount of mercury attributable to thimerosal-containing vaccines is quite small compared to the amount of glutathione available to the body.

Deth asserted that the condition of oxidative stress is closely related to and is a component of the condition of neuroinflammation. See id. at 653, 655. Third, glutathione is involved in other aspects of the body's metabolism where it performs a coenzymatic function and serves as a catalyst for certain chemical reactions. See id. at 2703 (Dr. Jones).

To facilitate an understanding of this part of petitioners' theory, the undersigned briefly reviews the function of the brain cells that are implicated in petitioners' proposed mechanism of harm.

b. The Role of Neuroglial Cells in Supporting Proper Brain Function

Neuroglia or glial cells form the supporting structure of nervous tissue. Dorland's at 1254; see also Mead Tr. at 797-798 (Dr. Kinsbourne describing glial cells as "connective tissue cells" in the nervous system). These cells are oddly branched cells of three types: (1) oligodendroglia or oligodendrocytes; (2) microcytes or microglia; and (3) astroglia or astrocytes. See Dorland's at 1254; see also Mead Tr. at 2581. The cell types have particular functions that are briefly described below.

The principal function of the oligodendrocytes is the formation of the myelin sheathing that insulates the nerve fibers that carry signals between the cells. See Dorland's at 1689, 1254-1255; see also Mead Tr. at 2581-2582 (Dr. Rust). As presently understood, the microglial cells play an important role in the innate immune system and the reactive immune system by phagocytizing (that is, killing and digesting) viral, bacterial or any other agents–including waste products of nervous tissue–that invade the nervous tissue. See Dorland's at 1254; Mead Tr. at 2582 (Dr. Rust); id. at 795 (Dr. Kinsbourne). In response to a chemical signal that a potentially threatening agent or material has been detected in the nervous tissue, the microglia become activated to attack and remove the identified agent or material. See Mead Tr. at 798-799 (Dr. Kinsbourne explaining that microglia are inactive until an invasive agent is detected).

The third cell type, the astrocytes, are involved in the transport of materials to the neurons or nerve cells and the maintenance of the ionic environment of neurons. Dorland's at 1254. Star-shaped cells in appearance, the astrocytes exercise certain caretaking functions. Mead Tr. at 795 (Dr. Kinsbourne); see also id. at 510 (Dr. Deth describing astrocytes as "nurse cells, taking care of neurons"). Additionally, astrocytes generate the antioxidant glutathione for use by neurons because neurons do not produce much glutathione on their own. Mead Tr. at 2581 (Dr. Rust).

Dr. Deth described the process by which astrocytes generate glutathione for use by neurons in more detail. He explained that the astrocytes assist the neuronal cells by

releasing excess glutathione that is converted, through a two-step chemical process, into cysteine. See Mead Tr. at 544-545; Mead Ps' Trial Ex. 3 at 18. The produced cysteine then becomes available for uptake by a specific transporter (known as the excitatory amino acid transporter 3 or EAAT-3) on the neuronal cell that, in turn, transports either cysteine or glutamate–each of which is a component of the three-part peptide glutathione–across the cell membrane and into the neuronal cell where the neuronal cell then generates its own glutathione, an antioxidant that buffers the neurons from the effects of oxidative stress. See Mead Tr. at 544-545; Mead Ps' Trial Ex. 3 at 18.

In each of the three types of neuroglial cells, as with all other cells in the body, are small organelle or subcellular components known as mitochondria that produce energy for cells. Mead Tr. at 521. Mitochondria are able to produce energy by absorbing molecular oxygen and converting it to water; the conversion process allows the release of energy from the cell. Id. Mitochondria also depend on a sufficiently available supply of glutathione to protect against the harmful effects associated with an environment containing too much oxygen. See id. at 519, 529.

The undersigned turns next to consider Dr. Deth's description of the how certain subcellular processes are involved in managing the oxidative process by maintaining a state of reduced oxidation–also known as the normal redox state–that is desired in the cellular environment.

c. Disruptions in Certain Methylation Processes that Petitioners Claim Cause an Adverse Skewing in the Oxidative Environment

As a predicate to the discussion of this aspect of petitioners' claim, a brief description follows regarding how the oxidative process is initiated.

(1) Creating a State of Oxidation

Physiological changes can occur when the body is presented with certain challenges or exposures. Mead Tr. at 149 (Dr. Aposhian). Among the known physiological changes is the release of "very reactive chemical substances" known as "free radicals." Id. As Dr. Roberts, who was respondent's expert on oxidative stress and oxidative damage as it pertains to disease, explained during his testimony, a free radical is created when an electron that is in orbit around the nucleus of an atom is separated from its partner electron and is removed from the atom. Mead Tr. at 2167-2168. The compound containing the unpaired electron becomes "very, very unstable" and is known as a free radical. Id. at 2168. Seeking another partner, the unpaired electron will extract an electron from another atom–whether in the same molecule or not–and thereby propagate a process of oxidation.

Id. at 2167-2169; see also Mead R's Trial Ex. 6 at 5 (slide illustrating the process of continued propagation of oxidation). The term oxidation describes the process of extracting an electron from an atom. Mead Tr. at 2167.

The ongoing process of oxidation can be stopped by the donation of an electron. Id. at 2169. The process of donating an electron to a molecule for pairing with another electron is called reduction. Id.; see also Mead R's Trial Ex. 6 at 6 (slide describing the reduction process). When the donated electron comes from an antioxidant molecule, the oxidation process is arrested because the unpaired electrons left in antioxidant molecules are not highly reactive and, thus, do not seek to extract electrons from other molecules. Mead Tr. at 2169-2170. The state of reduced oxidation (REDOX) that is desired in the body reflects a balance between the reduction and oxidation processes. Id. at 2170. An imbalance in the two processes that tilts toward oxidation reflects a state of oxidative stress. Id.

(2) Sufficient Glutathione Needed to Support Certain Cellular Processes and Manage the Oxidative Environment in the Brain

Dr. Deth emphasized the importance of having sufficient glutathione in cells to avoid the harm associated with an overly oxidated state (created by the presence of too many oxygen radicals). Mead Tr. at 519-520. Glutathione is generated from a series of four chemical reactions that occur along a transsulfuration pathway and involve the conversion of the three important thiols identified by Dr. Deth in the process of sulfur metabolism. Id. at 524-525; Mead Ps' Trial Ex. 3 at 8. Specifically, homocysteine is converted to cystathionine, which is converted to cysteine, which is converted to gamma-glutamylcysteine, which is converted to glutathione. Mead Ps' Trial Ex. 3 at 8 (flow diagram of the conversions that occur along the transsulfuration pathway).

The homocysteine that drives the transsulfuration process that generates glutathione is also an important compound in the methionine methylation cycle. Mead Tr. at 525; Mead Ps' Trial Ex. 3 at 8. The methionine methylation cycle, which is alternatively known as methionine synthase (or the process of making methionine), is the process of adding a methyl (or carbon group) to homocysteine to produce methionine. Mead Tr. at 539; see also Mead Ps' Trial Ex. 3 at 14 (illustrating a molecular model of methionine synthase). Importantly, methionine is involved in the determination of gene expression during early development. See Mead Tr. at 535. According to Dr. Deth, an increased demand for homocysteine in the transsulfuration process to create the glutathione necessary to preserve the proper oxygen status in cells concomitantly deprives the methionine methylation cycle of the homocysteine it requires. See id. at 525-526, 535.

The consequences of a disrupted methionine methylation cycle include "problems during development with inappropriate gene expression." Id. at 535.

Another methylation cycle affected by the methionine methylation cycle is the one involving the neurotransmitter identified as the D-4 dopamine receptor. See id. at 527-528; see also Mead Ps' Trial Ex. 3 at 8-9. The D-4 dopamine receptor is pertinent to Dr. Deth's proposed theory concerning mercury-induced disrupted brain function because it is a genetic risk factor for attention deficit hyperactivity disorder. Mead Tr. at 532. The risk for attention deficit hyperactivity disorder is three- to five-fold higher for those with a particular genetic form of the D-4 dopamine receptor than for those without it. Id. The D-4 dopamine receptor is found in neuronal cells with inhibitory functions. See id. at 528. The methylation cycle involving the D-4 dopamine receptor is affected when methionine synthase or the methionine methylation cycle is disrupted–such as occurs when there is an increased demand for the transsulfuration pathway to generate more of the antioxidant glutathione to respond to the presence of oxidative stress (too much oxygen in the cellular environment). See id. at 535; see also Mead Ps' Trial Ex. 3 at 11. One of the adverse effects of the disruption of the methylation cycle involving the D-4 dopamine receptor is impaired attention. See Mead Ps' Trial Ex. 3 at 11.

Dr. Deth also testified that human neuronal cells do not "operate the same" as the neuronal cells in other species, and he pointed to two differences observed in the methionine methylation cycle and in the transsulfuration process. In describing the first of the differences, he noted that studies of human neuronal cells performed in the laboratory–as compared to related studies on rat brains–indicate that one of the binding sites in the methionione methylation cycle (specifically, the S-adenosylmethionine- or the SAM-binding site) does not function in human neuronal cells. See Mead Tr. at 541. Without that binding site functioning properly in the methionine methylation cycle, a glutathione-dependent methyl group (known as methyl cobalamin or methyl B-12) is necessary to perpetuate the methylation cycle, id. at 541-542, and this glutathione-dependent methyl group requires an adequate supply of available glutathione.

In describing the second of the differences, Dr. Deth noted that a comparison of the brain cells (including the neurons) taken from a human brain to the brains cells taken from a monkey, a rat, a guinea pig, a cat, a cow, a chicken, and a duck shows that the human brain has markedly higher levels of cystathionine, which is the product of the first chemical reaction along the transsulfuration pathway that permits the generation of glutathione from homocysteine. See id. at 542-543; see also Mead Ps' Trial Ex. 3 at 17. But "[t]here appears to be a block in human brains after [the making of] the cystathionine that limits [the] ability" to make, in turn, cysteine and glutathione. Id. at 543; see also Mead Ps' Trial Ex. 3 at 18 (flow diagram illustrating the limitation associated with cystathionine in the transsulfuration pathway). This limitation serves to make human

neuronal cells more dependent on astrocytes because the astrocytes assist the neuronal cells in generating glutathione. See Mead Tr. at 544.

Dr. Deth observed that the noted differences in human neuronal cells create a particular vulnerability to oxidative stress because the cells do not have a robust transsulfuration pathway to create the glutathione needed for the methionine methylation process and to buffer against the adverse effects of oxidative stress. Id. at 545. He further observed that the remaining metabolic pathways must function properly to support the efforts of the brain cells to maintain a proper oxidative environment in the absence of a robust transsulfuration pathway. Id.

(3) Impaired Methylation Processes Have Been Detected in Autistic Children with Oxidative Stress

Having described how the brain's efforts to reduce oxidative stress are accompanied by a concurrent disruption of certain methylation processes in the brain based on competing demands for an adequate supply of glutathione, Dr. Deth pointed to evidence that there is an association between impaired methylation and the presence of oxidative stress in certain autistic children.

Dr. Deth relied on the 2005 James article, filed as PMRL 7,[163] for the proposition that thimerosal causes a significant reduction in the cellular levels of glutathione in "cultured" neuronal cells. Mead Ps' Ex. 17 at 4 (Dr. Deth's report). Also relying heavily on the 2006 James article, filed as PMRL 49,[164] as well as the body of related research articles published by Dr. Jill James, see PMRL 5 (2004 James article[165]), PMRL 705 (2008 James article[166]), Dr. Deth asserted that the plasma gathered from the 80 autistic children

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[163] S. James et al., Thimerosal neurotoxicity is associated with glutathione depletion: protection with glutathione precursors, Neurotoxicology 26(1):1-8 (2005). This same article was also filed as PMRL 554.

[164] S. James et al., Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism, Am. J. Med. Genet. B. Neuropsychiatr. Genet. 141(8):947-956 (2006).

[165] S. James et al., Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism, Am. J. Clin. Nutr. 80(6):1611-1617 (2004).

[166] S. James, Oxidative Stress and the Metabolic Pathology of Autism in Autism: (continued...)

and 73 neurotypical children included in the 2006 James study showed that the autistic children have genetic polymorphisms that predispose the children to having too little glutathione to combat oxidative stress and to suffering from impaired methylation. Mead Tr. at 536-537 (referring to the chart in the 2006 James article, found at PMRL 49 at 951, comparing transmethylation and transsulfuration metabolites for autistic children and controls). In Dr. Deth's view, the published work of Dr. James supported a finding that autistic children had a genetic vulnerability to disruptions in their sulfur metabolism.

Dr. Deth also turned to his own research, reported in the 2004 Waly study and filed in this case as PMRL 257,[167] as evidence that the mercury-containing compound thimerosal inhibits the activities of the methionine methylation cycle and of the dopamine methylation system, both of which are sulfur-dependent metabolic processes. See Mead Tr. at 546-547; see also PMRL 257 at 359, 365. Dr. Deth noted that although the 2004 Waly study examined the effect of thimerosal on in vitro or "cultured human neuronal cells," the "active species here is likely to be inorganic mercury released from thimerosal." Mead Tr. at 547, 621. Dr. Deth explained that the administered thimerosal exerted an inhibitory effect on the EAAT-3 transporter that permits the uptake of cysteine by neuronal cells for the production of glutathione. See Mead Tr. at 544-545, 547. Dr. Deth pointed to the substantial reduction in cysteine uptake associated with "exquisitely low concentrations" of thimerosal that, he asserted, were concentration levels commensurate with (or even lower than) those levels found in the blood plasma of children who received thimerosal-containing vaccines or the estimated levels of inorganic mercury reported in the 2005 Burbacher study to have accumulated in the brains of infant monkeys after administered injections of thimerosal-containing vaccines. Id. at 548, 555; see also Mead Ps' Trial Ex. 3 at 20-21; PMRL 26 at 1020 (the 2005 Burbacher article). Dr. Deth acknowledged that the measured inhibitory effect exerted by mercury was exerted as well by other heavy metals such as aluminum and lead that–like mercury–also have an affinity for thiols (sulfur-containing compounds). Mead Tr. at 549.

Dr. Deth observed that, due to the differences between the neuronal cells in humans and other species, including monkeys, the effect of the interference with cysteine uptake caused by the presence of thimerosal would be expected to be greater in humans than in monkeys or other species. See Mead Tr. at 549-550. He further observed that, as reported in the 2004 Waly study, the functional effect of thimerosal-induced inhibition of cysteine

[166](...continued)
Current Theories and Evidence, Chapter 11 (Humana Press 2008).

[167] M. Waly et al., Activation of methionine synthase by insulin-like growth factor-1 and dopamine: a target for neurodevelopmental toxins and thimerosal, Molecular Psychiatry 9:358-370 (2004).

uptake by neuronal cells was to limit the ability of the neuronal cells to make glutathione and thus, to put the neuronal cells at risk for the adverse effects of oxidative stress. Id. at 553; see also Mead Ps' Trial Ex. 3 at 24. He explained that the thimerosal-induced inhibition of cysteine uptake by neuronal cells that limited the ability of neuronal cells to make glutathione also might be expected to impact adversely the methionine methylation pathway that requires glutathione to proceed and, in turn, to support other dependent processes, including the D-4 dopamine methylation pathway that affects an individual's attention and awareness. See id. at 557. Dr. Deth posited that the long-term presence of inorganic mercury in the brain serves to "block the uptake of cysteine, and otherwise [to] maintain oxidat[ive] stress in the[] neurons." Id. at 557-558.

Referring to data obtained from the 2004 Waly study, Dr. Deth testified that not only was thimerosal found to inhibit dopamine methylation, but thimerosal also was found to inhibit the ability of a stimulating agent (such as the insulin-like growth factor 1 or IGF1 used in the 2004 Waly study) to stimulate "the signa[l]ing pathway that activates the cysteine uptake" by neuronal cells. Mead Tr. at 565. Dr. Deth noted, however, when copper was added to the cultured environment in which the 2004 Waly study was conducted, the inhibitory effects of the thimerosal were countered. Mead Tr. at 565-566. Dr. Deth also addressed the unpublished results of additional research he has conducted purporting to show that the lower brain level of methionine synthase at the DNA level in autistic subjects leads to the diversion of homocysteine from the methionine methylation pathway to the transsulfuration pathway that generates glutathione. See id. at 567-571. Dr. Deth opined that the detection of reduced cycles of methionine synthase at the DNA level in the same autistic brain samples found to contain neuroinflammation, as reported in the 2005 Vargas study, is suggestive of a relationship between the two conditions. Id. at 570-571. Dr. Deth posited that the lower levels of methionine synthase permitted more generation of glutathione through the transsulfuration pathway and reflected an adaptive response to the presence of oxidative stress and neuroinflammation in the brain. Id. He further posited, again based on his own unpublished research, that the impact of oxidative stress and the compensatory response of a reduction in methionine synthase (to allow the generation of the antioxidant glutathione along the transsulfuration pathway) is of "greater significance at younger ages." Id. at 573, 648-651.

Taking the published findings in the 2006 James article concerning the "normal variants" (or polymorphisms) of the genes involved in the methylation and transsulfuration pathways together with his own research concerning the inhibitory impact of thimerosal on the proper functioning of these particular pathways, Dr. Deth asserted that the "latent" genetic risk factors associated with the polymorphisms detected in Dr. James' research can become "real consequential risk factors" in the "presence of adverse environmental conditions" such as "the introduction of heavy metal toxicity" through thimerosal-

containing vaccines that, in turn, lead to the release of long-term deposits of inorganic mercury in the brain. Id. at 574-578. He further asserted that the affinity between mercury-containing compounds and sulfur-containing compounds (thiols) could affect the sulfur-dependent process of DNA methylation by altering gene expression during development in a manner that produces a developmental disorder. See id. at 578-579. Dr. Deth explained that "those who have a certain number of polymorphism or risk genes[] and are exposed to thimerosal[] have a high risk of having a neurological condition[] in which impaired methylation of methionine synthase activity plays a role." Id. at 615. Accordingly, it is his opinion that thimerosal "has the molecular capability to cause autism[] and to account for the major symptoms of autism," which include impairments in attention, awareness, and sociability. Id. at 581. Dr. Deth reasoned that because autistic individuals have exhibited signs of oxidative stress throughout the body, any correction of heavy metal toxicity "peripherally . . . c[ould] have benefits for neurological function," even though administered chelating agents do not penetrate the brain to remove mercury from the brain. Id. at 579-580.

Dr. Deth's proposed theory of vaccine-induced subcellular brain disruption is informed primarily by the published research of Dr. James and by his own largely unpublished research. The limitations of the research on which Dr. Deth relies and the difficulties with his opinion are considered in turn.

(4) The Flaws Identified in Petitioners' Claim that Impaired Methylation Processes and Oxidative Stress Result from Mercury-Induced Inhibition of the Cellular Activity Needed to Generate Glutathione and that These Functional Disturbances Can Lead to the Appearance of Autism in Certain Children

There are three principal problems with petitioners' claim that impaired methylation processes and oxidative stress result from thimerosal-induced inhibition of the cellular activity needed to generate the antioxidant glutathione and that these functional disturbances are causally related to the appearance of autism in certain genetically susceptible children. First, the conclusions reached in the scientific articles on which petitioners have relied most heavily are more limited than petitioners have asserted. Second, Dr. Deth's own research that purports to support petitioners' claim is of questionable reliability, and, third, Dr. Deth's testimony in furtherance of the claim was inconsistent with what is scientifically known about the mechanisms he described. The undersigned addresses each of these problems in turn.

a) The Conclusions Reached in the Scientific Articles on which Petitioners Relied were More Limited than Petitioners have Asserted

The 2006 James article on which Dr. Deth relied did report a finding, based on a conducted subset analysis, that a significant number of the studied autistic children had "severely abnormal" metabolic profiles that could affect the transmethylation and transsulfuration pathways. PMRL 49 at 950, 952. The researchers also acknowledged that abnormalities in the transmethylation and transsulfuration pathways have been associated variously with heart disease, cancer, birth defects, and neurologic disorders. Id. at 953. The researchers speculated that "the abnormal metabolic profile . . . discovered in autistic children is an endophenotype that may reflect subtle changes in gene products that regulate flux through methionine transmethylation and transsulfuration pathways." Id. at 952 (emphasis added). Describing their findings as "preliminary," the researchers suggested further research in larger population-based studies to confirm what they had found. Id. at 954. In contradistinction to Dr. Deth's presentation of the work done by Dr. James, the very researchers who authored the 2006 James article carefully avoided overstating the significance of their findings.

Dr. Jones, respondent's expert on biomarkers of oxidative stress, also observed that the findings reported in the 2006 James article must be interpreted cautiously because "in almost every disease population . . . studied, the glutathione levels are different from control [subjects]." Mead Tr. at 2789-2790. Decreases in glutathione levels have been found, for example, in cardiovascular disease, diabetes, renal disease, liver disease, and lung disease. Id. at 2790. A very common occurrence in different disease processes, Dr. Jones urged that, based on his extensive experience studying sulfur metabolism and oxidative stress, a more apt interpretation of the detected difference in glutathione levels between control subjects and autistic subjects would be that the reduced glutathione level was a response to a disease rather than a cause. Id. at 2789-2790. He added that the frequency with which reduced glutathione levels are found in persons with different diseases "would seem" to be more consistent with a response to a disease process rather than a response to a specific disease. Id. at 2790.

Dr. Jones further observed that in one critical respect the differences reported in the 2006 James article between the metabolic profiles of the control subjects and the children with autism failed to support and, in fact, were "completely inconsistent with" Dr. Deth's hypothesis. Mead Tr. at 2745-2747. Dr. Deth had posited that the metabolic differences would result in a reduction in glutathione levels and a correlative increase in oxidative stress in the children with autism. But, the data in the 2006 James article showed that the

level of cysteinylglycine, an important and compulsory intermediate in the pathway that generates glutathione, was no different between the two study groups and was in abundant supply. See id. at 2746-2747. This rich supply of cysteinylglycine protects against the adverse effects on sulfur metabolism that Dr. Deth's hypothesis predicts. Id.

Dr. Deth also relied, in part, on the 2005 James article for the proposition that "thimerosal significantly reduces cellular levels of [glutathione] in cultured neuronal cells. Mead Ps' Ex. 17 at 4 (Dr. Deth's report). But his reliance on the 2005 James article, filed as PMRL 7, has been criticized by respondent's experts in this case because the study was conducted in a laboratory environment (in vitro) that used a tumor cell line that typically "has about one thousandth the amount of glutathione tha[t] normal cells have." Mead Tr. at 1830 (Dr. Brent). The selected cell line for the study–the results of which petitioners have offered here for the proposition that the administration of thimerosal lowers glutathione levels–was "highly deficient in glutathione" prior to the conduct of the study. Id. Moreover, the micromolar amounts of thimerosal that were added to the cells during the study exceeded by 1,000 times the amount of ethylmercury (measured in parts per billion or nanomolars) to which brain cells would be exposed in the body (in vivo). See id. at 1830 (Dr. Brent); see also id. at 2735-2736 (Dr. Jones commenting that the conditions in the 2005 James article "were probably irrelevant to the question of in vivo toxicity because the concentrations [of better than 10,000-fold higher in the experimental environment] were really out of line" with in vivo conditions). The authors of the 2005 James article acknowledged that there was no effort to simulate in the study what happens in the body after receipt of a thimerosal-containing vaccine. See id. at 1831 (Dr. Brent). Rather, the authors explained, "[a]cute high dose exposures to Thimerosal ([measured in micromoles per liter] μmol/L) in cultured cells were used to study mechanistic aspects of Thimerosal toxicity and [were] not intended to mimic exposures of developing brain cells in vivo to Thimerosal in vaccines ([measured in nanomoles per liter] nmol/kg)." PMRL 7 at 3 (emphasis added).

Unlike an in vivo study that is conducted in an intact living body (whether an animal or a human), an in vitro study is conducted in an artificial environment, such as a petri dish or a test tube. See Mead Tr. at 1824 (Dr. Brent); Dorland's at 948. An in vitro experiment permits the study of a cell to generate hypotheses about what effects a chemical might have in humans. Mead Tr. at 1825. But no conclusions can be reached from such a study because the laboratory environment is "radically different" from the environment in the body. Id.; see also Alza Corp. v. Mylan Laboratories, 464 F.3d 1286, 1297 (Fed. Cir. 2006) (stating that a party's evidence of results obtained in the in vitro environment are "irrelevant absent evidence demonstrating that the in vitro system is a good model of actual in vivo behavior"). The principal difference between the two environments is that the complex cellular interactions that are present in the body are

missing in the in vitro environment. Stated in other words, more of the added reactive material is available to be taken up by the cells in the artificially constructed in vitro environment than would occur in the more carefully balanced in vivo environment. See Mead Tr. at 2725-2728, 2730-2733 (Dr. Jones); Mead R's Trial Ex. 9 at 11; Mead Tr. at 2204-2205 (Dr. Johnson addressing the limitations that counsel against extrapolating results from in vitro experiments to the in vivo environment). Additionally, the toxicity threshold is lower in cells examined in an in vitro medium because more of the administered substance goes directly to the cells, and once the toxicity threshold is achieved, the response by the cells is similar and generally occurs at the same time. Id. at 2729.

b) Dr. Deth's Own Research that Purports to Support Petitioners' Claim is of Questionable Reliability

Also relying on research performed in his own laboratory, Dr. Deth acknowledged that his only published work describing his original research is the 2004 Waly article that concerned methionine synthase. See Mead Tr. at 598-599 (Dr. Deth explaining that, after the publication of the 2004 Waly article, he discovered "the role of oxidative stress in regulating methionine synthase"[168]). Notable among the criticisms of the 2004 Waly study, filed as PMRL 257 and co-authored by petitioners' expert Dr. Deth, is the fact that the conducted study was an in vitro one, and as Dr. Deth himself pointed out, the observed interaction between thimerosal and the selected cells would not occur in the body. Mead Tr. at 1827 (Dr. Brent); see also id. at 2003-2005 (Dr. Mailman cautioning that an in vitro finding can be quite an erroneous predictor of in vivo action); accord id. at 626-627 (Dr. Deth distinguishing the "free" thimerosal concentrations presented to human neuronal cells in his experimental in vitro studies from the thimerosal concentration found in vivo and, in particular, in the human brain).

In addition, the very low concentration of administered thimerosal that Dr. Deth reported in his expert opinion as having inhibitory effects (in the nanomolar range or parts per billion range) on glutathione levels was based on unpublished data obtained from studies conducted in Dr. Deth's own laboratory and was of questionable reliability. Respondent's expert Dr. Jones, an expert on oxidative stress mechanisms, testified that the reliability of the findings purportedly made in Dr. Deth's own lab were questionable for three reasons. First, the concentration level of thimerosal claimed by Dr. Deth to effect changes in glutathione levels falls well below the detection threshold of the most sensitive

[168] He has not published any work reflecting original research on the subject of oxidative stress. Id. at 599.

methods available to the scientific community for measuring changes in glutathione levels. Id. at 2719-2724, 2733-2735. Second, the concentration level of thimerosal reported in the unpublished Waly manuscript (and cited in Dr. Deth's expert report) to have caused certain toxic effects is substantially below the ranges (in the micromolar range or parts per million range) consistently reported in the published scientific literature to cause toxicity. Id. Third, Dr. Deth based his opinion regarding the in vivo effects of thimerosal on sulfur metabolism on in vitro studies, the results of which cannot be applied reliably to in vivo conditions. Id.

The inhibitory effects on cells, caused by the thimerosal in the 2004 Waly study, were not particular to thimerosal (or mercury) but were caused as well by other toxicants that the investigators studied. Id. at 1830 (Dr. Brent). One of the key criticisms leveled against the 2004 Waly study was Dr. Deth's failure to control for factors that are known to interact with dopamine and for which he did control in earlier studies he conducted in his laboratory. See id. at 2012-2017 (Dr. Mailman); id. at 2220 (Dr. Johnson criticizing the decision in the 2004 Waly study to use non-specific chemical inhibitors that were able to interact with a number of different proteins).

Of further note, the selected cells were neither brain-derived cells nor healthy cells but rather were a tumor cell line taken from a neuroblastoma. See Mead Tr. at 1827-1828 (Dr. Brent); see also id. at 630-631 (Dr. Deth). The cells selected for study did not reflect either normal cells found in the body or normal neurons found in the brain, and the failure to perform a parallel study of another cell line (such as, cultured brain neurons) "markedly weaken[ed] what lessons . . . [could be] draw[n] from this particular study." Id. at 1995-1996 (Dr. Mailman). Dr. Johnson, respondent's pharmacologist, explained that the studied neuroblastoma cell line offered no insight to the functioning of normal cells because the neuroblastoma cell line grows "spontaneously" and uncontrollably, tends to have an "aberrant number of chromosomes," and expresses in a "dedifferentiat[ed]" state (that is, the cells express characteristics in the in vitro environment that the cells do not express in vivo). Id. at 2205-2206.

Also generating questions about the validity of the results reported in the 2004 Waly study was Dr. Deth's decision to conduct the experiment in an in vitro medium without a copper presence, as there is in the body. See id. at 1828. The absence of copper was notable because, as Dr. Deth acknowledged, the inhibitory effects of the thimerosal exposure were reversed when copper was added to the cultured environment. Id. at 565-566.

c) Dr. Deth's Testimony in Furtherance of Petitioners' Claim was not Consistent with What is Scientifically Known about the Mechanisms He Described

In addition to the limitations of the research on which he relied, Dr. Deth's own testimony exposed certain deficiencies in his proposed theory. Of note, Dr. Deth acknowledged that oxidative stress "represents a very general mechanism that could express itself as, and does express itself as, . . . different diseases," such as Parkinson's disease and Alzheimer's disease. Mead Tr. at 606-608. He further acknowledged that: (1) oxidative stress is thought to play a role–not just in autism–but in a wide variety of physiological events, including aging; (2) glutathione is the body's primary inter-cellular antioxidant and is available in abundant supply; and (3) the body has numerous compensatory processes for coping with oxidative stress. Id. at 606-608, 614, 3960-3965. He conceded that there are limitations to what he knows about oxidative stress, that he has published only one review article on the subject of oxidative stress, and that respondent's expert Dr. Jones has published prolifically on the subject. Id. at 606-607, 3965-3966.

He explained that his theory of thimerosal-induced autism is not limited to the regressive form only. Id. at 614. Under his theory of thimerosal-induced autism, neuronal cells are compromised in efficiency and function, but do not die. See id at 610-611, 3973. He added that in the in vitro studies performed in his laboratory, the neuronal cells changed shape (by becoming more rounded and showing fewer pointy features) when the cells were exposed to thimerosal. Id. at 612-613. He acknowledged, however, that the discernible changes in cellular appearance were "reversible." Id. at 611. Dr. Deth further acknowledged that his experiments which were performed in a "cultured-cell model" (that is, in vitro)–and not in a brain–had "limitations." Id. at 553. Moreover, he pointed out that his hypothesis concerning vaccine-induced autism is still awaiting critical testing. Id. at 655, 3990.

Respondent's expert neurotoxicologist, Dr. Johnson, was critical of Dr. Deth's laboratory techniques and the presentation of his findings. Dr. Johnson pointed out that Dr. Deth's discussion of the differences between brains cells taken from a human and brain cells taken from a monkey, a rat, a guinea pig, a cat, a cow, a chicken, and a duck was presented without reference and, thus, appeared to suggest that it was his own research. See Mead Tr. at 2227. But, a subsequent internet search revealed that the data was taken directly from "a paper published in 1958 by Harris et al." and, in Dr. Johnson's

view, the presentation of the data–without a proper reference–called into question Dr. Deth's scientific integrity. Id.

Dr. Johnson also pointed to Dr. Deth's presentation of his own unpublished work involving his investigation of a cell line (namely, the SH-SY5Y cell line) that is commercially available from a company that banks the cell line and, due to the single source of the cell line, tends to yield consistent results between the different laboratories that have worked with the cell line.[169] Id. at 2222-2223. Dr. Deth reported a glutathione level that is at least 250 times higher than has been reported previously in the scientific literature for the same line of cells.[170] See id. at 2228-2229 (citing Mead Ps' Trial Ex. 3 at 24, 28 (Dr. Deth's trial slides)). The discrepancy between Dr. Deth's reported finding and the findings that have been consistently reported in the scientific literature–even if merely a calculation error in Dr. Deth's lab–indicates that the data were not carefully evaluated and further compromises the reliability of Dr. Deth's assertions. See Mead Tr. at 2229.

In addition to questioning the reliability of the unpublished work on which Dr. Deth relied in support of his offered opinion, respondent's experts were also critical of the underlying premises of Dr. Deth's theory of vaccine-related causation. Dr. Roberts, respondent's expert on oxidative stress and oxidative damage in relation to disease, carefully explained during his testimony that although a certain level of oxidative stress is always present in the body, a battery of protective mechanisms exists to prevent "rampant" oxidative stress. Id. at 2171. The protective mechanisms are antioxidant enzymes that maintain balance in the state of oxidation. Id.

When the body detects the moderate level of oxidative stress that follows–for example–exercise, the body upregulates antioxidant enzymes to a level that is sufficient to address the induced oxidative stress and any ongoing oxidation. Id. at 2171-2172. The body's protective response of upregulating antioxidant enzymes in the face of moderate oxidative stress not only seeks to restore the desired state of reduced oxidation but also seeks to avoid oxidative damage. Id. at 2172-2173. Dr. Roberts made clear that oxidative stress is not necessarily equivalent to oxidative damage, and he defined damage as a

[169] The results may reflect differences in sensitivity that are five- to 10-fold (or five to 10 times) different, but not two to three orders of magnitude (that is, 100 or 1000 times) in difference. Mead Tr. at 2223 (Dr. Johnson).

[170] Dr. Johnson pointed out that in the scientific literature addressing work with that cell line, all reported levels of basal glutathione in the SH-SY5Y cells to be between 12 and 30 nanomoles per milligram of protein. Mead Tr. at 2229. Dr. Deth, however, found levels of basal glutathione that ranged between 700 and 1,500 nanomoles per milligram of protein in the SH-SY5Y cells. Id. at 2228.

detrimental change to a cell–to include both a functional change in the cell and the death of the cell. Id. at 2172, 2189; Mead R's Trial Ex. 6 at 7; accord Mead Tr. at 149 (Dr. Aposhian stating that free radicals are reactive chemical substances that induce oxidative stress which can cause damage to the structure of proteins in the body). Dr. Roberts further clarified that there is a normal level of oxidative damage that occurs in the body and is managed at a level that does not cause harm. Id. at 2196. That type of oxidative damage is distinguishable from oxidative damage that generates more damage and creates a grave risk. Id.

Dr. Roberts also made clear that any detection of oxidative stress in the periphery of the body is not indicative of its presence in the brain. Id. at 2173. He explained that because the free radicals that drive the oxidation process are extremely reactive, they do not travel distances through the body, but rather trigger reactions in the area in which the free radicals are created. Id. at 2173-2174. For this reason, Dr. Roberts testified, petitioners' claim that the measurement of an altered ratio of oxidized glutathione to reduced glutathione in the plasma of autistic children–as taken by the researchers conducting the 2006 James study on which petitioners here rely–is evidence of oxidative stress in the brains of autistic children lacks scientific reliability. See id. at 2176-2177. As Dr. Roberts reiterated, the measurement in the plasma does not speak to the presence of oxidative stress in the brain, and the detection of oxidative stress is not necessarily indicative of oxidative damage. Id. at 2176.

Additionally, respondent's biochemist, Dr. Jones, a distinguished expert in the subjects of sulfur metabolism and oxidative stress, testified that glutathione has many functions in the body and some of them are "in a sense" competing functions. Mead Tr. at 2704. Nonetheless, glutathione is able to support all of its diverse functions in the body simultaneously–without the activation of one function necessitating the inactivation of another–because it has an abundant presence in the body. Id. at 2705. The ample supply of glutathione supports a broad spectrum of activities "even at the lowest level." Id. at 2706.

Dr. Jones asserted that the amount of mercury content in the prescribed pediatric schedule of thimerosal-containing vaccines would not affect sulfur metabolism in any significant way. Id. at 2707. He indicated that less than one minute would be required for the body to replace the amount of glutathione that is used to bind and deactivate a thimerosal-containing vaccine, even if the first six-month load of vaccines were administered entirely at one time. Mead Tr. at 2719.

To put into perspective the cumulative load of thimerosal received from childhood vaccinations as compared to the scope of sulfur metabolism occurring in the body, Dr.

Jones put various measures obtained from the scientific literature into common units to show that: (1) the total body content of sulfur-containing compounds or thiols is approximately 20,000 micromoles per kilogram, (2) the total body content of glutathione is between 800 and 1,000 micromoles per kilogram, (3) the recommended dietary allowance of sulfur (to prevent a sulfur deficiency) is 500 micromoles per kilogram, (4) the estimated dietary intake of sulfur by individuals in America is between 250 and 500 micromoles per kilogram; and (5) the approximate cumulative dose of thimerosal from pediatric vaccines is one micromolar per kilogram (for a child conservatively estimated to weigh one kilogram or two pounds). Id. at 2707-2712; Mead R's Trial Ex. 9 at 6. The comparative levels in the body illustrate how limited is the amount of thimerosal available for the alleged disruption of sulfur metabolism and how plentiful is the amount of sulfur involved in metabolic activity.

Dr. Jones noted that the principal dietary source of sulfur amino acid intake is from eating animal products or drinking milk. Mead Tr. at 2711. He further noted that plant products provide about half of what animal products provide for sulfur amino acid intake. Id. He observed that the ingested food that provides sulfur amino acid intake also contains reactive materials that are deactivated in the body by glutathione. Id. at 2712-2713. Pointing to cow's milk and apple juice as examples of glutathione-reactive food substances to which young children might be exposed, Dr. Jones testified that a four-ounce cup of milk requires 10 times as much glutathione for deactivation in the body as does the thimerosal contained in the prescribed pediatric schedule of thimerosal-containing vaccines. Id. at 2713; Mead R's Trial Ex. 9 at 7. He added that a four-ounce cup of apple juice requires four times as much glutathione for deactivation in the body as does the cumulative thimerosal content estimated to have been received in childhood vaccinations over a six-month period. Mead Tr. at 2713-2714; Mead R's Trial Ex. 9 at 7. Accordingly, a half-glass of milk or apple juice contains "substantially" more glutathione reactive material than does the full pediatric schedule of childhood vaccines at issue in this case. Mead Tr. at 2713-2714.

Dr. Jones also testified that glutathione levels show an average natural variation of 25 to 30 percent over the course of a day. Id. at 2715. This variation in the level of glutathione directly correlates with the variation in oxidation reduction (which is a measure of the antioxidant activity of the glutathione) that occurs over the course of a day, and the variation in the oxidation reduction state corresponds directly with the change in the absolute concentration of sulfur-containing compounds or thiols that also occurs during the course of the day. Id. at 2716-2717. These changes reflect the normal variations that occur in a day. Nonetheless, even with the normally occurring glutathione levels, the human body has "very, very, very large amounts of glutathione . . . [a]nd

glutathione is never limited in terms of being able to handle heavy metals." Id. at 4347-4348 (Dr. Brent).

Dr. Jones observed that the body has in place a central system to protect against agents which would perturb glutathione levels. Mead Tr. at 2739; Mead R's Trial Ex. 9 at 15. He stated that when there is a low level of a component that would perturb the glutathione system or that would otherwise disrupt the function of the glutathione system, another system (referenced as the Nrf-2 system) responds protectively.[171] Mead Tr. at 2739-2740. Dr. Jones added that eating cruciferous vegetables (including broccoli, cauliflower, and brussel sprouts) or apples is sufficient to activate the systems that compensate for changes in the glutathione system. Id. at 2741-2743; see also Mead R's Trial Ex. 9 at 16 (Dr. Jones also identifying garlic, onions, and green tea as agents capable of turning on the systems that compensate for changes in the glutathione system). Because a broad range of agents can set the compensatory Nrf-2 system in motion, variations in the glutathione system are not intrinsically indicative of a toxic condition. See id. at 2743-2744; see also id. at 2230 (Dr. Johnson, respondent's neurotoxicologist, concisely noting that when–as in Dr. Deth's experiments–cells experience a very acute depletion of glutathione, the cells sense the depletion, generate the proteins that synthesize glutathione, and within 24 to 48 hours, have a two- to three-fold increase in the level of glutathione).

Further underscoring the robustness of the systems involved in the body's sulfur metabolism, Dr. Jones discussed not only the concentrations of the components and their naturally-occurring variations, but also the "cycling" rate of the body's sulfur metabolism. Id. at 2717. The rate of "cycling" glutathione into the blood, then out of the blood and into cells, shows the "turnover" of the system, which is approximately one micromole per kilogram body weight per minute. See id. In other words, Dr. Jones explained, more thiol is turned over through normal metabolic processes in one minute than there is cumulative thimerosal in the prescribed pediatric vaccine schedule at issue here. See id. at 2718. Accordingly, based on the dynamism and resilience of the body's sulfur metabolism, the amount of thimerosal delivered to the body in doses commensurate with the prescribed

[171] He explained that the Nrf-2 system is bound to a thiol-sensitive protein known as Keap-1 that acts as a sensor to measure materials that react with thiols. Id. The Keap-1 protein is comprised of 26 different cysteines that protrude from the structure of the protein and that respond to oxidants, chemicals, and "even some metals" by changing the structure of the Keap-1 protein to permit the release of the Nrf-2 that is bound to it. Id. at 2740. The released Nrf-2 then moves into the nucleus of a cell to interact with the DNA there. Id. In the process of penetrating a cell's nucleus to interact with DNA, the Nrf triggers other antioxidant systems to respond that operate to compensate for the disrupted glutathione system. See id. at 2740-2741.

pediatric vaccination schedule is unlikely to have "any detectable effect" on that metabolic process. Id. at 2718, 2738.

Dr. Mailman, respondent's distinguished expert on dopamine receptors, also challenged the aspect of Dr. Deth's hypothesis pertaining to the D4 dopamine receptor. See Mead Tr. at 1984-1985. Before addressing the problematic assumptions in Dr. Deth's hypothesis, however, Dr. Mailman described how dopamine binds to specific receptors. Id. at 1987. He explained that the nerve cells that generate dopamine are located in the area of the brain that affects motor control and in the area of the brain that affects attention, arousal, cognition and emotion. Id. When electrically excited, the dopamine generating nerve cells release small amounts of dopamine that travel along long fibers to various parts of the brain. Id. at 1987. When released from a nerve, the dopamine binds to proteins referred to as dopamine receptors. Id.

There are two types of dopamine receptors, known as D1-like receptors and D2-like receptors respectively. Id. Five different genes, namely D1, D2, D3, D4, and D5, make up the two dopamine receptor families, with D1 and D5 comprising the D1-like receptor family and the balance comprising the D2-like receptor family. Id. at 1988. The dopamine receptors from both of the dopamine receptor families effectively weave in and out of the membrane of a cell seven times, leaving a beginning tail and three loops outside of the cell membrane as well as three loops and an ending tail on the inside of the cell membrane. Id. The difference between the D1-like receptors and the D2-like receptors is the length of the ending tail inside of the cell membrane; the D1-like receptors have a very long tail while D2-like receptors have a very short tail on the inside. Id. at 1988-1989. Dr. Mailman pointed out that a number of proteins interact with the loops formed by the dopamine receptors, and in turn, interact "with what are called scaffolding proteins and a whole variety of other signaling molecules and other receptors." Id. at 1986, 1992 (Dr. Mailman noting that nearly "80[%] of the nerve cells . . . in the brain" use dopamine). Importantly, one must give consideration to this complex network of interactions when one considers the effect of a single compound on a receptor. Id. at 1992. But, Dr. Mailman observed, Dr. Deth did not do so in this case. Id. Instead, Dr. Deth identified a few pathways that "purportedly were [a]ffected by thimerosal," without addressing at all "a whole variety of signal[ing] mechanisms that are very, very important for this receptor and related receptors." Id. With "very, very little support" for the hypothesis that Dr. Deth put forth, Dr. Mailman asserted that little weight could be afforded to his claims. See id. at 2005.

d) Summary of Findings

Petitioners have alleged in this case that the inorganic mercury deposited in the brains of certain children after receipt of thimerosal-containing vaccines preferentially binds to sulfur-containing compounds, inhibiting certain processes in the brain. Petitioners contend that as a result of the inhibited processes, insufficient amounts of glutathione are generated to combat the oxidative stress created, in part, by the very presence of the inorganic mercury in the brain. Among the other inhibited processes of concern to petitioners are: (1) the disrupted methionine methylation process that cannot–in the alleged inhibited state–regulate gene expression, and (2) the disrupted dopamine methylation system that cannot–in the alleged inhibited state–release the inhibitory neurochemical dopamine to modulate the state of overexcitation that petitioners maintain is created by an oxidatively stressed brain. But when evidence of the abundant supply of glutathione within the body as well as the complex system of compensatory mechanisms for addressing oxidative stress is considered, in comparison to the amount of inorganic mercury that could be attributable to the prescribed pediatric schedule of thimerosal-containing vaccines, the likelihood that the administered vaccines could have the disruptive effects that petitioners have asserted is greatly diminished.

(5) Petitioners' Further Claim that Mercury-Induced Microglial Activation Causes an Excitotoxic Brain Injury that Leads to a Functionally Overaroused State and the Manifestations of Autistic Behavior

Petitioners' expert pediatric neurologist, Dr. Kinsbourne, described another subcellular process able to cause neuroinflammation and oxidative stress that, in turn, could lead to the development of autistic symptoms in certain genetically susceptible children. Dr. Kinsbourne asserted that his proposed mechanism of cause and effect is a continuous one and is simply expressed as: "Whatever provokes a microglial activation, including a metal, [that leads] to . . . glutamate excess, [then] to . . . overarousal and [in turn] to . . . autistic behavior." Mead Tr. at 833. Dr. Kinsbourne testified that a critical underpinning to his theory is the presence of neuroinflammation in autistic individuals.

a) The Proposed Mechanism of Excitotoxicity

As a predicate to understanding his hypothesis, Dr. Kinsbourne explained that neuronal brain cells communicate with each other through an exchange of

neurotransmitters (containing chemical messages) across the synaptic cleft[172] between neurons. Mead Tr. at 795-796. Communication occurs when a neurotransmitter carrying a chemical impulse leaves the presynaptic end of a neuron, diffuses across the synapse, and then attaches to the receptor surface of the receiving neuron. Id. at 796. Dr. Kinsbourne testified that proper brain function requires not only the transmission of the chemical messages between neurons–which are "always" firing–but also adequate control of the amount of chemical transmitted. Id. at 796, 798. He stated that when a released chemical in the synaptic region fails to reach the intended receptor surfaces, there is the potential for harm because the diffused chemical may stimulate other unintended synapses and "blur the message." Mead Tr. at 797. Identifying the neurotransmitter of particular interest to his proposed theory of excitotoxicity and overarousal as glutamate, Dr. Kinsbourne testified that "[i]f too much glutamate escapes from synaps[e]s[,] it can actually damage neurons [by] mak[ing] them fire too much causing seizures or even kill[ing] them." Id. This process is called excitotoxicity. See id.

Astrocytes, one of the three earlier identified neuroglial cells, are equipped with structures known as transporter sites that permit the astrocytes to "mop up spare glutamate . . .and . . . then pass it back to the neuron[s] . . . for later use."[173] Id. at 797-798. The astrocytes' ability to reabsorb excess glutamate–that is both an excitatory neurochemical as well as one of the three components of the antioxidant glutathione–operates to recycle existing glutamate and avoid manufacturing more than is necessary. Id.

In contrast to the ongoing busyness of the neurons and the astrocytes, the microglia (another of the earlier identified neuroglial cells) are inactive until they are alerted by the astrocytes that a "potentially threatening substance" is in the vicinity. Id. at 798-799. The alert triggers chemical changes that cause the microglia to swell, engulf the invading agent, and emit chemicals. Id. at 799. Among the emitted chemicals from the microglia are proinflammatory cytokines (cytokines that cause inflamation) and reactive oxygen species (forms of oxygen–as described by Dr. Deth–that cause oxidative stress). Id. Dr. Kinsbourne indicated that when the invasive presence is a persistent one–such as the inorganic mercury at issue in this case–the microglia continue to exert an inflammatory response, emit reactive oxygen species, and thereby set up an ongoing chronic process that damages the structure and function of the neighboring cells. See id. at 800-801. As the

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[172] The synaptic cleft is the narrow fluid-filled space between neurons. See Mead Tr. at 796 (Dr. Kinsbourne).

[173] As Dr. Deth noted in his testimony, glutamate is a component of the antioxidant glutathione. Mead Tr. at 506-507.

process continues, the microglia increase in number (a process known as microglial proliferation), and the effects of the microglial activation are multiplied. See id. at 804.

Dr. Kinsbourne identified the astrocytes as the neuroglial cells that are "particularly apt to damage" by microglial activation, and the resultant damage includes the impairment of the "astrocytes' ability to scavenge glutamate." Id. at 801. Without functional astrocytes "scavenging the glutamate," the glutamate accumulates and spills out from the astrocytes, enabling synapses to cause more firing of cells than is required and creating a state of general excitation in the brain. Id. at 802. Should the level of excitation become too great in the brain, it could kill the astrocytes, produce the appearance of gliosis (creating, as a result of the astrocytic death, what Dr. Kinsbourne described as a presentation that is "analogous to a scar on the body"), and in severe cases, cause the loss of neurons. Id. at 802, 805, 808.

b) The Scientific Literature on which Petitioners Rely in Support of the Proposed Excitotoxic Mechanism

In support of the theory that microglial activation is involved in the mechanism proposed by petitioners here to cause autism, Dr. Kinsbourne pointed to the 2008 Lopez-Hurtado article, filed as PMRL 446.[174] Noting that the investigators decided to focus their examination of "a wide age range" of autistic brains on the area involving language because language is one of the skills frequently affected in autistic persons, Dr. Kinsbourne described the investigators' findings of "a proliferation of microglia, a diminution of the density of astrocytes, the presence of gliosis and some loss of neurons." Mead Tr. at 806-807 (referencing PMRL 446 at 140). Based on the investigators' further finding that the changes observed in the autistic brains were more striking in the older brains, Dr. Kinsbourne reasoned that the changes resulted from a long, ongoing process that was initiated "by some challenge to the microglia many, many years earlier." Id. at 807 (referencing PMRL 446 at 140-141). Dr. Kinsbourne observed that the investigators identified lead, iron, and mercury as metals that are known specifically to cause glial proliferation that is consistent with the process of neuroinflammation that he described in his testimony and in his expert report. Id. at 809 (referencing PMRL 446 at 140).

Acknowledging that neuroinflammation is an important component of the specific biological mechanisms of harm that he and Dr. Deth addressed, Dr. Kinsbourne addressed several other studies (in addition to the 2008 Lopez-Hurtado article) on which petitioners

[174] E. Lopez-Hurtado and J. Prieto, A Microscopic Study of Language-Related Cortex in Autism, American Journal of Biochemistry and Biotechnology 4(2): 130-145 (2008).

relied for reported findings of neuroinflammation in autistic individuals. In particular, Dr. Kinsbourne pointed to the 2005 Vargas article (filed as PMRL 69) and the 2005 Pardo article (filed as PMRL 72).

In the 2005 Vargas article, the investigators gathered data from the autopsied brains of persons with autism and from the cerebral spinal fluid of children living with autism. See Mead Tr. at 834; PMRL 69 at 68 (2005 Vargas article). The investigators found microglial responses in the autistic brains, and–as Dr. Kinsbourne stated–noted that chronic microglial activation "appears to be responsible for a sustained neuroinflammatory response" that leads to the "production of multiple neurotoxic mediators," that include the reactive oxygen species and the cytokines discussed in the testimony of both Dr. Deth and Dr. Kinsbourne. PMRL 69 at 77. The researchers also noted that the microglial responses detected in the brains of autistic individuals were similar to what is seen in the brains of persons with the neurodegenerative disorders of Alzheimer's disease and Parkinson's disease and with the dementia associated with human immunodeficiency virus (HIV) infection. Id. The researchers speculated that neuroinflammatory activation might be a common pathway leading to central nervous system dysfunction in each of the disorders. Id. The researchers observed that "'[i]n the case of autism, the presence of microglial activation supports the view that innate immune responses are present' both in the cortex and in the lower levels of the brain" and that a state of chronic activation and reactivity–similar to what Dr. Kinsbourne described in his testimony– may be involved in the mechanism of neuronal and synaptic dysfunction. Mead Tr. at 836-837 (Dr. Kinsbourne quoting from PMRL 69 at 77-78).

In the 2005 Pardo article, the investigators recognized that in normally functioning brains, astrocytes help neurons to survive certain chemical attacks by removing excitotoxic neurotransmitters, including glutamate. PMRL 72 at 489. The researchers noted, however, that when astrocytes become activated due to injury, they produce factors that can cause inflammation. Id.; see also Mead Tr. at 838. The researchers observed that changes in both the astrocytes (or astroglia) and the microglia can produce "marked" neuronal changes that are likely to contribute to central nervous system dysfunction in a disease process. PMRL 72 at 489. Dr. Kinsbourne testified that his proposed theory of causation involved the particular neuronal dysfunction of firing too many excitatory signals that, in turn, could lead to the "disorganization . . . seen in autism." Mead Tr. at 840. Dr. Kinsbourne asserted that the presence of inorganic mercury in the brain is akin to an injury that is able to initiate and sustain the type of inflammatory response identified by researchers in the scientific literature. See Mead Tr. at 839.

Noting that "[n]euroinflammation is often associated with the activation, proliferation and ultimate disintegration of astrocytes, as well as [an] increase in neural

excitability," Dr. Kinsbourne stated that thimerosal-containing vaccines must be considered as one of a number of potential causes of the neuroinflammation in the brain of an autistic child. See Mead Ps' Ex. 30 at 13. Dr. Kinsbourne allowed that before focusing on thimerosal-containing vaccines as the potential cause of neuroinflammation in an autistic brain, scientists should rule out other sources of neuroinflammation–such as neuropathic viruses or neurodegenerative diseases–first. Mead Ps' Ex. 30 at 13; see also Mead Tr. at 810-812. Ruling out other conditions as a threshold matter is important because, as Dr. Kinsbourne acknowledged, excitotoxicity "is a very well-known phenomenon . . .[that] occurs in numerous disorders." Id. at 802. It is not a disease-specific phenomenon but a general mechanism of harm. Id.

Dr. Kinsbourne also acknowledged that the neuroinflammatory mechanism that he proposed in this case requires a disturbance of the neuronal homeostasis in the brain. As Dr. Kinsbourne explained, the level of excitation in the brain normally is maintained within certain boundaries because the effects of excitation induced by the neurotransmitter glutamate are modulated by the effects of inhibition produced by the neurotransmitter GABA. Id. at 802-803; accord see id. at 2492 (Dr. Rust stating that a balance of cytokines–proinflammatory and anti-inflammatory–is in place for normal brain homeostasis and for aspects of normal brain development). That balance between excitation and inhibition could be disrupted, however, when the presence of inorganic mercury in the brain leads to an excess of released glutamate–through the mechanism Dr. Kinsbourne described–and affects the D4 receptor sites and impairs the production of GABA–as Dr. Deth described. See id. at 803-804. It is these mechanisms, asserted Dr. Kinsbourne, that result in the type of overexcitation of the brain at issue in this case. Id.

Informing Dr. Kinsbourne's belief that mercury can cause neuroinflammation by the excess glutamate mechanism that he described and that such neuroinflammation can be expressed symptomatically as regressive autism were several scientific articles. Dr. Kinsbourne pointed to the 2007 Aschner review article,[175] filed as PMRL 570,[176] in which Dr. Aschner, a respected neurotoxicologist, addressed the question of how mercury–methylmercury in particular–becomes neurotoxic. Mead Tr. at 816. Dr.

[175] A review article provides a summary of the findings reported in various conducted studies, but does not include the underlying data from the conducted studies. See Mead Tr. at 4325 (Dr. Johnson indicating that although "the interesting points" are contained in a review article, the "real data" is not); id. at 4334 (Dr. Brent pointing to the actual data that informed the observation made in the review article).

[176] M. Aschner et al., Involvement of glutamate and reactive oxygen species in methylmercury neurotoxicity, Braz. J. Med. Biol. Res. 40(3):285-91 (2007).

Kinsbourne asserted that the mechanisms that Dr. Aschner proposed–specifically involving reactive oxygen species and glutamate–are the mechanisms that petitioners' experts (Dr. Deth and Dr. Kinsbourne himself) have proposed here. See id. at 816-817. In particular, Dr. Aschner stated that methylmercury, in micromolar doses, inhibits glutamate uptake by astrocytes and "stimulates [astrocytic] efflux, thereby increasing glutamate concentrations in the extracellular fluid." PMRL 570 at 286; Mead Tr. at 4325 (Dr. Johnson pointing out that the mercury doses typically used in Dr. Aschner's work are in the micromolar range, a much higher dose than is administered in thimerosal-containing vaccines); see also id. at 4333-4335 (Dr. Brent pointing to the micromolar amounts of mercury detailed in figure 2 of the 1996 Aschner article, filed as PMRL 206,[177] and referenced in the review article on which Dr. Kinsbourne relied). Dr. Aschner further stated that the increased glutamate concentrations in the extracellular fluid cause hyperactivation of certain glutamate receptors and lead to intracellular chemical changes that are associated with the generation of reactive oxygen species that causes oxidative stress. See PMRL 570 at 288. Dr. Kinsbourne urged that the mechanism that Dr. Aschner described is the same mechanism he described that creates an environment of excess glutamate and leads to excitotoxic injury. See Mead Tr. at 817.

Dr. Kinsbourne also pointed to the later 2000 Aschner article, filed as PMRL 568,[178] in which Dr. Aschner observed that glutamate and cysteine (two of the three components of the antioxidant glutathione) could compete for the same transporter sites on astrocytes and compromise the production of glutathione for transport into astrocytes. Mead Tr. at 821-822 (referencing PMRL 568 at 202). Dr. Kinsbourne asserted that Dr. Deth's testimony was consistent with the reported observations of Dr. Aschner. Mead Tr. at 822-823. Dr. Aschner also observed in the 2000 Aschner article that methylmercury preferentially accumulates in astrocytes, PMRL 568 at 201-202, and Dr. Kinsbourne reasoned that the effect of the accumulation was to disable the astrocytes and impair the functioning of the neurons without necessarily killing the neurons, Mead Tr. at 823-824. It is this neuronal dysfunction, hypothesized Dr. Kinsbourne, that leads to a state of hyperexcitability in the brains of certain autistic children.

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[177] M. Aschner et al., Differential sensitivity of neonatal rat astrocyte cultures to mercuric chloride (MC) and methylmercury (MeHg): studies on K+ and amino acid transport and metallothionein (MT) induction, Neurotoxicology 17(1):107-116 (1996).

[178] M. Aschner et al., Methylmercury alters glutamate transport in astrocytes, Neurochemistry International 37:199-206 (2000).

c) Petitioners' Claim that an Overactivated Brain Can Manifest Symptomatically as Autism

Dr. Kinsbourne described how an overactivated brain might be expressed symptomatically as autism. He testified that there is some evidence that the brains of autistic individuals are overaroused in the amygdala (the region of the brain that influences emotion) and there is at least one study showing that autistic subjects had elevated heart rates. Mead Tr. at 824-826; see also PMRL 496 (2006 Goodwin article[179]) (the filing is limited to one page of an appendix showing the mean heart of a subject in alternating states of rest and activity). These factors (which are suggestive of a state of hyperexcitability) are consistent, in Dr. Kinsbourne's view, with the observed behavior in autistic children of panic when a routine or accustomed order is disturbed and of stereotypic and repetitive movements (such as flapping, whirling or foot tapping) when the children are placed in unfamiliar circumstances. See id. at 826, 829, 832.

Also consistent with an increase in the arousal level in the brain is the observed constriction of the areas of focus in autistic persons. See id. at 827. Such unusually narrow areas of focus might include gaze avoidance (that is, a gaze that looks at details beyond the subject rather than looking at the subject), a preference for limited sets of items (such as dinosaurs or sharks), and a propensity for lining up or carefully arranging things (such as toy cars or boxes of diapers sitting on a store shelf). Id. at 827-831. In this manner, Dr. Kinsbourne asserted, the cellular changes induced in the brain by the inorganic mercury deposits that follow the receipt of thimerosal-containing vaccines can manifest as symptoms of autism.

d) Integrating the Testimony of Dr. Kinsbourne with the Testimony of Dr. Deth

At the conclusion of his testimony, Dr. Kinsbourne clarified how the testimony that Dr. Deth offered about oxidative stress fits with the neuroinflammatory process that he described. He explained:

> In neuroscience, different specialists study the brain at different levels of organization all the way down from behavior, which is the highest level of organization for the individual, to molecular changes, which is the lowest level. High and low, it's just descriptive. It doesn't mean better or worse.

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[179] M. Goodwin et al., Cardiovascular Arousal in Individuals With Autism, Focus on Autism and Other Developmental Disabilities 21(2):100-123(24) (2006).

> Dr. Deth works at the molecular level. At that level, he gave a very complete account of oxidative stress, and how it affects the workings of the cell and what the mediators are because in the nervous system it isn't just a one on one situation, it tends to be a cascade, A causes B, and B causes C and so on.
>
> He gave us elegant illustrations of that. I am discussing at the systems level. I'm discussing at the level of the cells in the brain. What he says speaks to particular points in that system, the effect of the oxidative stress that I discussed as being caused by the microglial activation. Well, he really explains that.
>
> I mentioned it to say it damages cells. He tells you how, what goes on[, by explaining oxidative stress very expertly at the molecular level]. We have in common that both of us are explaining changes to the brain which are not killing cells. We both talk about functional changes. Now, when there is an acute invasion of the brain by viruses or an acute mercury-toxicity, it doesn't stop at changing function. A lot of cells simply die. That's a different situation.
>
> Both of us were discussing how cells will keep on working but working inefficiently and in a deviant fashion, and I was discussing the consequences for behavior of them doing that.

Mead Tr. at 841-842.

e) The Flaws Identified in Petitioners' Claim that Mercury-Induced Microglial Activation Causes an Excitotoxic Brain Injury that Leads to a Functionally Overaroused State and Expresses Behaviorally as Autism

The difficulty with petitioners' claim that mercury-induced microglial activation causes an excitotoxic brain injury that leads to a functionally overaroused state and expresses behaviorally as autism is three-fold. First, Dr. Kinsbourne's own testimony identified material uncertainties with respect to the hypothesis he put forward. Second, Dr. Kinsbourne's proposed hypothesis was at variance with well-known scientific principles concerning the mechanisms he described and was too general to be limited to only the regressive form of autism (pertaining instead to all forms of autism). Third, the overarousal theory that Dr. Kinsbourne has endorsed does not adequately account for the

behavioral abnormalities observed in autistic individuals. The undersigned addresses each of these problems in turn.

(1) The Uncertainties Regarding the Hypothesis that Dr. Kinsbourne Identified in His Own Testimony

Unlike Dr. Aposhian, petitioners' toxicologist–who identified an alleged mercury efflux disorder–and Dr. Deth, petitioners' pharmacologist–who identified an alleged lowered level of glutathione, Dr. Kinsbourne was unable to point to a particular source of hypersusceptibility that made certain persons with regressive autism more vulnerable than other persons to the biological mechanism of causation that he proposed. See Mead Tr. at 853-855. He also acknowledged that excess glutamate is not known to be a cause either of regressive autism or of autism in general. Id. at 908.

He also acknowledged that exposure to thimerosal-containing vaccines indeed involves a low level of mercury exposure. Id. at 858. But, he explained, the exposure becomes a chronic (even if low-dose) exposure once the thimerosal is degraded to inorganic mercury in the brain because the inorganic mercury remains "chronically present" there. Id. Dr. Kinsbourne further explained that the premise of his opinion is that "mercury in sufficient amounts, will set the process of neuroinflammation with its consequences," and the source of the mercury does not matter–whether derived from inhaled mercury vapor, ingested fish, or received thimerosal-containing vaccines. See id. at 860. He pointedly deferred to the toxicologists involved in this case for the determination of whether the amount of mercury in thimerosal-containing vaccines is sufficient to trigger the microglial activation and astrocytic death involved in the neuroinflammatory process he described. Id. at 860, 862-863, 888-890. Stating that he lacked the qualifications "to figure . . . out" how much mercury would be required to provoke the hyperglutamatergic state that he theorized would result in a manifestation of autistic behavior, Dr. Kinsbourne emphasized that he was not addressing the "quantitative aspects" of petitioners' proposed theory, but rather a qualitative mechanism.[180] See id. at 866-867, 869, 886. He conceded, however, that "whether a particular form of administer[ed] mercury contains enough mercury" to trigger microglial activation that causes neuroinflammation and a hyperglutamatergic state is a point of "contentio[n]." Id. at 872-873.

[180] He added that the location within the brain of the overexcitation–"whether it is overactivation of the neurons in the cerebrum or whether it is brainstem nuclei that are firing excessively overactivating the cerebrum[–]makes no difference at the level of analysis" that his theory contemplates. Mead Tr. at 892.

Of the view that the presence of inorganic mercury in the brain could trigger an excitotoxic response, Dr. Kinsbourne testified that he would expect to find a loss of Purkinje cells in a brain that is in a mercury-induced excitotoxic state. See id. at 878. But, he acknowledged, studies have shown that in cases of mercury poisoning in non-autistic persons, the granule cells rather than the Purkinje cells are more likely to die. Id. at 883. Again endeavoring to clarify his position, Dr. Kinsbourne stated that his theory of causation does not pertain to the state of overexcitation that is sufficient to cause neuronal cells to die but instead pertains to "a functional state of overactivation" (that is, a state in which the neuronal cells are not able to function properly).[181] Id. at 880-882. He indicated that the level of neuronal dysfunction contemplated in his theory would persist–through a process of continued neuroinflammation–at a level below which it would lead to neurodegeneration (that is, the stage at which neurons begin to die). See id. at 948.

When asked what would be the time period between the deposition of inorganic mercury in the brain and the start of the neuroinflammatory process about which he had hypothesized, Dr. Kinsbourne confessed not only that he did not know, but also that he did not believe that "a fixed time is known." Id. at 896. He commented that he would expect the process to "begin within a short time," and he defined a short time as "days or a few weeks." Id. at 896-897. He also commented that he would expect the neuroinflammatory process to continue as long as inorganic mercury was present in the brain and if the level of inorganic mercury increased, he would expect the neuroinflammatory process to increase. Id. at 900.

Dr. Kinsbourne reiterated that the opinion he put forth included a possible mechanism of vaccine-related causation that was biologically plausible based on contemporary scientific literature. Id. at 4111. He added that one of the many possible

[181] Dr. Kinsbourne testified that sometime after he filed his expert report in the OAP test case of Snyder v. Sec'y of Health and Human Servs in November 2007, he "realized that mercury can set up essentially the same neuroinflammation that viruses can," and he began to take seriously the question of the possible intervention of mercury. Mead Tr. at 916-917, 931-932. Thus, significant portions of the causation mechanism he has proposed in his expert opinion in this case (that was filed in April 2008) are exactly the same as the causation mechanism he proposed in the first group of autism test cases that focused on the measles component of the MMR vaccine. Id. at 916. The difference in his submitted written reports, after "an awful lot of hours" of analysis, is the replacement of the phrase "measles virus" with the phrase "thimerosal-containing vaccines." Id. at 917-918 (comparing page 16 of Petitioners' Exhibit 29 filed in the OAP test case of Snyder v. Sec'y of Health and Human Servs. with page 13 of Petitioners' Exhibit 30 filed in this case).

triggers of excess glutamate in the brain is the presence of low levels of inorganic mercury in the brain. Id. at 4154.

(2) Dr. Kinsbourne's Hypothesis Is at Variance with Well-Known Scientific Principles Concerning the Mechanisms He Described

Respondent's experts criticized the biological mechanism of harm that Dr. Kinsbourne proposed as being at variance with well-known scientific principles concerning the mechanisms he described. Moreover, as put forward, Dr. Kinsbourne's hypothesis was too general to be limited to regressive autism only, but would apply more broadly to autistic disorders–with or without regression.

Dr. Kemper, respondent's expert neuropathologist, noted that the mechanism of harm that Dr. Kinsbourne proposed does not involve the prenatal process of neuronal maldevelopment that has been implicated in autistic subjects or the developmental processes that he addressed in his testimony. Mead Tr. at 2834. Dr. Kemper observed that in the 2005 Pardo article,[182] filed as PMRL 72 and heavily relied upon by petitioners, the investigators recognized that developmental abnormalities that have been present since gestation could produce microglial activation and result in neuroinflammation.[183] Id. at 2850-2851 (referring to PMRL 72 at 489-490). Dr. Kemper further observed that in the 2005 Vargas article, filed as PMRL 69 and also heavily relied upon by petitioners, the investigators acknowledged that the presence of microglial activation in the autistic brain may reflect the abnormal persistence of fetal patterns of development. Mead Tr. at 2851 (citing PMRL 69 at 78). Dr. Kemper made clear that microglial activation is present during normal brain development and is not a response that is specific to the presence of a neurotoxin–such as mercury–in the brain. Mead Tr. at 2850. Moreover, in certain

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[182] C. Pardo et al., Immunity, neuroglia and neuroinflammation in autism, Int. Rev. Psychiatry 17(6):485-495 (2005).

[183] Dr. Kemper noted his personal communication with Dr. Pardo during a scientific conference in 2007, and in a letter dated May 13, 2008, from Dr. Pardo to Dr. Kemper, Dr. Pardo made clear that the findings of microglial activation and neuroinflammation that were reported in the 2005 Pardo article were "inconsistent with the hypothesis of a potential toxic effect on astrocytes by neurotoxins or toxic material." Mead Tr. at 2886, 2902-2904; see also Mead R's Ex. LL at (Dr. Pardo's letter). The undersigned does not rely, however, on the letter from Dr. Pardo in evaluating Dr. Kinsbourne's offered hypothesis.

circumstances, activated microglia function to repair neuronal damage. See id. at 2242-2243 (Dr. Johnson).

Respondent's experts also challenged petitioners' theory that the detected microglial activation in the brains of autistic individuals reflected an immune system response to the long-term presence of inorganic mercury in the brain after receipt of thimerosal-containing vaccines. Dr. Kemper asserted that the finding of increased numbers of glial cells and decreased numbers of neurons in examined autistic brains as reported in the 2008 Lopez-Hurtado article–on which petitioners relied–was of questionable scientific reliability because the methodology employed by the investigators was flawed.[184] Mead Tr. at 2856-2859. That microglial cells function as part of the brain's innate immune system is undisputed. See Mead Tr. at 2893 (Dr. Kemper). But, as respondent's medical toxicologist Dr. Brent specifically observed, there are no studies showing that the amount of mercury in thimerosal-containing vaccines, whether individually or cumulatively, can modulate the immune system in any way. Mead Tr. at 1848; see also id. at 1949 (Dr. Brent noting that the 2005 Vargas paper did not mention mercury). He noted that during the proceedings on the first theory of general causation, thimerosal-containing vaccines were alleged to act as an immunosuppressant, and now the second theory of general causation involves an allegation that thimerosal-containing vaccines stimulate the immune system. Id. at 1848. Dr. Brent strongly contended that mercury does "neither." Id.

Dr. Brent further asserted that no studies show that the amount of mercury contained in thimerosal-containing vaccines–whether individually or cumulatively–"can cause, can exacerbate or can contribute to oxidative stress or oxidative damage." Mead Tr. at 1847 (Dr. Brent). Dr. Brent reiterated that the amount of mercury detected in the human brain ranges in the low nanomolar amount or between two to 40 parts per billion, and he noted that the scientific literature on which Dr. Kinsbourne relied–particularly the work of Dr. Aschner, for the proposition that inorganic mercury can inhibit glutamate uptake in astrocytes–involved doses of 400 parts per billion mercury. Id. at 4335. Dr. Brent stated that the doses of mercury used in the Aschner work were significantly greater than the amount of inorganic mercury ordinarily found in human brains and were

[184] Dr. Kemper stated that the investigators failed to specify carefully, by "proper cyto[-]architectonic definition," the area of the brain under examination, a process necessary to ensure that all measurements were made in the same place. Mead Tr. at 2856. The investigators did not study microglia, and the cell counting methods that they used were problematic. Id. at 2856-2857. Dr. Kemper observed that the identified issues with the investigators' applied methodology were of sufficient significance to preclude acceptance of the article by any of the critically refereed journals. Id. at 2857.

significantly greater than the additional two to three parts per billion inorganic mercury burden imposed by the receipt of thimerosal-containing vaccines. Id. at 4336. Dr. Brent also pointed out that because the sources of inorganic mercury deposition in the brain are not limited to vaccinations, the persistence of inorganic mercury in the brain cannot be attributed solely, or even primarily, to vaccinations. See Mead Tr. at 3414 (Dr. Rutter); see also id. at 1804, 1847 (Dr. Brent). The chief source of the inorganic mercury load in the body is dietary, and the common acts of breastfeeding or eating fish do not induce significant oxidative damage. Mead Tr. at 1847 (Dr. Brent).

With respect to that part of Dr. Kinsbourne's theory pertaining to astrocytes, Dr. Kemper noted that, contrary to Dr. Kinsbourne's representation, gliosis is not a sequela of astrocytic death. Mead Tr. at 2852. Rather, gliosis reflects the enlargement of the nucleus of the glial cell body, and the process is not associated with the death of astrocytes. Id.; see also id. at 2243-2244 (Dr. Johnson explaining that gliosis or glial scarring results, not from astrocytic death, but from activated astrocytes entering a damaged area, and "secreting proteins that lay down [the] matrices that form the scar"). Dr. Kemper pointed out that Dr. Kinsbourne's hypothesis that astrocytic malfunction or inactivation occurs in the brains of thimerosal-exposed children who develop autism is not supported–but instead contradicted–by the findings in the 2005 Vargas article. Id. at 2852-2853. The work of Dr. Vargas showed an increase, not a decrease, in astrocytic activity in autistic brains. Id.

Dr. Rust testified that "a good deal" is known "about how [inflammatory] conditions behave, both clinically and pathologically, and . . . increasing amounts [are known] about what . . . microglial cells do both in inflammation [and] in brain injury." Mead Tr. at 2483. Microglial cells appear to clean up injured cells–which appear after exposure to methylmercury–and microglial cells function similarly in inflammatory conditions. Id. There is also increasing evidence that "the presence of inflammatory cells [i]s a very important and normal element" of brain development. Id. Dr. Rust noted that Dr. Kinsbourne's hypothesis about the astrocytic and microglial changes that occur in the autistic brain is inconsistent with what is known about those particular neuroglial cells and with what is known about inflammation. Id. at 2482.

Dr. Rust also testified that if too much glutamate, the excitatory neurotransmitter, were released from the end of a cell, as Dr. Kinsbourne hypothesized in this case, then the inhibitory neurotransmitter GABA would be released to down-regulate the effects of the excess glutamate. Id. at 2500. Asserting that the communication between cells through neurotransmitters is "exquisite[ly] . . . sensitiv[e]," "highly regulated" and "dynamic," and that excess glutamate does not disable only–but instead kills–cells, Dr. Rust questioned the plausibility of Dr. Kinsbourne's hypothesis. See id. at 2499-2500, 2501-2502.

Dr. Rust further testified that one of the jobs of astrocytes is "to store glucose as glycogen[, a source of cellular energy,] and then to break it down and give it to neurons . . . to support them" in the performance of their various tasks. Id. at 2506. Astrocytes have a plentiful source of this enrichment while neurons have very little. Id. Accordingly, without the energy supplied by astrocytes, neurons lack the energy necessary to "get out of control . . . [and] become hyperexcitable." Id. at 2507. As a result, and contrary to Dr. Kinsbourne's assertions, neuronal function "diminish[es] and then stop[s]." Id.

Dr. Johnson, a lauded neurotoxicologist with a research focus on neurodegenerative diseases, testified that Dr. Kinsbourne's theory that chronic cell dysfunction can occur without inducing a progressive disease or causing cell death is scientifically invalid. Mead Tr. at 2247-2248. Dr. Johnson explained that in the short-term, the failure of astrocytes to re-uptake glutamate will lead to hyperactivity in neurons on the post-synaptic side of the neuronal communication. Id. at 2246. In the long-term, however, the increase in glutamate excitation caused by dysfunctional astrocytes will lead to neuronal death. Id. at 2246-2247, 4321; see id. at 2507 (Dr. Rust testifying that if astrocytes are damaged, neurons cannot function). The process that leads to neuronal death is a neurodegenerative one. See id. at 4328-4329. According to Dr. Johnson, once the process of neurodegenerative disease is initiated, the disease progresses–without a plateau–until it becomes fatal. See id. at 2247, 4324. The biological mechanism that Dr. Kinsbourne has proposed in this case contemplates a neurodegenerative process that is inconsistent with what is known about autism–specifically, that autism does not progress in the same manner as a neurodegenerative disease. See id. at 2255-2256; see also id. at 2502-2503, 2512-2513 (Dr. Rust testifying that "a progressive course of deterioration . . . is quite at variance with what we see in autism [b]ecause as a rule, . . . individuals with autistic features improve over time[,] . . . includ[ing] children that have a regressive appearance").

Moreover, Dr. Kinsbourne's hypothesis as set forth does not pertain solely to the regressive form of autism–as petitioners' general causation theory contemplates. Id. at 2592. Rather, respondent's expert pediatric neurologist Dr. Rust observed that the theory that Dr. Kinsbourne has proposed applies, without distinction, to both the regressive and the classic form of autism. See id.

(3) The Overarousal Theory Does Not Adequately Account for the Behavioral Abnormalities Observed in Autistic Individuals

Respondent's experts also challenged the overarousal theory that Dr. Kinsbourne put forth as an explanation for the observed behavior in autistic children. Criticizing the proposed theory for its lack of specificity, Dr. Lord, an expert psychologist testifying for respondent, observed that the overarousal theory has been advanced over the last 40 to 50 years as an explanatory model for "many different disorders." Mead Tr. at 3585. Dr. Lord added that the proposed theory does not adequately explain why many of the observed characteristic behaviors in autistic persons–such as flapping of hands or other self-stimulatory behaviors–that are asserted to be responses to overstimulation are the same behaviors that are observed to occur in a number of contexts, including in circumstances of underarousal. Id. at 3585-3586; see also id. at 2433-2434 (Dr. Rust stating that describing autistic behaviors as "manifestations of a hyper-excitable state in the nervous system . . . [is] certainly not in keeping with the data" or his clinical experience with a considerable number of patients).

Dr. Rutter, one of respondent's expert pediatric psychiatrists, described Dr. Kinsbourne's theory of overarousal as "an old theory . . . [that] no longer even gets referenced in textbooks." See id. at 3315-3316. He explained that the theory "disappeared simply because of the contradictory findings which did not really support the notion." Id. at 3316 (Dr. Rutter). Dr. Rutter pointed out that in the 2006 Baron article[185] and the 2006 Goodwin article,[186] filed respectively as PMRL 550 and PMRL 496, on which Dr. Kinsbourne relied in support of his theory, the researchers specifically address the difficulties associated with observing an individual who appears to be aroused and tying those observations to physiological measures–such as heart rate–that confirm the observations. See Mead Tr. at 3316-3317, 3319. Dr. Rutter observed that for the overarousal hypothesis to account for the abnormalities in social reciprocity in individuals with autism, measurable physiological changes must be demonstrated to occur in affected

[185] M. Baron et al., Stress and Coping in Autism, Oxford University Press, p. 536 (2006).

[186] M. Goodwin et al., Cardiovascular Arousal in Individuals With Autism, Focus on Autism and Other Developmental Disabilities 21(2): 100-124 (2006) (as one page filing taken from an appendix for the purpose of showing the mean heart of a subject in alternating states of rest and activity).

persons in social situations. Id. at 3319-3320. He noted that no such showing has been made for autism in general or regressive autism in particular. Id.

Here, petitioners have asserted that the inorganic mercury deposited in the brain after receipt of thimerosal-containing vaccines can trigger and sustain a microglial response that leads to certain cellular dysfunction. But Dr. Kinsbourne expressed some uncertainty regarding the amount of mercury exposure required and the length of time needed to initiate the mechanism that he described. Petitioners also have asserted that mercury-induced cellular dysfunction permits a chronic state of hyperexcitability without setting into motion a neurodegenerative process that results in cell death. But it is well-understood in the scientific community that once begun, an initiated neurodegenerative process is a progressive one. The final component of petitioners' hypothesis is the view that hyperexcitability at the cellular level provokes overarousal in behavior that manifests with autistic-like symptoms. But the overarousal theory that petitioners have put forth is not new and is not disease-specific. Providing a limited explanation for certain behavior observed in autistic persons, it is a speculative theory that is not viewed by the broader scientific community as a likely explanatory model for autism. Because this aspect of petitioners' theory lacks sound scientific support, it cannot be credited.

The undersigned turns now to evaluate the theory of general causation that petitioners have advanced in this proceeding–specifically, that receipt of thimerosal-containing vaccines contributes to the development of autism spectrum disorder--under the applicable legal standard set forth by the Federal Circuit in Althen.

H. Factual Conclusions Regarding the General Causation Evidence

As addressed in the preceding discussion, the undersigned is persuaded that a preponderance of the evidence presented supports the following factual findings.

There is a strong underlying genetic component in autistic spectrum disorders.

The phenomenon of regressive autism varies widely in presentation and, in some instances, regressive features may appear after a period of ostensibly normal development. The appearance of a normal period of development, however, is not determinative of developmental normalcy. Regressive features are not uncommon in autistic spectrum disorders, and regressive autism is not a distinct phenotype of autism.

Epidemiologic studies have failed to detect an association between thimerosal-containing vaccines and the development of autism. Additionally, the removal of thimerosal in 1999 from pediatric vaccines administered in the United States has not been

shown to have had an impact on the number of reported cases of autistic spectrum disorder.[187]

The mercury component of the thimerosal preservative formerly found in pediatric vaccines could lead to the deposition of inorganic mercury in the brain. The half-life property of inorganic mercury permits such mercury–when deposited in the brain–to remain for a long time. Regardless of the source of the inorganic mercury, significant inorganic mercury deposits in the brain have not been found to cause the same degree of neurological impairment as methylmercury deposits in the brain, and the neurological impairments that are associated with toxic levels of mercury exposure do not resemble the differences in behavior, communication and social skills that are characteristic of autistic spectrum disorders.

The thimerosal component formerly contained in pediatric vaccines was not a significant source of mercury exposure. The amount of inorganic mercury found to accumulate in the brain after receipt of thimerosal-containing vaccines is in the range of two to three parts per billion and is less than the amount of inorganic mercury that accumulates in the brain after eating fish (which contains methylmercury).[188]

Petitioners have speculated that based on mercury's strong affinity for thiols (sulfur-containing compounds)–some of which are involved in certain metabolic processes that generate the antioxidant glutathione, the mercury component in the vaccines that formerly contained thimerosal could cause oxidative stress by disrupting the function of a glutathione-generating metabolic process. But, there is an abundant supply of glutathione in the body and a complex compensatory system for ensuring that adequate levels of glutathione are available in the body to manage the oxidative environment in the brain.

Petitioners have further speculated that the inorganic mercury deposited in the brain as a result of received thimerosal-containing vaccines could cause neuroinflammation that

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[187] The undersigned need not and does not make a finding in this case regarding whether the reported cases of autism over the last 20 years have reflected a true increase in the number of cases.

[188] Total mercury levels in the brain (which include both inorganic and organic forms of mercury) have been estimated to reach 300 parts per billion with no observable toxic effects. See RMRL 294 at 700-701 (1995 Lapham article). That level of total brain mercury was found on autopsy of brains taken from Seychelles Island neonates who had prenatal exposure to high levels of maternal fish consumption. See id. Notably, background levels of total mercury found in the brains of both infants and adults were under 50 parts per billion. See id.

leads to persistent oxidative stress. Petitioners suggest that oxidative stress can cause cellular dysfunction (without cell death) that expresses as autistic disorder spectrum. Ongoing oxidative stress that leads to a disease state, however, does not result merely in cellular dysfunction but in eventual cell death. The known diseases involving ongoing oxidative stress are classified as neurodegenerative, and autism is not a neurodegenerative process.

The legal significance of these factual findings will be considered in the Althen analysis section of this decision. Before reaching the Althen analysis, the undersigned addresses the specific causation claim presented by the Meads on behalf of William.

III. Petitioners' Specific Causation Claim in William Mead's Case

The parties do not dispute that William received vaccines containing thimerosal. See Mead Ps' Brief at 18 n.6; Mead R's Response at 82. Nor do the parties dispute that William is autistic. See Mead Tr. at 3700, 3811 (Dr. Fombonne). Although the parties disagree on whether William's development was entirely normal prior to his regression and whether William's regression occurred abruptly or subtly, the parties do not dispute that William showed symptoms of regression or that his medical records document normal development during the first year of life. See Mead R's Response 82-85. The sharpest dispute between the parties is whether the thimerosal-containing vaccines that he received during his first two years of life were causally related to the development of his autism. Before addressing the crux of the parties' dispute, the undersigned addresses William's medical history.

A. William's Medical History

1. The Medical Records and the Testimony of William's Father[189]

a. From William's Birth to His Autism Evaluation

William Mead was born on May 5, 1998. Mead Ps' Ex. 3 at 13. He weighed 9 pounds 4 ounces. Id. at 14. His Apgar scores were 8 and 9.[190] Id. at 30. His newborn screening test results were normal. Id. at 32. Before he was discharged from the hospital, William received his first hepatitis B vaccine.[191] Mead Ps' Ex. 1 at 3.

William is one of two children. He has a healthy older sister. His extended family–including two siblings on his mother's side and two siblings on his father's side–shows "no evidence for autism or any neurodegenerative condition." Mead Ps' Ex. 4 at 30. But see Mead Ps' Ex. 21 at 12, infra at p.150.

On July 21, 1998, William had his two-month pediatric visit. He received the following vaccines during that examination: diphtheria, tetanus, and acellular pertussis

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[189] The medical records were the principal source of William's medical history. Although the undersigned found that Mr. Mead's testimony was largely consistent with the medical records and that he testified sincerely, the undersigned found that one aspect of Mr. Mead's recollection of details–in particular, his memory of the number of William's words prior to his apparent regression–conflicted with the notations in the medical records and in the view of respondent's expert pediatric psychiatrist, Mr. Mead's testimony that William was speaking in three-word sentences at twelve months "quite difficult to actually believe." Mead Tr. at 3805. The undersigned credited the contemporaneous medical records, rather than Mr. Mead's testimony, as providing the more reliable assessment of what language skills William had acquired. Cucuras, 993 F.2d at 1528.

[190] An Apgar score is "a numerical expression of the condition of a newborn infant . . . being the sum of points gained on assessment of the heart rate, respiratory effort, muscle tone, reflex irritability, and color." Dorland's at 1670.

[191] The hepatitis B vaccine is "a noninfectious viral vaccine derived by recombination from hepatitis B surface antigen and cloned in yeast cells; administered intramuscularly for immunization of children and adolescents and of persons at increased risk for infection." Dorland's at 1999.

("DTaP"),[192] hemophilus influenzae type b ("Hib")[193] and inactivated polio virus ("IPV").[194] Mead Ps' Ex. 1 at 3. William also received his second hepatitis B vaccine. See id.

On September 17, 1998, William had his four month well-baby examination. At that time, he received three vaccinations, specifically his second DTaP, Hib, and IPV. Id. Thereafter, William visited the pediatrician with some frequency to address a series of ear infections and upper respiratory infections.

On October 31, 1998, William's parents took him to the emergency room because he had ear drainage. Mead Ps' Ex. 1 at 48. The on-call emergency room physician examined William and diagnosed him with an infection in his left middle ear ("left-sided otitis media") as well as a rupture of the tympanic membrane and drainage of the middle ear fluid. Id. The emergency room physician also noted that William showed "evidence of mild reactive airway disease" which could be treated more effectively "with an albuterol metered dose inhaler." Id. at 48, 50. He suggested that this health concern could be addressed further when William's pediatrician next evaluated him. Id.

Two days later, on November 2, 1998, Beverly Wittkopp, M.D., William's pediatrician, examined him in her office. It was her assessment that William had developed bilateral otitis media with a perforation in his left ear. See Mead Ps' Ex. 1 at 15. She prescribed a 10-day course of the antibiotic amoxicillin. See id.

Almost two weeks later, on November 13, 1998, Dr. Wittkopp again examined William. Mead Ps' Ex. 1 at 14. The medical records from the visit indicate that William had an upper respiratory infection and reactive airway disease. Id. Dr. Wittkopp's plan

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[192] The DTaP vaccine is "a combination of diphtheria toxoid, tetanus toxoid, and pertussis vaccine; administered intramuscularly for simultaneous immunization against diphtheria, tetanus, and pertussis." Dorland's at 1998.

[193] Dorland's prefers the alternative spelling "Haemophilus" in its definitions. Id. at 834. The Haemophilus influenzae type b vaccine protects against infection by the Haemophilus influenzae type b. Dorland's at 1999.

[194] The IPV vaccine is "a suspension of formalin-inactivated poliovirus . . . administered intramuscularly or subcutaneously for immunization against poliomyelitis." Dorland's at 2000.

was to treat William with a course of albuterol.[195] See id. Ten days later, on November 23, 1998, William returned to see Dr. Wittkopp again. See Mead Ps' Ex. 1 at 13. At this visit, William presented with the following symptoms: cold for one week, fever on and off for three days, a cough that worsened at night and drainage from the left ear. See id. In Dr. Wittkopp's assessment, William had an upper respiratory infection, conjunctivitis, bilateral otitis media, and reactive airway disorder. See id. She prescribed Septra,[196] urged that William continue to take his albuterol, and indicated that she would re-evaluate William at his six-month well-child visit scheduled to occur two weeks later. See id. Dr. Wittkopp directed William's parents to call if he had not shown improvement in two or three days. See id.

On December 3, 1998, when William was seven months old, he had his six-month well-child visit. See Mead Ps' Ex. 1 at 3, 12. At that time, William received his third DtaP, HiB, and hepatitis B vaccinations. See id. at 3. The check list for development completed during the office visit showed that William had achieved the following developmental milestones: head control, rolls, hand-to-mouth, follows 180 degrees, localizes, coos and laughs. See id. at 12. Dr. Wittkopp reported that William's physical exam was "normal" and William's ears were "clear." See id.

As reflected in the medical records, William saw his pediatrician during his first year not only for well-baby visits but also for a number of "sick" visits. From the sick visits, he received treatment for at least three ear infections, including a burst eardrum.[197] See Mead Ps' Ex. 1 at 16, 48, 50, 15, 13, 11, 10 (see visits on 10/11/98, 10/31/98, 11/2/98, 11/23/98, 12/12/98, 1/23/99).

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[195] Albuterol is "a bronchiodilator that relaxes muscles in the airways and increases air flow to the lungs." http://www.drugs.com/albuterol.html.

[196] Septra is an antibiotic combination that kills sensitive bacteria. http://www.drugs.com/septra.html.

[197] Medical records from a visit to Dr. Wittkopp dated January 23, 1999, state "third otitis media this fall." Mead Ps' Ex. 1 at 10. However, a review of the medical records indicates at least five instances of otitis media occurring in this time frame. See Mead Ps' Ex. 1 at 16, 48, 50, 15, 13, 11, 10 (see visits on 10/11/98, 10/31/98, 11/2/98, 11/23/98, 12/12/98, 1/23/99). In addition, William was prescribed eight different courses of antibiotics during his first year of life. See id.; Mead Ps' Ex. 2 at 1-3, Mead Ps' Ex. 1 at 30.

On May 10, 1999, five days after William's first birthday, he received his first measles, mumps and rubella ("MMR")[198] and varicella[199] vaccinations. Mead Ps' Ex. 1 at 3. The records pertaining to this one-year visit also indicate that William "pulls to stand/cruise[,]" uses "pincer" action, "waves [and] claps[,]" and uses "Dada" and "Mama" appropriately. Mead Ps' Ex. 1 at 29. The records further reflect that William's physical exam was otherwise unremarkable. See id.

By this time–at a little more than one year of age–William had received nine doses of vaccines that contained thimerosal.[200] William's father, George Mead, testified that, other than William's bronchial issues and ear infections, he developed normally during his first year of his life. See Mead Tr. at 954. Mr. Mead added that by his first birthday, William was "basically getting his needs met using two to three word sentences." Id. at 956. Respondent's pediatric psychiatrist Dr. Fombonne, however, found Mr. Mead's testimony that William was speaking in three-word sentences at 12 months of age "quite difficult to actually believe" based on the inconsistency in the medical records about "the extent to which [William] had fully developed language at the time he lost his skill" and about when William's regression occurred during the time period identified between 18 and 27 months of age. Id. at 3805-3807. The undersigned has credited the more modest estimates of word acquisition noted in the medical records rather than Mr. Mead's conflicting testimony. The factual determination that William's initial acquisition of words was documented to have been more limited than his father later recalled at hearing, however, does not disturb the finding, based on all of the evidence presented, that William eventually demonstrated symptoms of regression.

A review of William's medical records indicates that William saw his pediatrician nine times for illnesses in his second year of life. Details are provided in the following paragraphs. It does not appear that William saw his pediatrician for any regular well-child visits during this time period.

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[198] The MMR vaccine is "a combination of live attenuated measles, mumps, and rubella viruses, administered subcutaneously for simultaneous immunization against measles, mumps, and rubella." Dorland's at 1999.

[199] The varicella vaccination is "a preparation of live, attenuated human herpes virus 3 (varicella-zoster virus) administered subcutaneously for production of immunity to varicella and herpes zoster." Dorland's at 2000. Varicella is commonly known as chickenpox. Id. at 2008.

[200] At no time have the IPV, MMR, and varicella vaccines ever contained thimerosal. RMRL 254 at 27 (2001 IOM report).

On July 25, 1999, almost three months after William's first birthday, he was examined by an emergency room physician for breathing difficulties. See Mead Ps' Ex. 7 at 6-7. The records from this emergency room visit state that William had a history of reactive airway disease and had respiratory syncytial virus (RSV) at six weeks of age. See id. His diagnosis was "[r]eactive airway disease/URI, probably viral." See id. at 7.

Two months later, on September 28, 1999, William returned to his pediatrician Dr. Wittkopp for a cough that had persisted for nearly two weeks and a fever of 100 to 101 degrees. See Mead Ps' Ex. 1 at 27. Dr. Wittkopp's assessment was that William had an upper respiratory infection and reactive airway disease. See Mead Ps' Ex. 1 at 27.

Almost two months later, on November 14, 1999, William saw Dr. Wittkopp again, this time for an upper respiratory infection that had persisted for three weeks and for a check of his ears. See Mead Ps' Ex. 1 at 27. Dr. Wittkopp attributed William's persistent cough to brochospasms. See id. She advised William to continue with Albuterol and prescribed a course of amoxicillin. Id.

Almost five weeks later, William returned to Dr. Wittkopp, again with an upper respiratory infection that had persisted for seven days and with increased crankiness in his behavior. See Mead Ps' Ex. 1 at 26. Dr. Wittkopp prescribed a 10-day course of Septra. See id.

A little more than three weeks later, on January 11, 2000, when William was 20 months old, he returned to Dr. Wittkopp's office with croup. See Mead Ps' Ex. 1 at 26. William presented reporting a fever of 102 degrees that morning. See id. Dr. Wittkopp's notes from this visit reflect that William was "very active" during this visit and "resist[ant] to [her] exam." Id. Dr. Wittkopp prescribed Prelone syrup.[201] Id.

Three days later, on January 14, 2000, Dr. Wittkopp again examined William, and her notes from this visit reflect that William had finished the Prelone the previous evening. Id. at 25. Dr. Wittkopp re-checked William's ears because he had been tugging on them, and her assessment was that William had the flu. See id.

Five days later, on January 19, 2000, William returned to Dr. Wittkopp. See Mead Ps' Ex. 1 at 25. William was "very fussy" and continued to have a persistent cough. Id.

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[201] Prelone syrup is a corticosteroid, which functions by modifying the body's immune response to various conditions and decreasing inflammation. http://www.drugs.com/cdi/prelone-syrup.html. Prelone syrup is used to treat a variety of conditions, including allergies and breathing problems. Id.

Dr. Wittkopp's assessment was acute otitis media in the right ear. Id. Dr. Wittkopp prescribed a 10-day course of amoxicillin. Id.

Almost three weeks later, on February 7, 2000, William returned to Dr. Wittkopp's office to have his ears checked. See Mead Ps' Ex. 1 at 24. Dr. Wittkopp's notes indicate that William had an upper respiratory infection and that she recommended symptomatic care and Robitussin. Id.

Two weeks later, William was examined again for "cough x 2 mo[nths]", wheezing, yellow/green discharge from his nose, and intermittent fever. Id. It appears that William was examined by another physician in Dr. Wittkopp's group, and the medical records reflect that William had improved on antibiotics, that he was continuing to use albuterol, and that his parents declined to explore further use of Prelone for treatment of William's cough because it "ma[de] him act weird." Id. The assessment from this visit was "sinusitis" and "asthma." Id. The plan from this visit included a 10-day course of Augmentin, and direction to William's parents to call back in a few days if William showed no improvement. Id. The notes reflect that the doctor discussed with William's mother the possible need to add an anti-inflammatory to William's asthma treatment plan was discussed with William's mother. Id. at 24.

On April 7, 2000, William fell down some stairs with a toy hammer and lacerated his forehead, either from the contact with the hammer or with the stairs. Mead Ps' Ex. 1 at 46-47. William was taken to the emergency room. See id. The examining physician closed William's wound with sutures and recommended that he see his pediatrician in approximately six days for suture removal. See id.

On April 12, 2000, three weeks before William's second birthday, William presented to his pediatrician Dr. Wittkopp for removal of his sutures. Mead Ps' Ex. 1 at 23. At this visit, William received his fourth DTaP, his fourth Hib, and his third Prevnar vaccination. Id. at 23; see also id. at 3. After this visit and at just under two years of age, William had received 11 doses of vaccines that, more likely than not, contained thimerosal.

Mr. Mead testified that he and William's mother first noticed changes in William's behavior when William was approximately 18 months old, in particular, the Meads first noticed that William was starting to withdraw. See Mead Tr. at 961-962. According to Mr. Mead, things changed dramatically as of May 2000. "Within a matter of a few weeks William lost all the language he had, he didn't recognize us, his eye contact diminished, he really kind of looked through us, and one of the things that I remember as kind of a milestone for me on this is, and the ta-ka-ta-ka-ta-ka increased more and more." Id. at

964-965. Mr. Mead specifically recalled that his parents had come to visit in the summer of 2000 and told the Meads that "this kid has something very wrong with him and you need to do something about it." Id. at 965.

But respondent's pediatric psychiatrist Dr. Fombonne noted that the medical records were not consistent about the time frame during which symptoms of William's regression began to appear. Dr. Fombonne noted that, at the beginning of the school year in 1999 when William was 16 months of age, he was "asked to leave the daycare [he was attending] because he was not fitting in." Id. at 3807. He further noted that some of William's medical records mention the summer of 2000 "as being a critical time" when his parents recognized that William was having certain difficulties. Id. Although it was Dr. Fombonne's view, after reviewing video clips of William before he turned 18 months of age, that William's produced language was "extremely limited," Dr. Fombonne acknowledged that there was nothing in the medical records or the testimony of William's father that indicated that William was deficient in the areas of social skills or imaginative play before the age of 18 months. Id. at 3808-3810. Dr. Fombonne further acknowledged that William lost skills in all three developmental domains associated with autism between 18 and 27 months of age. Id. at 3810.

The medical records indicate that on May 15, 2000, William had his two-year well-child check-up.[202] See Mead Ps' Ex. 1 at 22. The medical notes from this visit

[202] The testimony of both Mr. Mead and Dr. Mumper raised a factual issue concerning whether or not William received a fifth DTaP during this visit to Dr. Wittkopp. See Mead Tr. at 964, 1252-1254. Mr. Mead testified that William received vaccinations on April 12, 2000, and that he was vaccinated again "six weeks later at the second visit." Id. at 964. During his testimony, Mr. Mead was unable to recall which visit was a well-baby check and which visit was for bronchiolitis. See id. The medical records reflect that the visit–to which Mr. Mead referred as the "first"–occurred in April 2000. See Mead Ps' Ex. 1 at 3. It was during this visit that William's sutures were removed and he received vaccinations. Id. at 23. The next visit to Dr. Wittkopp's office occurred in May of 2000, and as reflected in the medical records, was for William's two-year well-baby check. Id. at 22. Neither the records for that visit nor William's immunization record reflect that any vaccinations were administered in May of 2000. Id. at 3, 21.

Asked at hearing if it would be reasonable to conclude that a DTaP shot had been given on May 5, 2000, Dr. Mumper testified that she "typically trust[s] the parents' history." See Mead Tr. at 1253. In support of her view that William received a fifth DTaP administration at the May 15, 2000 visit, Dr. Mumper relied not only on the

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identified–as an area of concern–"no speech" from William. Id. Under the heading of development in the medical notes, the line item for "vocabulary 15-20 words/combines two words" is unchecked and the word "no" has been written next to this selection. Id. Under the plan section of the medical notes are notations that William had "no words" and that he did "not point or know body parts." Id. In addition, under the assessment portion of the notes are the comments that William "hears well," "acts on language," and "responds to commands." Id. The notes also reflect that William had a history of four head injuries with no loss of consciousness. Id.

Two weeks later, on May 26, 2000, William's mother called Dr. Wittkopp's office and reported that William had been experiencing diarrhea for ten days. See Mead Ps' Ex. 1 at 65. Subsequently, on July 11, 2000, Dr. Wittkopp evaluated him. See Mead Ps' Ex. 4 at 12. Her subjective notes from the office visit reflect that William had been experiencing brief episodes of diarrhea on and off for six months. Id. At that time, William was two years and two months old. Id.

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[202](...continued)
testimony of Mr. Mead, but also on a copy of William's immunization records–which appear to indicate that a fifth DTP vaccination may have been administered to William at some point. Id. at 1253. Dr. Mumper stated that "although we typically wouldn't give a fifth DT[a]P then, [the four-week] interval between shots would . . . . be a reasonable interval." Id. Dr. Mumper explained that when you administer "catch-up immunizations, you're advised to wait four to six weeks." See id.

There is no evidence to support the position that the fifth DTaP vaccination was intended to be a "catch-up vaccination" because William was not behind in his immunizations. According to the Recommended Childhood Immunization Schedule applicable in the year 2000, William was not eligible for his fifth DTaP until between the ages of four and six years. See http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4902a4.htm. This recommended schedule is a "harmonized" childhood schedule of childhood vaccinations that is published annually with the approval of the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP).

Because the medical records are, at best, unclear on the issue and because the immunization at issue would have been administered in contravention of the recommended schedule, the undersigned cannot conclude that the weight of the evidence supports a finding that William received a fifth DTaP vaccination during his visit to Dr. Wittkopp in May 2000.

On August 29, 2000, William saw Dr. Wittkopp for the removal of sutures from his lower lip. Mead Ps' Ex. 4 at 10. Under the plan section of the medical record from this visit are Dr. Wittkopp's notations that she "discussed" William's lack of speech and that she would "obtain [an] audiology referral." Id.

Two days later, on August 31, 2000, Dr. Wittkopp referred William for a hearing assessment. Mead Ps' Ex. 1 at 54. The prompt for the referral was William's lack of speech at two years and four months of age. Id. The next month, on September 25, 2000, a speech pathologist assessed William's hearing. Mead Ps' Ex. 4 at 6. The medical records from this visit state that in the test room, William "would not make eye contact or engage in play." Id. The records further indicate that some testing was not carried out because of William's lack of cooperation. Id. Mr. Mead testified that at the audiology clinic, they first learned of the casein-free, gluten-free diet on which they started William in early October. Mead Tr. at 968.

About a week after William's hearing assessment, Dr. Wittkopp noted in her medical records–dated September 20, 2000–that William would be evaluated at Oregon Health Sciences University Developmental Clinic. Mead Ps' Ex. 1 at 7.

On October 14, 2000, two weeks after Dr. Wittkopp's recommendation that William receive a developmental assessment, William started a gluten-free, casein-free diet. See Mead Ps' Ex. 4 at 26 (a letter from Mr. Mead to Dr. Green). On October 18, 2000, William was seen in the Communications Disorders Clinic at OSHU for concerns related to his speech and language delay, as well as hearing concerns. Mead Ps' Ex. 4 at 32-33.[203] The medical records indicate that "[i]n that assessment, Will's language was assessed using the Receptive-Expressive Emergent Language Scale, Second Edition (REELS-II). On that measure, he achieved a receptive language age of 9 months and an expressive language age of 12 months." Mead Ps' Ex. 21 at 3. Chronologically, however, William was two and one-half years of age. Based on William's speech and language delays–as well as several other concerning behaviors–at the time of his language evaluation, a further recommendation was made for William to receive an assessment from an autism team. Id. That evaluation was scheduled for December 2000. Id.

[203] No medical records from this evaluation appear to have been filed into the record. However, this October 2000 visit to the Communications Disorder Clinic is referenced on more than one occasion in William's subsequent evaluation at the Child Development and Rehabilitation Center at OHSU. See Mead Ps' Ex. 21 at 3, 5, 10, 13, 15.

On November 28, 2000, William was evaluated at a different pediatric clinic by Alvan Pang, M.D. Dr. Pang's medical records show that he evaluated William for autism. Mead Ps' Ex. 4 at 4. According to the patient history provided by William's parents, William "was developing normally until he had his MMR vaccine at age 1 year." See id. Shortly after William received the MMR vaccine, "he developed signs of gastrointestinal disease with definite abdominal discomfort with diarrhea." Id.

Dr. Pang's assessment of William was "[a]utism, which may be autoimmune in nature and secondary to a MMR vaccination." Mead Ps' Ex. 4 at 4. Under the development section of the medical records are the following notes: "normal at age 1 year; social, motor? Intellectual deterioration after MMR." Id. at 2. Dr. Pang referred William's parents to John Green, M.D., an environmental medicine specialist, who works with autistic children. Mead Ps' Ex. 4 at 4.

b. Assessments and Treatments that William Received After His Autism Diagnosis

On December 12, 2000, when William was two years and seven months old, he presented to an autism clinic for an assessment that included the disciplines of psychiatry, social work, occupational therapy, education, and speech/language pathology. Mead Ps' Ex. 21 at 3.

As part of this assessment, William's language was evaluated again, this time by Robert Buckendorf, Ph.D., a speech and language pathologist and an assistant professor of pediatrics. Mead Ps' Ex. 21 at 3-6. Dr. Buckendorf found it "noteworthy that Will's performance in receptive and expressive language, as measured by scores of the REELS-II, ha[d] significantly improved since his previous evaluation on October 18, 2000." See Mead Ps' Ex. 21 at 5. Dr. Buckendorf reported that "[i]n two months[] time, [William] ha[d] gained approximately two-five months in language skills. In addition, Will's attending and engagement skills ha[d] notably improved." See id.

Also as part of William's autism assessment, he was evaluated by Gene Stubbs, M.D., a professor of pediatric psychiatry at OHSU. See Mead Ps' Ex. 4 at 35-36. William's parents reported to Dr. Stubbs that William had "what they felt to be normal development prior to the age of 18 months, at which time he received his MMR vaccination."[204] See id. Dr. Stubbs took comprehensive notes of William's history that included statements from his parents that "a definite change [occurred] in both William's

[204] William actually received his MMR vaccination on May 10, 1999. He received that vaccination at the age of one year and five days. See Mead Ps' Ex. 1 at 3.

relatedness socially, as well as his verbal skills" after his MMR vaccination. Id. According to the recollection of the Meads, at "the age of 14 months William was talking in three- to four-word phrases, pointing at objects, and making good eye contact; however, beginning in October of 1999, following [the MMR] vaccination, they noticed William being less socially responsive or being less engaging, and that he had suffered the loss of all verbalization, except for some guttural gurgling noises." Id. William's parents identified the months of August and September of 2000 as the worst period for William because that was the time when William "became progressively less interactive [with] his environment, when he was seen to have significant . . . sensitivities to sound, when he was seen to be covering his ears, and when he began engaging in self-stimulatory behavior, including spinning, copying, and head rocking." Id. Emphasized in the medical records from this evaluation is the Meads' "very strong sense that there may be a measles, mumps, and rubella (MMR) [vaccination] connection" to William's autism. Id. at 37. Dr. Stubbs' diagnostic impression was that "[b]efore intervention, William would [have met] the classic criteria for autism. Currently he is making good progress." Id. at 38.

Referenced under the family history portion of the medical records from Dr. Stubbs' assessment is a family history of autoimmune disorders. There is also a "history of [William's] father's brother having 'a psychotic break' and [the paternal uncle] is [also] described as somewhat socially abrasive and near-genius. Maybe some people might consider him to be on the autism spectrum." Mead Ps' Ex. 21 at 11-12.

Following a comprehensive evaluation for autism, William began treatment with Dr. Green, an environmental medicine specialist, to whom the Meads had been referred by Dr. Pang, the pediatrician who appears–from the medical records–to have first diagnosed William with autism. Dr. Green examined William on January 4, 2001. See Mead Ps' Ex. 15 at 3-5. The medical records from this office visit indicate that William had "multiple complex problems." Id. at 3. Dr. Green noted the following:

> 1. Suspect fungal overgrowth and bacterial dysbiosis from multiple courses of antibiotics. 2. Suspect adverse reaction to live virus vaccines in an immune compromised child with possibility of lymphonodular hyperplasia induced by the live measles vaccine given at a time when his health was compromised, and the mix with other vaccines was more than he could tolerate. 3. H[istory] of multiple food allergies, and an atopic family background.

Mead Ps' Ex. 5 at 54. Based on his suspicions concerning William's condition, Dr. Green ordered a battery of tests. See Mead Ps' Ex. 5 at 53. Dr. Green's plan was also to "investigate heavy metal toxicity as a contributing factor due to the amount of mercury he

received in vaccines, and due to his oral habits."[205] Id. at 53. Dr. Green continued to follow William.

On March 6, 2001, when William was 34 months old, he presented for an evaluation at the Medical and Molecular Genetics Division of the Metabolic Clinic at the Child Development and Rehabilitation Center at OHSU. Mead Ps' Ex. 4 at 29. William was evaluated by Markus Grompe, M.D., a professor at OHSU who is board certified in genetics and pediatrics.

Dr. Grompe's medical records indicate that William's diagnosis of autism was based on the earlier clinical evaluations at OHSU by speech and language pathology as well as by psychiatry. The purpose of Dr. Grompe's evaluation was to determine whether there might be a potential metabolic cause for William's autism given the existence of "quite good documentation that his development was normal, at least throughout the first year of life." Id. Dr. Grompe observed that after 18 months of age, William "lost many of the skills that he originally had, particularly in the area of communication speech and language. [And] there does not appear to have been much deterioration in gross-motor or fine-motor skills." Mead Ps' Ex. 21 at 20-21.

Dr. Grompe noted that the presentation of William's condition raised concern that he might be suffering from a neurodegenerative condition rather than from classic autism. Mead Ps' Ex. 21 at 21. That concern prompted the undertaking of a thorough evaluation to determine whether William had such a disorder. See id. Dr. Grompe discussed with William's mother the need for a head MRI, a retinal eye examination, and a variety of laboratory tests to further explore the possibility of a neurodegenerative condition, as well as tests of William's mercury and lead levels–to put the issue of mercury poisoning to rest. Id.

Among the conditions that Dr. Grompe identified for consideration in William's differential diagnosis were: "mitochondrial respiratory chain defects, paroxysmal disorders, lactisomal leukodystrophies, [and] many other inborn errors of metabolism."

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[205] Investigating possible mercury toxicity in William appears to have been the secondary strategy for treating what was believed to be the onset of autism that was causally related to William's receipt of thimerosal-containing vaccines. The first strategy of Dr. Green appears to have been investigating a possible causal relationship between William's autism and the receipt of the MMR vaccine. The theory of MMR vaccine-related autism was considered and rejected by the undersigned in the Hazlehurst case, one of three test cases addressing that theory of general causation. The other two test cases, Cedillo and Snyder, also considered and rejected the theory.

Id. Dr. Grompe added to that list: fragile-X syndrome because it "has been associated with autistic behavior" and the condition known as ataxia telangiectasia–given William's frequent infections and an apparently low IgA immunoglobulin level. Id.

The medical records from William's visit with Dr. Grompe indicated that William already had undergone a "variety of 'metabolic evaluations' and a special amino acid diet ha[d] been concocted for him" based on the amino acid levels measured in his blood. Mead Ps' Ex. 21 at 19. The medical records further indicated that William also had seen "an autism specialist in the community who ha[d] found 'increased mercury levels.'" Id. Dr. Grompe recorded Mrs. Mead's concern that "William's autism ha[d] been caused by mercury poisoning, particularly mercury acquired during the course of immunizations." Id.

At the time of Dr. Grompe's evaluation, William was taking a number of supplements. Among the supplements identified in Dr. Grompe's records were: Supra New Thera, vitamin B5, acidophilus, taurine, amino acid compound, GIA herbal extract, cod liver oil, melatonin, glutathione, lipoic acid, enzyme-A during meals, and benzonite trisalts when his stomach became upset. Mead Ps' Ex. 21 at 20.

Consistent with the investigatory plan that he had proposed, Dr. Grompe referred William to an ophthalmologist for a retinal eye examination and a determination of whether William had "any telangiectasia in [his] eye." Mead Ps' Ex. 4 at 31. Dr. Grompe also ordered a MRI for leukodsytrophy and other CNS lesions and a battery of screens for William's urine and blood. Id. He directed William to return to the Metabolic Clinic as soon as the prescribed testing had been completed. See id.

One month after William's evaluation at OHSU, Dr. Pang–the physician who initially diagnosed William with autism–wrote a letter on January 17, 2001, addressed generally "To Whom It May Concern." Mead Ps' Ex. 4 at 42. Discussing William's social history, Dr. Pang wrote that William's parents had reported to him that William had been enrolled in a preschool during the 1999-2000 academic year. Id. Dr. Pang also wrote that William's preschool teacher had observed that William was not exhibiting "age-appropriate parallel or cooperative play and that William was becoming increasingly isolated. As William's lack of engagement with others continued, the director . . . [of the program] asked that William be withdrawn from their program to seek a more appropriate placement." Id.

Nearly six months later, by letter dated July 2, 2001 to the Meads from a certified medical assistant with the Metabolic Clinic where William had seen Dr. Grompe–the Meads were informed that further to their March 2001 office visit and a subsequent MRI,

Dr. Grompe did not need to see William back at the clinic at that time. See Mead Ps' Ex. 21 at 22. But Dr. Grompe still urged the Meads to have a "urine organic acid and metabolic screen done" for William. Id.

Ten days later, on July 12, 2001, George Young, M.D., performed an MRI on William. Mead Ps' Ex. 10 at 1. Dr. Young noted that William had "[h]igh urine levels of mercury[, and] [s]peech delay. Neurodevelopmental delay. Probable mercury toxicity." Id. Dr. Young's impressions from the MRI were that "[d]iminished signal intensity" was present in certain areas of the brain. Mead Ps' Ex. 10 at 1. Dr. Young found the areas of "[d]iminished signal intensity" to be "indeterminate [of] whether this represents normal brain iron development or abnormal heavy metal deposits. There is mild incidental sinusitis. The study is otherwise normal and shows no other acquired or congenital abnormalities." Id.

After receiving Dr. Young's assessment, William's parents requested an independent consultation and second opinion concerning the results of William's MRI. See Mead Ps' Ex. 10 at 7, 9-10. As reflected in the filed medical records, the impression on referral continued to be that William's MRI showed a normal brain. Id. at 7. Of note, the evaluators wrote as part of their findings that "[i]n our experience, we are not aware of sites of abnormal mercury deposition. Rather, mercury toxicity may lead to congenital structural abnormalities." Id. at 7.

Other than the MRI, it does not appear from the filed medical records that the additional tests ordered by Dr. Grompe were ever performed. Subsequent correspondence from Dr. Grompe's assistant to the Meads suggests that the Meads declined to pursue the recommended testing any further. By letter dated December 19, 2001, Dr. Grompe's assistant noted that although the Meads had expressed interest in obtaining a metabolic evaluation of William during the consultation with Dr. Grompe, they no longer seemed to be "interested in pursuing the[] biochemical tests or the repeat MRI." See Mead Ps' Ex. 21 at 23.

2. Laboratory Testing and Reported Results for William

Petitioners did not complete the metabolic screen for William. But, petitioners identified both in Dr. Mumper's report and in her testimony a number of laboratory tests and results that petitioners asserted were supportive of their theory that thimerosal-containing vaccines caused William's autism. William was diagnosed with autism in November 2000 and was comprehensively assessed in December 2000. Extensive laboratory testing was performed after William's autism diagnosis–particularly during the year following his initial assessment. The undersigned examines the laboratory testing on

which petitioners rely to support their claim that William's autism is causally related to the thimerosal-containing vaccine that he received during his first two years of life.

Among the tests of interest that petitioners identified was a red blood cell elements test ordered by Dr. Green at his initial evaluation of William on January 4, 2001.[206] See Mead Ps' Ex. 5 at 5; Mead Ps' Ex. 15 at 3-4. Dr. Green sent the collected blood sample from William to [name redacted] Laboratory for testing that purported to measure the zinc level in William's red blood cells.[207] Dr. Mumper, petitioners' evaluating–but not treating–pediatrician, testified that William's test results indicated that "the amount of zinc in [William's] blood compared to the reference ranges was lower than about 98 to 99 percent of people." See Mead Tr. at 1266-1267. The low zinc levels were very indirect evidence that thimerosal-containing vaccines contributed to his injuries because, Dr. Mumper explained, zinc is necessary to escort heavy metals–mercury in particular–out of the body through some complex pathways better described by toxicologists. See id. at 1267. Dr. Mumper added that she relied on the test results for William's zinc levels because zinc is "important in 300 or so different reactions, many of those the types that Dr. Deth was talking about" in his testimony.[208] Id. at 1282.

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[206] According to the [laboratory] website, red blood cell analysis is "an invaluable diagnostic method for assessing insufficiency or excess of elements that have important functions within cells or on blood cell membranes." [Web address redacted] The website also states "RBC element analysis should be performed prior to and intermittently throughout the course of detoxification/chelation therapy. Monitoring essential element status is necessary to identify needs for and effectiveness of supplementation." See id.

[207] William's measured zinc level was 6.6 micrograms per gram, which fell below the reference range for normal provided by the lab of eight to 14.5 micrograms per gram. See Mead Ps' Ex. 5 at 5.

[208] Subsequently, in August 2002, another blood sample taken from William was submitted to Vitamin Diagnostics for zinc testing again. See Mead Ps' Ex. 15 at 106. The detected zinc level in whole blood and the intracellular concentration were low (below the reference range), but the detected zinc level in William's blood serum was high (exceeded the reference range). Id. Dr. Mumper explained that the purpose of the testing was to look for "different nutrients," such as zinc, in "different compartments" of the blood because autistic children may lack the ability to use zinc or other such elements on an intracellular level, and efforts to measure such elements in the blood in traditional ways might not be reflective of the children's "actual difficulties on a cellular level." Mead Tr. at 1281.

In addition to the low zinc levels, Dr. Mumper also identified as significant the levels of mercury in William's red blood cells. Dr. Mumper stated that the measured "mercury value [of] 0.022 micrograms per gram with the reference range being less than 0.01 [micrograms per gram], . . . put[] [William] above the 99th percentile in terms of the amount of mercury that was documented to be present in his blood." Mead Tr. at 1267-1268. Dr. Mumper testified that the measured mercury level in William's red blood cells was significant because "mercury is a known neurotoxin and its presence in the blood in the absence of other explanations ma[d]e [her] concerned" that it reflected a potential inability to handle thimerosal-containing vaccines. Id. at 1268.

Respondent's expert toxicologist, Dr. Brent, testified that a red blood cell elements test is not "an accepted [or] an appropriate test [for] determining toxicity." See id. at 1853. Dr. Brent pointedly observed that "[r]ed cell metal levels are [the] kind of lab [test] results you can get from [lab name redacted]," but the test is not the type of lab test "routinely use[d] in medicine to make . . . determinations" about heavy metal toxicity. Id. Dr. Brent asserted that the "only accepted, . . . validated test for assessing mercury exposure[–]except for the immediate short period of time after the exposure when you might look at blood levels[–]is a urine mercury [test], and the only accepted type of urine mercury [test] . . . that's been validated [and is] . . . interpretable" is a urine test performed on a non-chelated urine specimen.[209] Mead Tr. at 1850.

On January 16, 2001, Dr. Green sent a urine sample collected from William to Metametrix Clinical Laboratory in Norcross, Georgia, requesting that a Urine Organix Profile test be performed.[210] Mead Ps' Ex. 5 at 22. The test appears to have been

[209] As petitioners' expert Dr. Aposhian explained at hearing, mercury chelation involves the administration of a chemical substance that binds to mercury and promotes the urinary excretion of mercury–primarily from the kidney. See Mead Tr. at 223-224, 441-442; accord id. at 1843 (Dr. Brent).

[210] The Metametrix Clinical Laboratory performs testing only for Metametrix account holders. See http://www.metametrix.com/content/HowtoOrder/Main. (All healthcare providers who are licensed in their state of practice and who have a Metametrix account or are willing to open a Metametrix account may order Metametrix testing.). The Urine Organix Profile is:

> a complete quantitative organic acids test. The Organix provides a view into the body's cellular metabolic processes and the efficiency of metabolic function. Identifying metabolic blocks or problems with detoxification, gut

(continued...)

performed to evaluate the efficiency of William's cellular metabolic processes, certain of which petitioners have alleged–through Dr. Deth's testimony–to be subject to disruption by the deposit of inorganic mercury in the brain.

On January 22, 2001, an additional urine sample collected from William was sent to [lab name redacted] for urine toxic element testing. Mead Ps' Ex. 5 at 3. The medical record containing the results of the testing indicates, under the comments section, that the testing was performed following a post-provocative challenge (that is, after a chelation treatment).[211] Id. Dr. Mumper testified that William's test result "showed that mercury came out at 21 micrograms per gram of creatinine when the reference range would have been between zero and three. That basically is a many-fold excretion in response to a chelation challenge," and the interpretation of that test result would be that William's body burden of mercury had been mobilized.[212] Mead Tr. at 1272. Although Dr. Mumper conceded that no established reference ranges exist for the testing of chelated urine samples to assist in interpreting such tests, see Dwyer Tr. at 201; see also Mead Tr. at

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[210](...continued)

> dysbiosis, or oxidative stress that can be treated nutritionally allows for individual tailoring of interventions. Targeted treatment can help maximize patient responses and lead to improved patient outcomes.

See http://www.metametrix.com/content/DirectoryOfServices/0091OrganixComprehensive-Urine.

[211] Dr. Mumper identified this as a "provoked urine [test]" in her testimony. Mead Tr. at 1271. She explained "that the child [had been] given a challenged dose presumably of some kind of chelator." Id. Dr. Mumper noted that the laboratory result did not indicate what type of chelator was used. Id.

[212] The rate of urinary excretion of mercury is usually expressed either as µg Hg/g of creatinine or as a urinary concentration of µg Hg/L. PMRL 35 at 618. For ease of reference, the symbol µg is for a microgram, which is a measure of one millionth of a gram. Mead Ps' Trial Ex. 2 at 6 (Dr. Aposhian's slides). Creatinine is excreted in urine as a byproduct of an amino acid found in muscle tissue. See Dorland's at 432. Based on the average adult excretion of about 1.6 g of creatinine per day, 1g of creatinine is equivalent to 15 hours of urine flow. PMRL 35 at 619. In general, 1 µg Hg/g of creatinine is approximately the same as 1 µg Hg/L of urine except in cases of very diluted or concentrated urine samples. Id.

1554-1555, she appeared to rely on this test result, in addition to the red blood cell test, as further support for a finding that William has difficulty with mercury elimination.[213]

Respondent's expert toxicologist Dr. Brent again provided relevant testimony with respect to interpretation of this type of test results. See Mead Tr. at 1851-1853. When presented with the results of another urine toxic metals test subsequently performed by [redacted] on a urine sample from William in December of 2004, Dr. Brent pointed out that the results report itself states that the reference ranges that are used to assess these samples are "representative of a healthy population under nonchallenge or nonprovoked conditions." See id. at 1851-1852; see also Mead Ps' Ex. 15 at 118. Dr. Brent carefully explained that if a chelating agent is administered before the urine sample is taken "you will find excretion [of mercury] above the reference range, which is [intended] for nonprovoked urine [specimens]." Mead Tr. at 1852. When specifically asked about the urine mercury tests that were performed on William, Dr. Brent said that the tests "showed pretty much exactly what you'd expect for the normal population, that their unprovoked specimens are normal. Yet, when they give chelators, most of [mercury excretion results] are increased." Id. at 1852-1853. Dr. Brent expressed a concern about the use of data in this way to suggest that a condition exists that, in fact, does not. See id. at 1853. He stated that "it's data like this that has been used as an excuse to subject these children to

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[213] Additional urine samples were taken from William in July 2002 and in August 2002 for toxic metals testing respectively by [lab name redacted] and Great Smokies Diagnostic Laboratory (renamed as Genova Diagnostics). See Mead Ps' Ex. 15 at 87, 97. Dr. Mumper testified that the results of the July 2002 test, which had been performed on an unprovoked urine specimen, showed that "there [was] no mercury . . . being excreted." Mead Tr. at 1278. She stated that such a result "would be expected" in an unprovoked test. See id.

The results of the August 2002 test, which had been performed on a provoked urine specimen, showed results that exceed the reference range limit by five times (that is, the reported value for excreted mercury "was 15.76 micrograms per gram of creatinine where the expected reference range would be less than 2.31"). See id. at 1280; see also Mead Ps' Ex. 15 at 87-88. Dr. Mumper asserted that this test result was an important one in this case because the test showed that William was excreting a very high level of mercury in his urine. Mead Tr. at 1280. Acknowledging that the specimen most likely "was a provoked specimen" because "the mercury value was so high," Dr. Mumper posited that because William could not efficiently excrete mercury, she "would not expect him . . . to be able to mobilize that much mercury" on a non-provoked specimen. Mead Tr. at 1280-1281.

chelation therapy where . . . the data supports [a finding] that their urine mercury status is totally normal." Id. at 1853.

As a medical toxicologist, Dr. Brent reiterated that a urine mercury test performed on a non-chelated specimen is the only valid and medically acceptable "test for assessing mercury exposure."[214] Mead Tr. at 1850. He explained:

> There are plenty of reference ranges for what is normal in the population for a nonchelated urinary mercury excretion level. There are on the other hand no validated reference ranges for chelated mercury levels, so they are essentially uninterpretable. We know that since we all have mercury burdens in our body if any of us . . . take[] [a] mercury chelator our mercury urinary excretion would go up.

Id.

William's medical records also show that a sample of his blood was sent to Amscot Medical Labs in Cincinnati, Ohio, for an evaluation of his immunoglobulin levels in January 2001. See Mead Ps' Ex. 5 at 9. The ordered test appears to be for immunoglobulin electrophoresis, a procedure that involves measuring the blood levels of immunoglobulins A, G, and M (IgA, IgG, and IgM).[215] Id. Measures of immunoglobulin levels can assist in detecting medical problems and identifying the cause of the problems. See Mosby's Manual of Diagnostic and Laboratory Tests, 326-327 (3d ed. 2006). Although the test results indicate that William's IgG and IgA levels were low when compared to the reference ranges provided by the laboratory, the accuracy of the results is questionable because the reference ranges provided by the laboratory appear to be the normal ranges for an adult and not for a 21-month old (which was William's age at the time of testing). See Mosby's, at 326 (providing the ranges for IgA, IgG, and IgM). When William's test results are considered in an age-appropriate range, however, the measured immunoglobulin levels fall within the normal range. Compare id. with Mead

[214] Dr. Brent clarified that only in the short period of time immediately following mercury exposure would testing of blood mercury levels provide a valid measure of mercury exposure. See Mead Tr. at 1850.

[215] Immunoglobulins A, G, and M (respectively IgA, IgG, and IgM) are three of five classes of glycoproteins that function as antibodies. Dorland's at 912. Immunoglobulin electrophoresis "is used to assist in the diagnosis and monitoring of therapeutic response in many disease states. It is often ordered if a serum protein electrophoresis indicates a spike at the immunoglobulin (Ig) level." Mosby's at 326.

Ps' Ex. 5 at 9 (providing William's lab results). Dr. Mumper did not address whether the reference ranges used for William's test results were age-appropriate. Rather, it was her position that the provided test results were significant because they showed that William was "below the lower range of normal." Mead Tr. at 1269.

On January 28, 2001, Dr. Green collected an additional blood sample from William for additional testing by Metametrix Clinical Laboratory. See Mead Ps' Ex. 5 at 18-21. Among the tests performed was an amino acid analysis. See id. at 20. The test results showed that William's methionine level was within the reference limits for normal but was at the low end of the normal range.[216] Id. Dr. Mumper testified that this test result was evidence suggesting that William had a defect in his methylation pathway because methionine is an essential amino acid in the methylation pathway. Mead Tr. at 1273. Dr. Mumper also testified that this test result would be considered "supporting but not conclusive evidence" for Dr. Deth's "notion that [William was] undergoing oxidative stress[]." Id. at 1273-1274.

A blood sample taken from William on January 28, 2001 was analyzed for the presence of fatty acids in the blood plasma. See Mead Ps' Ex. 5 at 19. Dr. Mumper testified that the test results show "a pattern of a number of low essential fatty acids" that have "crucial roles in fighting inflammation." Mead Tr. at 1274. When asked about the significance of this test result, Dr. Mumper responded that she has a "concern" that "this generation of children" tends to have "very low" levels of essential fatty acids in their blood plasma. Id. at 1275. Expounding on her belief that low levels of essential fatty acids deprive children with regressive autism of an "inherent natural mechanism[] to treat inflammation," she testified that she feels that the children "deserve every benefit to have any anti-inflammatory interventions," through supplements, because it is both her belief and petitioners' theory that the children's regressive autism is causally-related to their thimerosal-containing received vaccines and a "chronic ongoing neuroinflammation" such as Dr. Kinsbourne described. See id. at 1275.

In October 2002, another blood sample taken from William was tested for evidence of blood clotting abnormalities. See Mead Tr. at 1278; Mead Ps' Ex. 15 at 105 (stating that William's blood work was subjected to an ISAC panel). Notes in William's medical records indicate that the test was ordered in error. Mead Ps' Ex. 15 at 105. Dr. Mumper stated that the test was neither "diagnostic of thimerosal toxicity" nor strongly correlated to her opinion that thimerosal-containing vaccines contributed to William's injuries. Mead

[216] The reference range was from 20 to 60 μmol/L, and William's methionine level was 22 μmol/L. Mead Ps' Ex. 5 at 20.

Tr. at 1278-1279. But, she asserted that the test results provided "another example of an aspect of [William's] body biochemistry that was out of whack." Mead Tr. at 1278.

In February 2001, William also had mercury hair testing performed by [lab name redacted] that reported high mercury levels as well as elevated levels of other metals. Mead Ps' Ex. 5 at 44. Respondent's expert toxicologist Dr. Brent challenged the validity of the performed hair tests, stating:

> I will tell you that I probably get two patients a month referred to me by their primary care physicians because the person went and got a hair test [at] [lab name redacted]. They almost always come back with very high levels of all kinds of things on it, and nobody ever knows how to interpret it, and I interpret it.
>
> I end up having to see these patients and am ultimately able to demonstrate that none of this has any validity when we do the appropriate testing . . . . Here you see this test of William Mead. If you take this test at face value, what does it tell us? It tells us that William Mead has elevated levels of aluminum, antimony, arsenic, bismuth, titanium and molybdenum in his hair.
>
> There is no reasonable reason why anybody would have these kinds of hair levels, these kinds of elevated hair levels.

Mead Tr. at 1854-1855. During Dr. Mumper's cross-examination, respondent presented a letter from the New York State Department of Health denying requests made in 1986 and again in 1999 by [lab name redacted] "to perform multi-hair analysis on patient specimens collected in New York State" based primarily on concerns about external specimen contamination and the lack of good reference values for specimen analysis. Id. at 1564; Mead R's Trial Ex. 2 at 1-2. Respondent also introduced a letter correspondence from the New York State Department of Health to [lab name redacted], including a 2006 survey report prepared by the state's health department criticizing the laboratory for failing to have a "system to monitor the technical competency of the assays." Mead Tr. at 1567; see also Mead R's Trial Ex. 3. Dr. Mumper acknowledged that, without knowing what the standards are for labs to undertake corrective measures, she found the evidence about [this lab] "very concerning." Mead Tr. at 1568. She further acknowledged that the laboratories that provide the type of testing on which petitioners rely in this case have received "a lot of criticism" for reporting unreliable test results (or "values"). Id. at 1352.

Dr. Mumper testified that those criticisms have prompted her to participate in a project to evaluate the reliability of those laboratories.[217] See id. at 1352-1354.

Dr. Mumper testified that the most compelling evidence informing her opinion of vaccine-related causation in William's case "was the demonstration that with chelating agents William was able to mobilize and excrete large amounts of mercury in his urine." Mead Tr. at 1295. Dr. Mumper added that the evidence on which she relied pertaining to William's "nutrient status, his zinc status, [and] his amino acids . . . [was] consistent with the idea that he was under nutritional deficiencies and oxidative stress, and . . . [was] consistent with but not diagnostic of anything related to mercury per se." Id. at 1296.

William's father testified that the laboratory testing performed after January of 2001 first identified mercury as a problem for William and caused the Meads to believe that thimerosal-containing vaccines were responsible for William's autism. See id. at 986. Later discovering that, at two and one-half years old, William had mercury levels that were "seven times the reference range," the Meads' "first order of business became . . . getting the mercury out." Id. at 986-987. After undertaking efforts to address the problems reported in the laboratory test results, the Meads filed this petition on William's behalf seeking compensation under the Vaccine Program.

The undersigned turns now to evaluate petitioners' claim under the Althen standard articulated by the Federal Circuit.

IV. Evaluating Petitioners' Claim Regarding the Role of Thimerosal-Containing Vaccines in the Development of Autism Spectrum Disorders under the Althen Standard

Althen requires that petitioners prove by preponderant evidence: (1) "a medical theory" that causally connects the vaccination and the injury; (2) "a logical sequence of cause and effect" that shows that the vaccinations were the "reason" for the injury; and (3) evidence of "a proximate temporal relationship" between the vaccination and the injury. Althen, 418 F.3d at 1278. The undersigned addresses each of the Althen prongs in turn.

[217] Based on acquired knowledge of problems with the laboratory work performed by the Great Smokies Diagnostic Laboratory, Dr. Mumper also admitted her own reluctance to rely on test results produced by that lab. See Mead Tr. at 1532-1533. Hair, stool, and urine samples taken from William were sent there for analysis. See Mead Ps' Ex. 5 at 16-17, 36; Mead Ps' Ex. 15 at 73-78, 87-88, 94-96, 104.

A. The Proposed Medical Theory

Petitioners' medical theory contemplates that the thimerosal component of the received childhood vaccines dissociates into the organomercurial ethylmercury once in the body. That ethylmercury then courses through the blood stream to diffuse across the blood-brain barrier to reach the brain. In the brain, the ethylmercury is de-ethylated to become inorganic mercury–a form of mercury that is not quickly removed from the brain–and once deposited, provokes a series of detrimental responses that ultimately manifest as autism.

Important to the evaluation of petitioners' theory is an understanding that, as the filed scientific literature informs and the parties' experts agree, the toxicological effects of mercury are determined by a number of variables including the type of mercury to which one is exposed, the exposure dose, and the duration of exposure.

In the first two years of life, children who received a full complement of the prescribed pediatric vaccines–prior to the recommended removal of thimerosal–are estimated to have received a cumulative dose of up to 237.5 μg (micrograms) of ethylmercury from the administered vaccines.

The half-life of ethylmercury in blood is less than two weeks. It is much shorter than the half-life of methylmercury, the organomercurial that is the chief source of human exposure to mercury (through fish consumption). Because ethylmercury has a shorter half-life, less ethylmercury–as compared to methylmercury–is available in the blood to reach the brain and to penetrate the blood-brain barrier. Unlike methylmercury, the method by which ethylmercury can penetrate the brain is limited to diffusion only. Given the different methods available for the two organomercurials to reach the brain, ethylmercury is thought to enter the brain more slowly than methylmercury.

Once in the brain, ethylmercury converts more rapidly to inorganic mercury than does methylmercury. But over time, more inorganic mercury will be deposited in the brain from methylmercury exposures than from ethylmercury exposures (which include the ethylmercury derived from injected thimerosal-containing vaccines). Regardless of the source of mercury exposure, however, the deposited amounts of inorganic mercury in the brain are extremely small (measured in nanograms per gram or parts per billion) and contribute little to the background level of inorganic mercury measured in autopsied brains (also in the nanogram per gram or part per billion range).

It is well-understood that deposits of inorganic mercury in the brain are not eliminated quickly from the brain and can persist for a period of time. Because inorganic mercury does not move easily into or out of the brain, the chief source of the inorganic mercury deposited in the brain is more likely than not to come from the principal source of human mercury exposure or, more particularly, a diet that includes fish. In infants, the chief source of mercury exposure comes from their mothers prior to birth.

Pertinent to the consideration of petitioners' claim here are studies that indicate that at the same doses, the toxicity of methylmercury exceeds that of ethylmercury. The relative toxicity of the two organomercurials is significant because it is methylmercury that remains in the blood stream longer than ethylmercury (the organomercurial derived from thimerosal-containing vaccines), enters the brain more quickly than ethylmercury and once in the brain, converts more slowly to inorganic mercury than does ethylmercury.

Studies–that include the filed 2006 Clarkson article–show that the characteristics of mercury toxicity (whether from ethylmercury, methylmercury, or inorganic mercury) typically involve, among other symptoms, some loss of motor control. The loss of motor control, however, is not one of the characteristic behavioral, communication, and social impairments that define autism. Although petitioners have introduced documentary and testimonial evidence concerning the effects of mercury toxicity, petitioners assert that their theory here does not focus directly on the toxic effects and symptomatic presentation of mercury poisoning, an acute medical condition that bears no clinical resemblance to the neurodevelopmental disorder of autism. Rather, petitioners contend, the focus of their theory is on the subcellular effects of a chronic, low-dose presence of inorganic mercury in the brain.

Close review, however, of the presented scientific articles–particularly the 2005 Burbacher study–on which petitioners relied most heavily reveals that the articles do not support the claim that a chronic, low-dose presence of inorganic mercury in the brain can cause the neurotoxic effects that petitioners' experts described. The low-dose exposures considered in the filed scientific articles are indisputably lower than the doses considered in those scientific articles that have examined the effects of the high-dose mercury exposures that were attributable to sources of either accidental contamination, industrial environments, or occupational hazards. Nonetheless, the low-dose exposures referenced in the filed articles still exceeded the exposure dosages attributable to thimerosal-containing vaccines, by at least an order of magnitude (or one power of 10), to ensure that the amount of administered mercury in the various studies had surpassed the detection threshold (that is, the level at which the effects, if any, of mercury exposure become detectable by the available tools for measurement). Because the toxic effects of mercury exposure are known to be dose-dependent and because the filed scientific articles

addressed certain conditions that were observed after reportedly low-dose mercury exposures that were still appreciably greater than the mercury exposure dosage attributable to received thimerosal-containing vaccines, the evidentiary support provided by those articles is necessarily limited.

Petitioners also failed to present scientifically reliable evidence showing that either a genetically hypersusceptible population to mercury exposures exists or a mercury efflux disorder exists. The scientific soundness of the studies on which petitioners relied in support of these propositions was questionable.

With the testimony of Dr. Deth, petitioners posited that the chronic presence of inorganic mercury disrupts the proper functioning of three particular chemical pathways in the brain and leads to certain neuroinflammatory conditions that have been observed in the autopsied brains of autistic individuals. Pointing out that astrocytes are the neuroglial cells that generate the antioxidant glutathione for use by neuronal cells–the cells that are responsible for transmitting communication signals within the brain and beyond–Dr. Deth explained that glutathione is an important resource for stemming the oxidation process (that results from unpaired and thus unstable electrons seeking a partner) and avoiding the consequences associated with an overly oxidated state.

Dr. Deth testified that glutathione is generated by a series of chemical reactions that occur along the chemical pathway known as the transsulfuration pathway. One of the sulfur-containing amino acids involved in the process of transsulfuration, specifically homocysteine, is also involved in another chemical process known as the methionine methylation cycle, a cycle that is involved in determining gene expression during the early stage of development. Dr. Deth also testified that the methionine methylation cycle has a functional impact on another methylation cycle, specifically the cycle that affects the D-4 dopamine receptor that is important in the neurotransmission of inhibitory signals.

Relying heavily on the 2005 James article for the proposition that thimerosal can cause a significant reduction in the glutathione level in neuronal cells, Dr. Deth asserted that a mercury-induced disruption of cellular glutathione levels would require the transsulfuration pathway to generate more glutathione. He posited that the increased demand for the transsulfuration pathway to function would disrupt the proper functioning of the methionine methylation pathway and, in turn, the methylation pathway affecting the D-4 dopamine receptor. Relying further on the 2006 James article for the proposition that autistic children are genetically susceptible to disruptions in their sulfur metabolism that impair their ability to generate glutathione, Dr. Deth reasoned that the receipt of thimerosal-containing vaccines could cause subcellular effects. The subcellular effects of particular interest to Dr. Deth included a demand for the generation of more glutathione

that adversely affected the chemical processes specifically involved in gene expression during early development (the methionine methylation cycle) and the transmission of inhibitory signaling within the brain (the methylation cycle pertaining to the D-4 dopamine receptor).

Dr. Deth postulated that the receipt of thimerosal-containing vaccines effectively provoked the need to generate more glutathione in the brain, the functional consequence of which was inappropriate gene expression during the early development of autistic children and impaired inhibitory signaling (an impairment that would exacerbate the mercury-induced excitatory condition in the brain that Dr. Kinsbourne addressed in his testimony). Dr. Deth explained that these molecular disturbances cause autism and its major symptoms, and he conceded that his theory was not limited to regressive autism. The proposed mechanism of harm, however, is scientifically untenable.

In support of his theory but in contravention of sound scientific practice, Dr. Deth extrapolated findings of studies conducted in artificial scientific environments to apply directly to processes that occur in human bodies. Dr. Deth also relied heavily on his own unpublished laboratory findings that were unprecedented and scientifically dubious.

In addition, as Dr. Deth himself acknowledged at hearing, glutathione is abundantly available in the body. Because the supply of glutathione is a rich one and because the body is equipped with numerous compensatory processes for coping with oxidative stress, there is very little likelihood that the amount of mercury contained in thimerosal-containing vaccines has any detectable inhibitory effect on sulfur metabolism. The aspect of petitioners' proposed medical theory that Dr. Deth addressed was not scientifically sound.

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Through the testimony of petitioners' expert Dr. Kinsbourne, petitioners asserted that the inorganic mercury deposited in the brain after receipt of thimerosal-containing vaccines created a chronic condition that triggered an immune response by the microglia–that is, the neuroglial cells tasked with the job of killing and digesting (or phagocytizing) unrecognized substances in the brain. Dr. Kinsbourne hypothesized that the provoked microglial activation leads to neuroinflammation and a chronic state of overexcitation in the brain that symptomatically manifests as autism. Dr. Kinsbourne's proposal is, however, scientifically unsupportable. The process that he contemplates–specifically, one that causes chronic cell dysfunction without inducing either progressive disease or cell death–is contrary to established scientific understanding and cannot be maintained biologically. Moreover, the proposed theory of excitotoxicity does not explain adequately the spectrum of autistic behavior.

The underpinnings for the opinions of petitioners' experts are scientifically flawed, and in the absence of a sound basis for the offered opinions of causation, those opinions cannot be credited. See Perreira v. Sec'y of Health and Human Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) ("An expert opinion is no better than the soundness of the reasons supporting it.") (internal citations omitted). Having carefully considered the evidence presented, the undersigned finds that petitioners have failed to establish, by preponderant evidence, the pertinent aspects of their theory about the administration of thimerosal-containing vaccines to certain children. Based on the developed record in this proceeding, the undersigned is unpersuaded that the thimerosal content of the prescribed childhood vaccines contributes to the development of autism as petitioners have proposed under this theory of general causation.

The undersigned finds that petitioners have failed to meet their burden of proof under the first prong of the Althen standard.

B. The Sequence of Cause and Effect

Petitioners contend that William's medical history and laboratory test results are consistent with the theory of causation that they have proposed. The laboratory tests results, however, do not show what petitioners purport they show. Samples of William's blood were initially examined at least twice for mercury levels that petitioners assert were found to be high–almost one year after the receipt of his last thimerosal-containing vaccines.[218] But, tests of mercury blood levels can be evaluated usefully only during a short period of time following the last mercury exposure of interest (due to the short half-life of organic mercury in blood). Once beyond that time frame, the most reliable method for assessing the severity of a body's mercury burden is to examine unprovoked (or non-chelated) urine specimens for mercury excretion levels.

Samples of William's blood also were examined for alleged nutritional deficiencies that petitioners identified as problematic for William. On questioning, however, petitioners' expert Dr. Mumper, a pediatrician, acknowledged that the tests to evaluate William's nutritional deficiencies were not diagnostic of either mercury toxicity or an

[218] William's initial blood mercury testing occurred in the first instance in January 2001, more than two years after his seven-month well-baby visit on December 3, 1998. See Mead Ps' Ex. 1 at 12. William received three thimerosal-containing vaccines at his seven-month well-baby visit, and by that time, he had received most of the thimerosal-containing vaccines that he would receive during the first two years of his life. See id. at 3, 12. William then received two more thimerosal-containing vaccines on April 12, 2000, one month before his second birthday. See id. at 3.

innate metabolic dysfunction–two conditions that could be evaluated through scientifically valid testing. Rather, Dr. Mumper asserted that the tests showed that William's problems were consistent with the impaired methylation process that Dr. Deth had described and the mercury-induced state of oxidative stress that both Drs. Deth and Kinsbourne addressed in their testimony. Both proposed mechanisms for causing autism, however, were critically flawed.

In addition, petitioners asserted that the results of William's urine tests showed that he had difficulty excreting mercury notwithstanding evidence that the mercury excretion levels measured in William's urine samples, when taken in the absence of chelation treatments, were entirely normal. Dr. Mumper maintained that normal mercury excretion levels obtained without chelation provided evidence that William was unable to excrete mercury properly even though the scientifically valid method of assessing mercury toxicity is to test non-chelated urine samples for mercury excretion. Dr. Mumper insisted that the results of William's urine tests after chelation were a more accurate indication of his mercury body burden and his mercury efflux disorder even though she acknowledged that there were no established reference ranges for the testing of provoked urine specimens. See Dwyer Tr. at 201.

Because the laboratory tests on which petitioners rely here include urine tests that were performed on a specimen sample type other than the type for which the tests were designed (that is, chelated urine samples rather than non-chelated urine samples) and blood tests which appeared to employ reference ranges that were not adjusted for William's age, the results of the performed tests are of questionable reliability and relevance. Further compromising the reliability of William's laboratory test results are the dubious practices of the laboratories that performed the testing and that triggered a measure of concern by petitioners' own expert, Dr. Mumper. Petitioners' assertion that these specious laboratory test results are evidence that is consistent with and supportive of the opinions given by Drs. Deth and Kinsbourne is unavailing. On the presented record, the undersigned does not find petitioners' causation theory to be medically supported or scientifically tenable. Efforts to bolster the fallacious medical theory with flawed test results of questionable reliability demonstrates the circularity of petitioners' theory and underscores the infirmity of the scientific basis for the offered theory. Without a sound scientific basis, the opinions of petitioners' experts cannot be credited, and petitioners' reliance on unreliable laboratory test results to support unreliable theories of causation cannot be sustained. See Perreira, 33 F.3d at 1377 n.6 (noting that the soundness of the reasons supporting an expert's opinion determine the soundness of the offered opinion).

Because petitioners have failed to present scientifically reliable evidence to support the different aspects of their second general causation theory concerning the role of

thimerosal-containing vaccines in the development of autism, their proposed sequence of cause and effect for William Mead lacks the requisite evidentiary support. In the absence of either scientifically or medically reliable evidentiary support for the respective components of petitioners' theory, the undersigned cannot find that the overall proposed sequence of a vaccine-related cause and effect between thimerosal-containing vaccines and the development of autism is either sound or logical in William's case.

The undersigned finds that petitioners have failed to meet their burden under the second prong of the Althen standard.

C. The Temporal Association

The presented evidence establishes that the thimerosal component of the administered childhood vaccines dissociates into the mercury form of ethylmercury upon injection into the vaccinee. The presented evidence further establishes that ethylmercury has a half-life of less than two weeks in the blood. Due to the short half-life of ethylmercury in the blood, it is rapidly eliminated from the body after vaccine injection. Also due to the short half-life of ethylmercury in the blood, less mercury–than is derived from the dissociation of thimerosal-containing vaccines at the time of vaccine injection–is ultimately available to reach the brain, to penetrate the blood-brain barrier, and to produce the neurological effects that petitioners have asserted.

Petitioners contend that the small amount of ethylmercury attributable to received thimerosal-containing vaccines that does breach the blood-brain barrier and is de-ethylated to become inorganic mercury is able to remain in the brain for a period of time and cause harm that manifests as autism. Although petitioners posit that this harm can occur in certain genetically susceptible children, petitioners could not identify the window of neurodevelopmental vulnerability during which administered thimerosal-containing vaccines would enhance the potential for the development of autism. Moreover, although petitioners assert that the deposition of inorganic mercury in the brain causes neuroinflammation that has adverse–but not fatal–cellular effects that produce symptoms of autism, petitioners could not identify the period of time between the deposition of inorganic mercury in the brain and the start of the neuroinflammatory process that was critical to their proposed mechanism of biological harm. See Mead Tr. at 896-897 (Dr. Kinsbourne stating that he did not believe "a fixed time is known" regarding the period of time between inorganic mercury deposition in the brain and the onset of neuroinflammation, but that he would expect the brain to "react" to an invasive agent "within a short time" and speculating that such a short time could range from days or a few weeks but less than three years).

Notably absent from petitioners' proposed theory of vaccine-related causation is evidence of a temporal linkage between the administered vaccines and the produced harm in William. Petitioners' theory of causation relies instead on evidence that symptoms of autism with regression first appeared after the administration of a full complement of thimerosal-containing vaccines. Without more, petitioners have not shown that the appearance of William's autistic symptoms occurred within a medically acceptable time frame to support a finding that the administered vaccines were causally related to his symptom onset.

The undersigned finds that petitioners have failed to meet their burden under the third prong of the Althen standard.

V. Conclusion

Autism is a neurodevelopmental disorder–characterized by impairments in the areas of social interaction, communication, and behavior–that typically appears before the age of three years. The disorder is described as autism with regression or regressive autism when the disorder becomes recognizable in a child following an apparent loss of previously acquired skills–often occurring sometime between the ages of 18 and 24 months. Petitioners here allege that the mercury component in thimerosal-containing vaccines can lead to the development of autistic spectrum disorder, with features of regression, in a group of genetically susceptible children.

Support for petitioners' claim does not come from the epidemiologic evidence, and petitioners' claim that the performed studies lack the requisite specificity to detect an association between the receipt of thimerosal-containing vaccines and the allegedly small subset of cases involving autism with clear signs of regression is unavailing.

Petitioners have failed to establish that autism with regressive features exists as a distinct phenotype of autism. To the contrary, studies indicate that regression is common in autistic children–following a predictable but not uniform pattern of acquisition and loss of skills. Studies also indicate that there is a continuum of the presentations of regression that range from subtle to striking, and due to that continuum of presentations, a determination of when the first signs of regression appeared can be difficult.

Petitioners have not shown either that certain children are genetically hypersusceptible to mercury or that certain children are predisposed to have difficulty excreting mercury. The scientific validity of the studies on which petitioners rely has been questioned and the conclusions drawn from the studies have been criticized as unsupported. While differences that reflect the range of naturally-occurring individual

variability are known to exist with respect to the responses of individuals to mercury exposure, these differences do not point toward the existence of a hypersusceptible population.

While petitioners have alleged correctly that inorganic mercury can remain in the brain for a period of time, petitioners have not shown that the inorganic mercury deposited in the brain–in the amount that could be received from a full complement of thimerosal-containing vaccines–can cause the effects that petitioners have alleged. Inorganic mercury is not the form of mercury understood to be most toxic in the doses involved in childhood vaccines, and a normal fish-eating diet by pregnant mothers produces a greater source of inorganic mercury for deposition in the brain than thimerosal-containing vaccines do. Moreover, the metabolic processes and complex compensatory systems in the body are sufficiently robust to address the cellular effects of inorganic mercury deposits in the brain. The mechanism of chronic cellular dysfunction that petitioners have hypothesized cannot be maintained without inducing progressive neurodegenerative disease that leads to death, and autism is not a progressive neurodegenerative disease.

Petitioners' theory of vaccine-related causation is scientifically unsupportable. In the absence of a sound medical theory causally connecting William's received vaccines to his autistic condition, the undersigned cannot find the proposed sequence of cause and effect to be logical or temporally appropriate. Having failed to satisfy their burden of proof under the articulated legal standard, petitioners cannot prevail on their claim of vaccine-related causation. Petitioners' claim is dismissed, and the Clerk of the Court **SHALL ENTER JUDGMENT** accordingly.[219]

IT IS SO ORDERED.

s/Patricia Campbell-Smith
Patricia Campbell-Smith
Special Master

[219] Pursuant to Vaccine Rule 11(a), entry of judgment is expedited by the parties' joint filing of a notice renouncing the right to seek review.

TABLE OF CONTENTS

1. Petitioners' Claim that the Accumulation of Inorganic Mercury in the Brain Leads to Neuroinflammation
2. Petitioners' Claim that Inorganic Mercury Deposits in the Brain Cause Subcellular Effects that Disrupt Sulfur Metabolism and Lead to Improper Brain Function
    a. The Bond Between Mercury and Thiols
    b. The Role of Neuroglial Cells in Supporting Proper Brain Function
    c. Disruptions in Certain Methylation Processes that Petitioners Claim Cause an Adverse Skewing of the Oxidative Environment
        (1) Creating a State of Oxidation
        (2) Sufficient Glutathione Needed to Support Certain Cellular Processes and Manage the Oxidative Environment in the Brain
        (3) Impaired Methylation Processes have been Detected in Autistic Children with Oxidative Stress
        (4) The Flaws Identified in Petitioners' Claim that Impaired Methylation Processes and Oxidative Stress Result from Mercury-Induced Inhibition of the Cellular Activity Needed to Generate Glutathione and that These Functional Disturbances Can Lead to the Appearance of Autism in Certain Children
            a) The Conclusions Reached in the Scientific Articles on which Petitioners Relied were More Limited than Petitioners have Asserted
            b) Dr. Deth's Own Research that Purports to Support Petitioners' Claim is of Questionable Reliability
            c) Dr. Deth's Testimony in Furtherance of Petitioners' Claim was not Consistent with What is Scientifically Known about the Mechanisms He Described
            d) Summary of Findings
        (5) Petitioners' Further Claim that Mercury-Induced Microglial Activation Causes an Excitotoxic Brain Injury that Leads to a Functionally