In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
E-Filed: February 12, 2009
No. 03-654V

ROLF and ANGELA HAZLEHURST, parents of WILLIAM YATES HAZLEHURST,	)	Omnibus Autism Proceeding; Test Case; Petitioners' First Theory of General Causation; Failure to Prove that the Combination of MMR and Thimerosal-Containing Vaccines Causes Autism
Petitioners,	)	
v.	)	
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	)	**TO BE PUBLISHED**
Respondent.	)	

Curtis R. Webb, Twin Falls, ID, for petitioners.

Linda Renzi, 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 to the parties prior to the public disclosure of an issued decision. In a 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 11/12/08. Petitioners add that the prompt public disclosure of an opinion based on information that they have furnished in this case "would not be an invasion of Yates Hazlehurst's privacy." Id. at 1-2. 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. at 2. Without private information necessitating protection and willing to facilitate the public disclosure of the issued decision, petitioners waive the prescribed time period within which to seek any redaction of the decision.

CAMPBELL-SMITH, Special Master

On March 26, 2003, Rolf and Angela Hazlehurst (petitioners or the Hazlehursts),[2] as parents of William Yates Hazlehurst (Yates) filed a short-form petition[3] pursuant to the National Vaccine Injury Compensation Program[4] (the Act or the Program), 42 U.S.C. § 300aa-10, et seq. Petitioners filed an amended petition on June 13, 2007, alleging that "[t]he MMR [(measles, mumps, rubella)][5] vaccination that Yates Hazlehurst received o[n] February 8, 2001, or a combination of the MMR vaccination and the Thimerosal containing vaccinations that he received during the first 12 months [of life], caused Yates Hazlehurst to develop [regressive] autism." Amended Petition (Am. Pet.) ¶ 5 (footnote added); see also id. at ¶ 8 (specifically alleging that "[b]y Summer 2001, his speech skills had begun to regress"). Petitioners also consented to the public disclosure of their claim as the second test case on the first theory of causation addressed in the Omnibus Autism Proceeding.[6] See Petitioners' Status Report dated July 26, 2007.

For the reasons discussed more fully in this decision, the undersigned finds that

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Respondent also elected to waive the period of time afforded under the Vaccine Rules for seeking any redaction of the issued decision. See Respondent's Consent to Disclosure at 1, filed on 1/30/09.

[2] On October 12, 2007, the undersigned granted petitioners' motion of the same date to amend the caption of the case to reflect the proper spelling of the petitioners' last name. All quotations in this decision spell petitioners' surname correctly, regardless of any error in the underlying document. Any alteration in the spelling of petitioners' surname is made without notation.

[3] 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 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 history of [the] vaccinee's disorder." Id. In addition, the vaccinee's medical records would not be required to accompany the petition. Id.

[4] 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 (2000).

[5] 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.

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

petitioners are not entitled to Program compensation on either the proposed general theory of causation or the specific theory of causation proposed in this case.[7]

I. Procedural Background

This case is one of three test cases heard in the Omnibus Autism Proceeding (OAP) addressing a theory of general causation advanced by petitioners. This theory involves the claim that thimerosal-containing vaccines in combination with the MMR vaccine can cause autism in children who have received these vaccinations. Before further considering petitioners' theory of general causation, the undersigned briefly describes the proceeding referred to as the OAP.

A. The Omnibus Autism Proceeding[8]

Vaccine Rule 3(b) tasks a special master with responsibility "for conducting all proceedings, including requiring such evidence as may be appropriate, in order to prepare a decision, including findings of fact and conclusions of law, determining whether an award of compensation should be made under the Vaccine Act and the amount of any such award." Rules of the Court of Federal Claims (RCFC), Appendix (App.) B, Vaccine Rule 3(b). The Rule permits a special master to "determine the nature of the proceedings" that are conducted. Id. Additionally, the Rule counsels that when determining how to conduct Vaccine proceedings, a special master shall consider "making 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." Id.

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 3000 to 5000 petitions alleging that certain administered childhood vaccinations were causing "injuries resulting in autism

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[7] As observed by one of respondent's expert witnesses, the terms "hypothesis," "postulate," and theory (or "theoretical") may be used interchangeably in the medical literature. See Cedillo Tr. at 1730-1731A (Dr. Wiznitzer). Dr. Wiznitzer explained that as used by scientists, a "hypothesis" is an idea proffered to explain the "evidence that they have." See id. at 1632, 1731A-1733. The evidence does not support the hypothesis; rather it is explained by the hypothesis. Id. at 1732-1733. The terms are used differently in the Vaccine Program.

[8] 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 2/1/09). The docket of OAP master file, 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.

spectrum disorder[s] or similar neurodevelopmental disorder[s]" in children. See Autism General Order #1 at 1-2. The OAP is the coordinated proceeding addressing the numerous filed petitions seeking compensation for the alleged vaccine-related autistic disorders. 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 Hastings, for consideration. The procedure adopted to address the OAP claims contemplated the conduct of a two-phase proceeding. The first phase of the proceeding would inquire into the general causation question of whether certain vaccinations can cause autism and, if so, under what circumstances. The second phase of the proceeding would involve applying the information acquired during the first phase of the proceeding to decide the specific causation question of whether the received vaccinations did cause the autistic condition alleged in each of the individual cases.

At the request of petitioners' counsel, through a designated Petitioners' Steering Committee (PSC), 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 information from various federal agencies, including the Food and Drug Administration (FDA), the Centers for Disease Control (CDC), and the Agency for Toxic Substances and Disease Registry (ATSDR). See 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 requests were obtained and were filed in the case of Taylor v. Secretary of Department of Health and Human Services, No. 02-699V. Id. At the request of the PSC, respondent made officials at the FDA, CDC, and ATSDR available for depositions. Id.

Subsequently, the PSC expressed an interest in seeking discovery from vaccine manufacturers, including Merck and Company. Id. The PSC requested authorization to issue a subpoena to Merck for "certain documents pertaining to that company's vaccine against the disease hepatitis type B, known as 'Recombivax.'" Id. The PSC subsequently withdrew that request, reserving the right to reinstate its request, and requested instead documents from Merck pertaining to its MMR and measles vaccine. Id. at 5. The PSC further narrowed its discovery request of Merck to: (1) documents relating to product safety research on the "neurological or neurodevelopmental human . . . health effects of the MMR or the single-antigen measles component thereof;"[9] and (2) materials created for,

[9] The requested product safety research included "[a]ny research, survey, study, test or other investigation, whether published or not, conducted by Merck or any of its subdivisions or predecessor corporations, or any entity employed by Merck, under contract to Merck, or funded by Merck regarding the human . . . health effects [including the neurological or neurodevelopmental human health effects] of the MMR or the single-antigen measles component" of the vaccine. Ruling Concerning Motion for Discovery

or produced in, litigation in the United Kingdom involving the MMR vaccine and its alleged link to gastrointestinal disease and autism spectrum disorders.[10] See id. at 5-6. For the detailed reasons set forth in the Ruling Concerning Motion for Discovery from Merck, dated July 16, 2004, at 6-22, the special master denied the request of the PSC for authorization to subpoena documents from Merck.

After the afforded time period for discovery and as part of the first phase of the OAP proceedings, which involved 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, filed July 18, 2006, at 2-4. The three general causation theories to be presented in the OAP 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. Refining its initial proposal, the PSC recommended conducting a hearing in one 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 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 Vowell and the undersigned, to hear and 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 designation of two additional 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 Regarding Reassignment, dated January 11, 2007, at 2.

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from Merck, dated July 16, 2004, at 5. The requested product safety research also included "[a]ny research, survey, study, test or other investigation, whether published or not, that was not conducted by Merck . . . but that Merck was aware of, regarding the neurological or neurodevelopmental human . . . health effects of the MMR or the single-antigen measles component" of the vaccine. Id.

[10] This request pertains to documents produced by Merck in litigation in the United Kingdom in which a number of families with autistic children filed suit against various vaccine manufacturers, including Merck, alleging that the children's MMR vaccinations caused their autistic disorders. See Ruling Concerning Motion for Discovery from Merck Re: MMR Vaccine, dated July 16, 2004, at 19. Eight lawsuits were designated as lead cases to be heard during a consolidated trial. Id. Both sides in the litigation, namely the families and the vaccine manufacturers, prepared written expert reports. Id. Petitioners in the OAP, through the Petitioners' Steering Committee, requested authorization to subpoena Merck to produce all of the documents that Merck produced in the United Kingdom litigation in response to the discovery requests of the plaintiffs and copies of all expert reports, summaries, witness statements and depositions prepared on Merck's behalf in that litigation. Id.

B. The Presentation of Petitioners' First Theory of General Causation

Consistent with the January 2007 Notice Regarding Reassignment, each of the three special masters assigned to hear the autism cases has one test case in which petitioners have asserted the first general causation theory. Separate hearings have been conducted in each of the three test cases for the first general causation theory. During each trial, the parties presented general causation evidence on the issue of whether thimerosal-containing vaccines in combination with the MMR vaccine could cause autism. Also during each trial, the parties presented specific causation evidence regarding whether the administered vaccines of interest had caused the autistic condition of the vaccinated child whose particular case was being heard. In each case, the special master to whom the particular test case has been assigned bears the sole responsibility for deciding that particular case.

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. The undersigned heard the general causation evidence presented during that hearing.

The undersigned conducted the hearing in this case, the second test case, in Charlotte, North Carolina, on October 15-18, 2007. The undersigned heard both general causation and specific causation evidence during that proceeding.

The third test case, Snyder v. the Secretary of Health and Human Services, No. 01-162V, assigned to Special Master Vowell, was heard in Orlando, Florida, on November 5-9, 2007. The undersigned heard the general causation evidence presented during that hearing.

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 each of the three test cases. Many of the experts who submitted written opinions also testified during the hearings. To ensure that the developed 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 literature, the general causation expert opinions, and the corrected hearing transcripts[11] from the other two test cases for consideration by the special master in deciding the general causation issue of whether thimerosal-containing vaccines and the MMR vaccine, in combination, can cause autism. These filings also inform the decisions of the special masters with respect to the specific causation issues presented in each of the

[11] 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 about 3000 pages of transcript testimony from the three hearings. The transcript correction process was completed on June 11, 2008. 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.

three test cases on petitioners' first theory of causation. Moreover, the general causation evidence developed in the first three test cases is expected to be helpful in resolving the other autism cases awaiting decision.

C. The Record in this Case

The Hazlehursts have pursued this vaccine claim on Yates' behalf and have consented to have this case heard as a test case in the OAP. The undersigned recognizes that Yates and his family have been profoundly affected by his autistic condition. The undersigned also recognizes that the Hazlehursts are devoted parents, who like others that 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 one particular theory that purports to explain why Yates developed autism. It is extremely important, both for Yates and for all the other families involved in the OAP, that the undersigned analyze this specific theory in great detail. This analysis requires extensive discussion of matters that are clinical and scientific, even abstract. Regrettably, throughout the many pages of scientific discussion that are required, there may be an appearance of detachment from the highly personal specifics of Yates' medical history. But the appearance is not the reality. Ultimately, this is a decision about an individual child and an individual family. The undersigned has remained mindful that this vaccine claim is a personal one while analyzing the wealth of scientific literature and the numerous expert opinions. The undersigned addresses the specifics of Yates' case after the foundational analysis has been completed.

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 Yates Hazlehurst. Additionally, as stated earlier, the Hazlehursts have designated for consideration in this case the general causation evidence introduced in the two other test cases Cedillo and Snyder. See Orders dated September 18, 2007, December 20, 2007, and March 18, 2008. By Order dated February 4, 2009,[12] one compact disc (CD) containing the general causation evidence introduced in the Cedillo case, specifically containing the final corrected transcripts of twelve days of hearing testimony and the trial exhibits, the expert reports and the curricula vitae of the experts, and the filed medical and scientific literature, was filed into this case. Additionally, by Order dated February 4, 2009, [13] one CD containing the general causation evidence introduced in the Snyder case, specifically containing the final corrected transcripts of five days of hearing testimony and the trial exhibits, the expert reports and the curricula vitae of the experts, and the filed medical and scientific literature, was filed into this case.

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[12] This order authorizes the filing of a CD that supercedes the two CDs filed earlier by Order dated August 12, 2008.

[13] This order authorizes the filing of a CD that supercedes the CD filed earlier by Order dated December 20, 2007.

The combined number of medical literature exhibits filed into the record is 1085.[14] The combined number of filed expert reports filed into the record is 50.[15]

1. The Testifying Experts

To address the general causation issue of whether thimerosal-containing vaccines in combination with the MMR vaccine can cause autism, petitioners offered the opinions of 7 testifying expert witnesses. Respondent offered the opinions of 14 testifying expert witnesses.[16] For ease of reference later in the opinion, the undersigned addresses here the

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[14] This combined number reflects 658 medical literature exhibits filed in the Cedillo case, 156 medical literature exhibits filed in the Hazlehurst case (with some repetition of exhibits that were filed in the Cedillo case), and 271 medical literature exhibits filed in the Snyder case (with some repetition of exhibits that were filed in the Cedillo case).

Medical or scientific articles that were filed in more than one record location are cited to only one record location. Subsequent citations to that article in this decision will be to the earlier cited record location. Exhibits are referenced by the name of the test case into which the exhibit was filed and the exhibit designation given by the citing party. Additionally, consistent with the exhibit designation practice in the Vaccine Program, petitioners' exhibits are numbered and respondent's exhibits are lettered. See http://www.uscfc.uscourts.gov/sites/default/files/OSMGuidelines1104.pdf (Guidelines for Practice Under the National Vaccine Injury Compensation Program at 12). For example, an article designated as either an attachment or a tab to an expert report filed by petitioners' expert Dr. Aposhian in the Cedillo case will be cited as Cedillo Ex. 55H (2006 Clarkson article).

[15] This combined number reflects 23 expert reports filed in the Cedillo case (including two from Drs. Hepner, Kennedy, and Wiznitzer), 4 expert reports filed in the Hazlehurst case, and 23 expert reports filed in the Snyder case (including multiple reports filed by a number of the experts).

Expert reports are referenced by the name of the test case in which the expert report was filed and the exhibit designation given by the citing party. Petitioners' experts' exhibits are numbered, and respondent's experts' exhibits are lettered. See http://www.uscfc.uscourts.gov/sites/default/files/OSMGuidelines1104.pdf (Guidelines for Practice Under the National Vaccine Injury Compensation Program at 12). Citations to attachments to the expert reports reflect internal pagination to the cited document and not the pagination of the expert's report. Where the parties' experts agree on a matter, whether in their reports or in their testimony, the undersigned notes the agreement by using the signal "accord" in the citation.

[16] Respondent filed expert reports from four additional witnesses who did not testify during hearings. These experts included: (1) Robert Fujinami, Ph.D, an immunologist and microbiologist, (2) Michael Gershon, M.D., a neurogastroenterologist,

(continued...)

qualifications of the experts and her impressions of the experts as witnesses.

Petitioners' experts included: (1) Vasken Aposhian, Ph.D, a toxicologist; (2) Vera Byers, M.D., an immunologist; (3) Jean Ronel-Corbier, M.D., a neurologist; (4) Karin Hepner, Ph.D, a molecular biologist; (5) Ronald Kennedy, Ph.D, a microbiologist; (6) Marcel Kinsbourne, M.D., a pediatric neurologist; and (7) Arthur Krigsman, M.D., a gastroenterologist. The qualifications of the experts are addressed in turn.

Dr. Aposhian is a Professor of Molecular and Cellular Biology and a Professor of Pharmacology at the University of Arizona in Phoenix. Cedillo Tr. at 63 (Dr. Aposhian).

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[16](...continued)
(3) Peter Simmonds, Ph.D, a virologist, and (4) Andrew Zimmerman, M.D., a pediatric neurologist. See Cedillo Ex. S (Dr. Fujinami's curriculum vitae), Cedillo Ex. E (Dr. Gershon's curriculum vitae), Cedillo Ex. T (Dr. Gershon's report), Snyder Ex. P at 8 (Dr. Simmonds' 2003 report on MMR/MR Vaccine Allegations prepared for the litigation in the United Kingdom and submitted to the High Court of Justice, Queen's Bench Division, In the Matter of the MMR Litigation) (including a descriptive summary of Dr. Simmonds' credentials), and Cedillo Ex. GG (Dr. Zimmerman's curriculum vitae).

Dr. Fujinami, who devotes a "major part of [his] research" to "investigating the role [of] viruses . . . in triggering autoimmune disease," addressed the immunology concepts that informed his opinion that neither the MMR vaccine nor thimerosal-containing vaccines contribute to the development of autism. Cedillo Ex. R at 3, 8 (Dr. Fujinami's report).

Dr. Gershon opined, as a researcher responsible for the "seminal discoveries" that underlie the current understanding of the "function and development" of the enteric (pertaining to the small intestine) nervous system, that there is no scientifically "supportable evidence" that the MMR vaccine causes either inflammatory bowel disease or autism. Cedillo Ex. T at 2-3, 18-22 (Dr. Gershon's report).

Dr. Simmonds addressed the shortcomings of the PCR techniques of the Unigenetics laboratory and concluded that the obtained test results were unreliable. See Snyder Ex. P at 56-68 (Dr. Simmonds 2003 report on MMR/MR Vaccine Allegations prepared for the litigation in the United Kingdom).

As a pediatric neurologist with a particular research interest in autism and with considerable clinical experience with autistic children, Dr. Zimmerman opined that "there is no scientific basis for a connection" between the MMR vaccination, mercury intoxication, and autism. Cedillo Ex. FF at 2, 4 (Dr. Zimmerman's report).

The undersigned has reviewed and considered the filed reports from these experts and finds that the opinions of the experts lend support to the conclusions reached in this decision. In reaching the conclusions set forth in this decision, however, the undersigned relies more heavily on the testimony and reports of the experts who were observed and heard during the hearings.

He received his doctorate in physiological chemistry from the University of Rochester. Cedillo Ex. 55 at 1 (Dr. Aposhian's report). Dr. Aposhian "ha[s] published numerous research papers in international scientific journals dealing with [his] research on DNA, gene transfer, treatments for and [the] mechanisms of the toxicology of mercury, arsenic, lead, and other heavy metals." Id. His laboratory is still active in research "dealing with mercury and arsenic." Id. Dr. Aposhian testified that although he is not a medical doctor, he has a background in virology. Cedillo Tr. at 119. Describing himself as an environmental toxicologist, Dr. Aposhian explained that "[e]nvironmental toxicologists are interested in understanding how chemicals in the environment will affect the health of human beings." Cedillo Tr. at 63 (Dr. Aposhian). Dr. Aposhian testified during the Cedillo hearing. Although a qualified witness, the undersigned did not find Dr. Aposhian's testimony about the effects of mercury exposure from thimerosal-containing vaccinations as persuasive as the testimony given by respondent's experts, in particular Dr. Brent and Dr. McCabe, about the dose-dependent biological effects of mercury exposure.

Dr. Byers received from the University of California at Los Angeles an undergraduate degree in microbiology and then a master's degree in protein chemistry. Cedillo Tr. at 863. She subsequently received from the University of California at San Francisco a medical degree and a doctorate in basic immunology. Id. Although she describes herself as "board eligible" in allergy and immunology, that status is neither used nor recognized by the American Board of Allergy and Immunology. See id. at 956-958. Dr. Byers is board-certified, however, in internal medicine. Id. at 863. After medical school, she joined the faculty at the University of California at San Francisco in the Department of Medicine and then in the Department of Dermatology. Id. In addition to teaching, she has conducted research in the areas of tumor immunology and immunodermatology. See id. at 864. She also maintained a clinical practice in allergy and immunology, seeing both pediatric and adult patients, from 1981 until 1998. Id. at 869A. She testified that she currently splits her time between working as what she alternatively described as either a medical toxicologist or an environmental toxicologist for litigation consultation purposes and working as a consultant to biotech companies. Id. at 866-867, 964A, 981A-982. She explained that her formal training as a medical or environmental toxicologist came as a medical student and through years of "on-the-job[]training." Id. at 982; but see id. at 2311 (requirements for board certification as a medical toxicologist described by respondent's witness Dr. Brent). Dr. Byers testified during the Cedillo hearing. Dr. Byers' credibility as a witness was reduced during her cross-examination. In her testimony on cross-examination, she offered what appeared to be a significant limitation on or partial retraction of her earlier direct testimony about her opinion of causation. Her insistence during cross-examination that her opinions were limited to the specific factual circumstances of a particular case seemed inconsistent with the opinion she appeared to have offered on a more general fact pattern earlier in her testimony. Her demeanor and her apparent discomfort during the questioning on cross-examination about the important premises for her offered opinion diminished her credibility and persuasiveness as an expert in the view of the undersigned.

Dr. Corbier received his undergraduate degree in biology from Andrews University

in Berrien Springs, Michigan. Hazlehurst Ex. 27 at 1 (Dr. Corbier's curriculum vitae[17]). He received his medical degree in 1995 from Michigan State University. Id. After completing medical school, he sought additional training at the Mayo Clinic in Minneapolis, Minnesota and at John Hopkins University in Baltimore, Maryland. Hazlehurst Tr. at 424A-425A; Hazlehurst Ex. 27 at 1 (Dr. Corbier's curriculum vitae). He spent one month in each location. Hazlehurst Tr. at 425. Thereafter, he completed a two-year residency in pediatrics at the Hurley Medical Center in Flint, Michigan, a one-year fellowship in adult neurology at the University of Cincinnati in Ohio, and a two-year fellowship in pediatric neurology at the Children's Hospital Medical Center in Cincinnati, Ohio. Hazlehurst Tr. at 424A; Hazlehurst Ex. 27 at 1 (Dr. Corbier's curriculum vitae). He is a board-certified neurologist with a special qualification in child neurology. Hazlehurst Tr. at 266A; Hazlehurst Ex. 27 at 1 (Dr. Corbier's curriculum vitae). He has worked in private clinical practice for seven years, the first six of which in a solo practice. See Hazlehurst Tr. at 334A, 349A-350A; Hazlehurst Ex. 27 at 2 (Dr. Corbier's curriculum vitae) (indicating that he began working in private practice in 2001). Currently, he works full time as a clinical neurologist in Concord, North Carolina. Hazlehurst Tr. at 266A. He treats children "with all types of neurological ailments, including autism." Id. He has treated children with autism for several years. Id. Dr. Corbier testified during the Hazlehurst hearing. Dr. Corbier was a sincere witness but not a persuasive one in this case. In support of his causation theory, he relied heavily on scientific literature that is considered and addressed in Section III.B (examining the claim that thimerosal-containing vaccines contribute to the development of autism) and in Section III.C (examining the claim that the MMR vaccine contributes to the development of autism) of this decision. As discussed in those sections of the decision, the key articles upon which Dr. Corbier relied have been discredited by the scientific community because the conducted studies were unsound and unreliable. The unsound basis for Dr. Corbier's opinions diminished his effectiveness as a witness.

Dr. Hepner began working at a molecular diagnostics laboratory at New York Presbyterian Hospital-Weill Cornell Medical College after graduating from college in 1994. Cedillo Tr. at 583A. There she began working with laboratory tests, in particular the polymerase chain reaction (PCR) techniques, that are of interest in the OAP litigation. Id. She received her doctorate in molecular biology from the University of California in Los Angeles in 2003, four years before she testified in the OAP litigation. Id. at 636; see also Cedillo Ex. 64 (Dr. Hepner's curriculum vitae). Currently, she is working on a collaborative project with Dr. Steve Walker at Wake Forest University. Cedillo Tr. at 583A. The focus of the project is "looking at RNA measles virus protection in patient bowel biopsies." Id. Although she has not published on the subject of detecting measles virus through PCR, see id. at 637, she stated that she has over ten years of experience working with PCR-based techniques, id. at 584A. She testified during the Cedillo hearing. The undersigned found Dr. Hepner to be a qualified expert witness but found respondent's expert Dr. Bustin, who has more than twenty-five years of experience developing and using PCR techniques, to be far more persuasive on the subject of the reliability of

[17] The document is unnumbered. The page citation is to the first unnumbered page of the document following the cover page (denoted by a handwritten "27") of the exhibit.

particular test results obtained by Unigenetics, the laboratory purporting to have detected persisting measles virus in the gastrointestinal tissues of autistic children. Notably, Dr. Hepner's testimony was consistent with that of Dr. Bustin regarding the important aspects of laboratory practice that ensure the reliability of the obtained results from PCR testing.

Dr. Kennedy is a professor and the current chairman of the Department of Microbiology and Immunology at Texas Tech University Health Sciences Center in Lubbock. Cedillo Ex. 111 at 2 (Dr. Kennedy's curriculum vitae). Dr. Kennedy divides his time roughly equally between administrative duties, research, teaching and sitting on various scientific review panels for, among others, the National Institutes of Health, the Department of Defense, and the National Science Foundation. Cedillo Tr. at 685-686. He obtained from the University of Hawaii in Honolulu a doctorate in microbiology with a specialty in immunology, with a particular focus on the immunochemistry and immunogenetics aspects of immunology. Cedillo Tr. at 684. With more than 240 peer-reviewed published scientific articles, he has published on the topic of viral persistence. Id. at 687. Additionally, he has published one peer-reviewed article on the MMR vaccine. Id. at 748. He testified during the Cedillo and Snyder hearings. Dr. Kennedy was a well-qualified witness. Because his work with the measles virus has not been as extensive as the research work of respondent's experts, Dr. Griffin, Dr. Ward, and Dr. Rima, the undersigned found the testimony of respondent's witnesses to be more persuasive on the subject of vaccine-strain measles virus persistence.

Dr. Kinsbourne attended Oxford University Medical School in England and trained at Guy's Hospital in London. Cedillo Tr. at 1028A. After receiving the British equivalent of a medical degree, he pursued postgraduate training in pediatrics and in neurology. Id. at 1028A-1029. Dr. Kinsbourne explained that the period of training in England at that time was eleven years. Id. at 1029. After he completed his post-graduate training, he obtained a university lectureship in experimental psychology at Oxford University. Id. From his lectureship position, he moved to Duke University Medical Center where he served as chief of the Division of Pediatric Neurology and as an Associate Professor of Pediatrics and Neurology at Duke University Medical School. Id. After seven years at Duke University, he moved to the University of Toronto and the Hospital for Sick Children in Toronto, Canada, where he served as a Professor of Pediatric Neurology. Id. After six years at the University of Toronto, Dr. Kinsbourne received an appointment at the Eunice Kennedy Shriver Center, a research institute dedicated to the study of developmental disabilities and mental retardation located in Waltham, Massachusetts. Id. At the Eunice Kennedy Shriver Center, Dr. Kinsbourne served as chief of the Division of Behavioral Neurology. Id. at 1029-1030A. His responsibilities included securing federal funding for the institute's research efforts and examining children with attention deficit hyperactivity disorder and similar conditions who were study participants. Id. at 1030A. He stopped seeing patients regularly after 1991. Id. Although he has not maintained an active pediatric practice in nearly seventeen years, he has continued to write medical articles and chapters for neurology textbooks. See id. at 1030A-1031A, 1163A. In 1995, he accepted a full-time position as a Professor of Psychology at the New School for Social Research in New York, New York, teaching graduate students "how the brain works . . . particularly with respect to disorders of high mental function, of emotion, intellect, [and] memory." Id. at 1032A. Additionally, he reviews medical files for litigation in the vaccine program primarily, but he also serves as a medical consultant in "some civil litigation." Id. Dr.

Kinsbourne testified during the Cedillo and Snyder hearings. Although he was an unquestionably qualified witness, his testimony was unpersuasive. His opinion lacked reliable evidentiary support.

Dr. Krigsman is board certified in pediatrics and pediatric gastroenterology. Cedillo Tr. at 409-410. From 1995 until 2000, he was the Director of the Pediatric Gastroenterology Department at Beth Israel Hospital in New York. Id. at 410. He was recruited in 2000 by Lenox Hill Hospital in New York, New York, to perform all of the hospital's in-house gastroenterology consultations. Id. at 410-411. Lenox Hill Hospital instituted disciplinary action against Dr. Krigsman on the ground that he was performing medically unnecessary colonoscopies on autistic children. Id. at 499A-500. See Cedillo R's Trial Ex. 2 at 2 (Texas State Board of Medical Examiners, Licensure Committee Meeting Minutes, August 25, 2005, addressing the $5000 fine imposed on Dr. Krigsman (applicant #391), in part, due to the disciplinary action instituted by Lenox Hill Hospital). Dr. Krigsman subsequently became a member of a general pediatric practice in Woodbury, New York. Cedillo Tr. at 411. He was in practice there from 1997 through 2005. Id. Currently, he is in private practice with Pediatric Gastroenterology Resources in Lawrence, New York. Cedillo Ex. 60 at 3 (Dr. Krigsman's curriculum vitae). He is also the Director of Gastroenterology Services at Thoughtful House Center for Children in Austin, Texas. Cedillo Tr. at 491-492A. Listed among Dr. Krigsman's four publications on his curriculum vitae and relevant to the OAP litigation are two presentations to the International Meeting for Autism Research (IMFAR) addressing the increased presence of nodular tissue (known as lymphonodular hyperplasia) in the intestinal systems of autistic children. See Cedillo Ex. 60 at 4 (Dr. Krigsman's curriculum vitae). He testified during the Cedillo hearing. Although the undersigned found Dr. Krigsman to be a qualified witness based on his medical training in gastroenterology, the undersigned found respondent's witnesses, in particular, Dr. Hanauer and Dr. MacDonald, to be far more credible, persuasive, and knowledgeably conversant on the gastrointestinal issues of interest in this litigation.

Respondent's testifying experts included: (1) Jeffrey Brent, M.D., Ph.D, medical toxicologist; (2) Stephen Bustin, Ph.D, molecular biologist; (3) Edwin Cook, Jr., M.D., child psychiatrist; (4) Eric Fombonne, M.D., child psychiatrist; (5) Diane Griffin, M.D. Ph.D, immunologist; (6) Stephen Hanauer, M.D., gastroenterologist; (7) Thomas MacDonald, Ph.D, immunologist; (8) Michael McCabe, Jr., Ph.D, immunotoxicologist; (9) Christine McCusker, M.D., pediatric immunologist; (10) Bertus Rima, Ph.D, virologist; (11) Robert Rust, Jr., M.D., pediatric neurologist; (12) Brian J. Ward, M.D., M.Sc., infectious disease specialist; (13) Max Wiznitzer, M.D., pediatric neurologist; and (14) Burton Zweiman, M.D., immunologist. The experts' qualifications are addressed in turn.

Dr. Brent is a clinical professor of Pediatrics and Internal Medicine at the University of Colorado Health Sciences Center in Denver. Cedillo Tr. at 2295 (Dr. Brent). He also maintains a private, single-specialty, group practice under the name of Toxicology Associates, the focus of which practice is to "deal[] solely with issues related to medical toxicology." Id. Dr. Brent is one of approximately 250 board-certified medical toxicologists in the United States. Id. at 2311-2312. As explained during the Cedillo trial, a board-certified medical toxicologist is distinguishable from a toxicologist (such as Dr. Aposhian), for whom there are no formal requirements. Id. at 2311. Eligibility for

certification by the American Board of Medical Specialties in the subspecialty of medical toxicology is based on completing a primary residency in a clinical field, a subsequent two-year full-time medical toxicology subspecialty fellowship in an accredited program, and then the medical toxicology medical certifying examination. Id. Board certification in the subspecialty of medical toxicology is conferred upon the successful completion of the certifying examination. Id. Dr. Brent treats patients for mercury toxicity and has presented on the topic of mercury toxicity. See Cedillo Tr. at 2298; see also Cedillo Ex. M (Dr. Brent's curriculum vitae). Dr. Brent testified during the Cedillo hearing. His testimony was credible and well-informed. His facility with the scientific literature was very helpful to the undersigned.

Dr. Bustin received his doctorate in molecular genetics at Trinity College in Dublin, Ireland. Cedillo Tr. at 1933. He completed postdoctoral studies on positive strand RNA viruses. Id. at 1933-1934. He spent a few years at a biotechnology company "looking at basic molecular biology techniques" before he returned to academic science as a senior research fellow at the London Hospital Medical College. Id. at 1934. Awarded the Chair of Molecular Science at Barts and the London, Queen Mary's School of Medicine and Dentistry, University of London, in the United Kingdom in 2004, Dr. Bustin primarily conducts research and, in limited measure, teaches medical students and postgraduate medical students. Id. He uses PCR techniques daily and, in the last five years, he has published fourteen peer-reviewed articles, eight book chapters, and a book on PCR. See id. at 1934-1935. He organizes conferences on PCR and frequently speaks internationally on the topic of PCR. Id. at 1937A. Dr. Bustin testified during the Cedillo hearing. Dr. Bustin testified knowledgeably and credibly.

Dr. Cook is a physician with board certifications in child and adolescent psychiatry. Cedillo Tr. at 1468-1469. Employed by the University of Illinois at Chicago, he serves as a Professor of Psychiatry and as the visiting Director of Autism and Genetics at the Institute for Juvenile Research, which is part of the Department of Psychiatry at the University of Illinois. Id. at 1470A. The Institute for Juvenile Research is the first child psychiatry clinic in the United States. Id. There, Dr. Cook evaluates and treats patients with a range of child and adolescent psychiatric disorders, including autism. Id. Additionally, he trains medical students, residents, and postdoctoral fellows, and he supervises several research faculty. Id. at 1470A. Dr. Cook's research interests include the neurochemistry of autism. Id. at 1473A-1474A. He has written approximately 50 peer-reviewed articles on the genetic influences associated with autism. See Cedillo Ex. O (Dr. Cook's curriculum vitae). Dr. Cook testified during the Cedillo hearing. The undersigned found Dr. Cook to be a forthright and credible witness.

Dr. Fombonne is a Professor of Psychiatry at McGill University in Montreal, Canada. Cedillo Tr. at 1239. He completed medical school and his residency in child psychiatry at the University of Paris. Id. at 1241-1242A. He is board-certified in the French system in child and adolescent psychiatry. Id. at 1243A. He also holds a master's certificate in biostatistical methods in human physiology (which are the various methods employed in the analysis of epidemiologic data). Id. at 1242A. For nearly 23 years, he has worked in the area of pervasive developmental disorders and specifically in the area of autism. Id. at 1244A. He treats about 200 autistic children a year. Id. at 1254A. He assesses about 175 new cases of autism a year. Id. Since the introduction by Dr. Andrew

Wakefield in 1998 of the hypothetical link between autism and the MMR and vaccines in general, Dr. Fombonne has been involved in research of the proposed causal association. Id. at 1239-1240A. He has published nearly a dozen articles addressing epidemiologic studies that have found a lack of association between childhood vaccines and the development of autism. See Cedillo Ex. Q (Dr. Fombonne's curriculum vitae). Dr. Fombonne testified during the Cedillo hearing. Dr. Fombonne testified credibly.

Dr. Griffin received her medical degree and her doctorate in immunology from Stanford University Medical School. Cedillo Tr. at 2739. After completing a postdoctoral fellowship in neurobiology and infectious diseases with a neurovirologist, she joined the faculty in the Department of Medicine and Neurology at Johns Hopkins University. Id. at 2740. In 1994, she became the Chair of the Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health, and she has retained her appointments at the Johns Hopkins School of Medicine. Id. She is also a fellow of the American Association for the Advancement of Sciences, a member of the Institute of Medicine, and a member of the National Academy of Science. Id. at 2742. She has written over 100 book sections and reviews, and she has published over 200 journal articles, a number of which concern viral persistence and the measles virus. See Cedillo Ex. W (Dr. Griffin's curriculum vitae). Dr. Griffin testified during the Cedillo hearing. She was a highly credible and knowledgeable witness. Her experience with the measles virus was unparalleled by any of petitioners' witnesses.

Dr. Hanauer is a full Professor of Medicine in Clinical Pharmacology and is Chief of the Gastroenterology, Hepatology and Nutrition Section at the University of Chicago. Cedillo Tr. at 2077A, 2081A. He is board-certified in internal medicine and in gastroenterology. Id. at 2078A. He is a fellow of the American College of Gastroenterology, and he currently sits on the board of trustees of the American College of Gastroenterology. Id. at 2078A. He has served on the governing board of the American Gastroenterologic Association and has chaired the section of Inflammation, Immunology and Inflammatory Bowel Disease of the American Gastroenterologic Association. Id. at 2079A. He also has served on the FDA's advisory panel for gastrointestinal drugs. Id. He currently sits on the research initiatives committee of the Crohn's and Colitis Foundation of America. Id. at 2080. Additionally, he currently serves on the editorial board of nine medical journals that address subjects related to gastrointestinal issues. Id. at 2083. He has written six books addressing inflammatory bowel disease, at least 50 book sections addressing inflammatory bowel disease, and many more than 100 published journal articles on inflammatory bowel disease. See Cedillo Ex. Y (Dr. Hanauer's curriculum vitae). Dr. Hanauer testified during the Cedillo hearing. Dr. Hanauer's testimony was clear, specific, and credible.

Dr. MacDonald presently is a professor of immunology and dean for research at Barts and the London School of Medicine and Dentistry. Hazlehurst Tr. at 603. He received his undergraduate degree in zoology from the University of Glasgow in Scotland. See Hazlehurst Ex. B at 1 (Dr. MacDonald's curriculum vitae). Interested in immunology but restricted to a parasitology course during his undergraduate studies because immunology was not a discrete course, Dr. MacDonald decided to pursue doctoral study in immunology. Id. at 603-604A. The focus of his doctoral study was "on how immune reactions particularly T-cell mediated immune reactions could damage the human and

mouse gut." Id. at 604A. His thesis was entitled "Delayed Hypersensitivity Reactions in the Small Intestine," and he received his Ph.D in 1976. Id. He subsequently completed postdoctoral training at the Trudeau Institute in Saranac Lake, New York, where he learned about "the way in which normal microbes in the gut could influence T-cell function." Id. After completing his postdoctoral training, he worked as an assistant professor in the Department of Microbiology at Jefferson Medical College in Philadelphia, Pennsylvania for nearly six years. See Hazlehurst Ex. B at 1 (Dr. MacDonald's curriculum vitae). Recruited from academia to work as a senior research fellow for Merck, Sharpe and Dohme Research Laboratories in Rahway, New Jersey, Dr. MacDonald worked there for ten months before electing to return to academia. See Hazlehurst Tr. at 605A (Dr. MacDonald testifying that he "discovered that . . . Merck was not a particular sort of place [he] wanted to work in"); see also Hazlehurst Ex. B at 1 (Dr. MacDonald's curriculum vitae). Dr. MacDonald then accepted a position as a research fellow with the Medical College of St. Bartholomews Hospital in London, where he continues to work. See Hazlehurst Ex. B at 1 (Dr. MacDonald's curriculum vitae); Hazlehurst Tr. at 605A-606A. research In his current position, he manages the institution's research budget of $76 million dollars, he runs a laboratory where he conducts research on inflammation in the human gastrointestinal system, and he teaches undergraduate and postdoctoral medical students and science students in the subjects of immunology and gastroenterology. Hazlehurst Tr. at 606A-607A. He has been an active researcher since 1973 and has written and published extensively in the area of gut immunology throughout his career. See id. at 604A, 607A-608A. He is a seasoned reviewer for various scientific journals and he is a member of a number of learned scientific societies. See id. at 609A-611A. Most of his current research is centered on studying the human gastrointestinal immune system . . . especially [in] children . . . [with] inflammatory bowel disease." Id. at 605A. He testified during the Hazlehurst hearing. He was a knowledgeable and persuasive witness.

Dr. McCabe received his doctorate in microbiology and immunology in 1991 from the Albany Medical College in Albany, New York. Snyder Tr. at 734A. He completed a two-year post-doctoral fellowship at the Karolinska Institute in Stockholm, Sweden. Id. at 735A. Dr. McCabe pursued the opportunity at the Karolinska Institute because the laboratory there was conducting leading research in the area of apoptotic cell death,[18] an area of research in which Dr. McCabe had particular interest. Id. at 736. Upon the completion of the fellowship, Dr. McCabe accepted a position as a faculty member at the Institute of Chemical Toxicology in Detroit, Michigan. Id. After seven years there, he was recruited in 2000 to join the faculty in the Department of Environmental Medicine at the University of Rochester School of Medicine and Dentistry. Id. Dr. McCabe is currently an Associate Professor in that department. Id. at 734A, 736. He teaches graduate students on topics related to metal toxicology, immunotoxicology, and autoimmunity. Id. at 740. Additionally, he is the principal investigator and chief of the laboratory doing research on the activation of lymphocytes (which are important cells in the body's adaptive immune system), the signals that alert these cells to divide and

[18] Apoptotic cell death is the process by which a cell dies "in response to problems within the cell or signals from outside the cell." See L. Sompayrac, How the Immune System Works at 24 (2d ed., Blackwell Publishing 2003). Apoptotic cell death is also referred to as a programmed cell death. See id.

differentiate, and the effect of mercury exposures on the signals to the cells. Id. at 741-742. Dr. McCabe also serves as associate editor of Toxicology and Applied Pharmacology, "arguably one of the two leading journals in toxicology," and he sits on the editorial board for Toxicological Sciences, "arguably the second of the two leading journals in toxicology," and for the Journal of Immunotoxicology, a newer and more specialized journal. Id. at 743-744. Dr. McCabe testified during the Snyder hearing. His testimony was clear and credible.

Dr. McCusker completed her undergraduate studies at the University of Toronto in Canada, majoring in microbiology and immunology. Cedillo Tr. at 2202. She completed her graduate studies in molecular virology and three years of a Ph.D thesis degree in immunogenetics at McMaster University in Hamilton, Ontario. Id. She also received her medical degree from McMaster University. Id. She subsequently completed her residency in pediatrics, a clinical fellowship in allergy and clinical immunology, and a two-year postdoctoral research fellowship in immunology in the Meakins-Christie Laboratories at McGill University, in Montreal, Quebec. Id. She is board-certified in pediatrics both in the United States and in Canada. Id. at 2202-2203. She is also board-certified in allergy and immunology in Canada. Id. at 2203. She is currently an assistant professor at McGill University teaching immunology to undergraduates, graduate students, medical students, and residents. Id. In addition, she has clinical and research responsibilities at the university. Id. As part of her clinical responsibilities, she is the Clinical Director of the Immunology Laboratory at Montreal Children's Hospital. Id. at 2204. In that capacity, she is responsible for the conduct and quality assurance of the clinical immunological testing–particularly, for the diagnosis of primary immunodeficiency. Id. She evaluates about 200 pediatric patients a month and sees pediatric patients on an emergency basis several times a month when she works in the emergency room at Montreal Children's Hospital. Id. at 2205A-2206. As part of her research responsibilities, she is the principal investigator at the Meakins-Christie Laboratories at McGill. Id. at 2203. Among her research interests is understanding how the immune system develops from infancy through adolescence. Id. at 2203-2204. She testified cogently and persuasively during the Cedillo and Hazlehurst hearings.

Dr. Rima was educated as a chemical engineer in Delft, the Netherlands. Snyder Tr. at 825. Upon his graduation in 1970, he received "what was the Anglo-Saxon equivalent of" a masters of science degree with a specialty in bacterial genetics. Id. He completed his doctoral degree in bacterial genetics in Canada and then traveled to Queens University in Belfast, Ireland to do postdoctoral work with the measles virus. Id. He has remained at the university since that time and is currently the head of the School of Biomedical Sciences there. Id. In his current position, his non-administrative duties include teaching graduate students and conducting laboratory research, the primary focus of which has been the neurovirology of the measles virus. Id. at 825-826A. With nearly 33 years of experience working with the measles virus, Dr. Rima has published over 100 articles on the measles virus. Id. at 826A. Dr. Rima testified during the Snyder hearing. He was a knowledgeable and credible witness.

Dr. Rust is a board-certified physician in both pediatrics and neurology, with special qualifications in child neurology. Hazlehurst Tr. at 449A. He is currently the Director of Child Neurology, the Director of Child Neurology Training Programs and the

Co-Director of the Epilepsy and Child Neurology Clinic at the University of Virginia in Charlottesville. Id. at 446A; see also Hazlehurst Ex. F at 1 (Dr. Rust's curriculum vitae). He estimates that in his clinical experience, he has seen "several hundred patients" with autism and that "it has become a very common experience" for him to diagnose children with autism. Hazlehurst Tr. at 452A. He testified during the Hazlehurst hearing. Dr. Rust was a credible and persuasive witness.

Dr. Ward is a physician at McGill University. Cedillo Tr. at 1795. A former Chief of the Division of Infectious Diseases at McGill, he is currently the Associate Director of the Tropical Diseases Center. Id. at 1797. He completed his residency in internal medicine and infectious diseases at Johns Hopkins University and performed two years of research on the measles virus in the lab of Dr. Diane Griffin, another of respondent's experts in this proceeding. Id. at 1796. He is board-certified in the United States in internal medicine and in infectious diseases. Id. at 1797. He is also board-certified in the province of Quebec "in infectiology, which combines microbiology and infectious diseases." Id. His research activities include basic studies of vaccine-induced immunity and basic studies of the factors influencing measles virus replication. See Cedillo Ex. CC (Dr. Ward's curriculum vitae). Dr. Ward testified during the Cedillo and Snyder hearings. Dr. Ward was a well-informed, credible and persuasive witness.

Dr. Wiznitzer is board-certified in pediatrics, pediatric neurology, and neurodevelopmental disabilities. Cedillo Tr. at 1565. He received his medical degree from Northwestern University in Chicago, Illinois. Id. at 1565. After receiving his medical degree, he completed a pediatrics residency at Children's Hospital Medical Center in Cincinnati, Ohio. Id. at 1566A. He also completed a year-long training program in developmental disorders at the Cincinnati Center for Developmental Disorders. Id. Additionally, he completed a three-year training program in pediatric neurology through the University of Pennsylvania at the Children's Hospital of Philadelphia. Id. Thereafter, he completed a two-year fellowship, funded by the National Institutes of Health, at the Albert Einstein College of Medicine in the Bronx, New York. Id. at 1567. The focus of that fellowship was on disorders of higher cognitive function in children, specifically, the disorders of language and autism. Id. at 1567. He is an Associate Professor of Pediatrics, Neurology, and International Health at Case Western Reserve University School of Medicine in Cleveland, Ohio. See id. at 1568. He also serves as a staff child neurologist at the Rainbow Babies and Children's Hospital. Id. at 1568-1569A. There he works on the epilepsy team and is affiliated with the local autism center. Id. at 1569A. For 21 years, he has treated patients with autism spectrum disorders. Id. at 1576A. He sees approximately 200 to 250 patients a month, which includes patients with ASDs. Id. Dr. Wiznitzer testified during the Cedillo and Snyder hearings. Dr. Wiznitzer was a credible and persuasive witness.

Dr. Zweiman received his undergraduate and medical degrees from the University of Pennsylvania in Philadelphia. Snyder Tr. at 570A. After completing his residency, he accepted a fellowship in allergy and clinical immunology. Id. He is board certified in internal medicine with a subspecialty of allergy and immunology. Id. In 1963, he accepted a position as a faculty member at the University of Pennsylvania, School of Medicine. Id. For 24 years, he served as the Chief of the Division of Allergy and Clinical Immunology at that institution. Id. He "founded and helped supervise for many years the

laboratory that performs autoantibody determinations in our medical center," and he has conducted research related to autoantibodies as well as research related to neuroimmunology. Id. He recently became an emeritus professor of medicine and neurology. Id. Prior to becoming an emeritus professor, he treated patients. Id. Dr. Zweiman testified during the Snyder hearing. He testified succinctly, knowledgeably, and credibly.

On balance, the undersigned found respondent's witnesses to be much more persuasive than petitioners' witnesses. The substance of the testimony offered by respondent's witnesses was well supported by the filed medical literature. Additionally, the extensive research conducted by respondent's witnesses on topics of particular relevance in this litigation, such as pediatric immune function, mercury toxicity, inflammatory bowel disease, and the nature of the measles virus, was often accompanied by significant clinical experience in these same areas. Moreover, respondent's witnesses generally used care when discussing topics where differences and particularly differences in degree mattered. Respondent's witnesses exercised such care when: (1) addressing the various degrees of an impaired immunological state and describing the proper terms for the various immunological states, (2) discussing the toxicological effects of the various forms of mercury and describing the exposure doses involved, and (3) discussing the adverse effects associated with wild-type measles virus as distinguished from the effects associated with vaccine-strain measles virus. When respondent's witnesses discussed the literature upon which petitioners' witnesses relied, they presented specific, detailed criticisms carefully explaining why the articles did not support the propositions for which petitioners advanced them or why the articles were not scientifically reliable.

Petitioners' expert witnesses, in contrast, were not as disciplined in their discussion of topics where differences mattered, specifically, in degree of produced impairment, in type of mercury or type of measles virus (whether wild-type or vaccine-strain), and in exposure dosage. Additionally, when referring to the filed medical literature, petitioners' experts tended to assign greater weight to speculative conclusions offered by the investigators involved in the studies than did the investigators themselves. Petitioners' experts also urged reliance on a few carefully selected sentences from particular articles which, when considered in the proper context of the referenced articles, did not support the propositions advanced by the witnesses. Moreover, because petitioners' experts relied on a number of scientifically flawed or unreliable articles for several important aspects of their causation theory, their testimony on those aspects of their offered theory could not be credited as sound or reliable. Finally, petitioners' experts made several key acknowledgments during testimony that rendered their proposed theory of vaccine causation much less than likely.

2. 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 of the three

test cases.[19] This case is now ripe for decision.

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©. 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.[20] 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 id. A "Table" claim benefits from a rebuttable presumption of causation. 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. § 300aa-13(a)(1). Petitioners satisfy this evidentiary standard by demonstrating that the vaccination 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 factfinder must "believe that the existence of a fact is more probable than its nonexistence before [she]

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[19] The parties filed supplemental expert reports, the final report of which was filed on April 10, 2008.

[20] 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.

may find in favor of the party who has the burden to persuade the [factfinder] of the fact's existence."); see also Althen v. Sec'y of Health and Human Servs., 418 F.3d 1274, 1279 (Fed. Cir. 2005) (internal citation omitted) (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."). Offered opinions that reflect mere conjecture or speculation do not satisfy the preponderance standard. See 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 need not show that the vaccination 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 Yates 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 Hazlehursts 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 vaccinations "caused" Yates' regressive autism. Petitioner satisfies this burden of proof by presenting: (1) "a medical theory" that causally connects Yates' vaccinations and his autism; (2) "a logical sequence of cause and effect" that shows that Yates' vaccinations were the "reason" for his injury; and (3) evidence of "a proximate temporal relationship" between Yates' vaccinations and his injury. Althen, 418 F.3d at 1278.

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 mater's requirement that petitioner prove biological plausibility); Pafford v. Sec'y of Health and Human Servs., 451 F.3d 1352, 1356 (Fed. Cir. 2006) (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 v. Sec'y of Health and Human Servs., 35 F.3d 543, 548 (Fed. Cir. 1994); 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 legal burden under 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 v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 594 (1993). Terran v. Sec'y of Health and Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999) (emphasis added), cert. denied, Terran v. Shalala, 531 U.S. 812 (2000) (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) (citations omitted), on remand, 509 U.S. 579 (1993); see also Daubert, 509 U.S. at 592-94.

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 593-94 (citations omitted) (emphasis added).

Medical certainty is not required. Knudsen v. Sec'y of Health and Human Servs., 35 F.3d 543, 548-549 (Fed. Cir. 1994). But, 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." Id. at 548; Grant v. Sec'y of Health and Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992) (same); Hines v. Sec'y of Health and Human Servs., 940 F.2d 1518, 1525 (Fed. Cir. 1991) (citations omitted) (same).

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 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 v. Sec'y of Health and Human Servs., 440 F.3d 1317, 1326 (Fed. Cir. 2006). And medical records, particularly those rendered contemporaneously to the onset of the alleged injury, receive "favored" consideration. Id. See also Curcuras v. Sec'y of Health and Human Servs., 993 F.2d 1525, 1528 (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").

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," petitioners are not required to present particular types of evidence, such as "epidemiologic studies, [evidence of] rechallenge, the presence of pathologic markers or [a] genetic disposition, or general acceptance in the scientific or medical communities." Capizzano, 440 F.3d at 1325. 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, 590 U.S. at 590 (stating that scientific knowledge requires "more than subjective belief or unsupported speculation"); Althen, 418 F.3d at 1278 (quoting Grant, 956 F.2d at 1148, and 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).

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 id. Identification and proof of specific biological mechanisms are not required. Id. However, special masters must examine the soundness and reliability of the offered medical or scientific explanations. See Althen, 418 F.3d at 1278 (stating that a logical sequence is supported by a "sound and reliable" medical or scientific explanation); Knudsen, 35 F.3d at 548 (same); Grant, 956 F.2d at 1148 (same); see also RCFC App. B, Vaccine Rule 8© (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), or when the reasons underlying the expert's offered 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."). The Federal Circuit has further instructed that a decision about the credibility and persuasiveness of a witness is not reviewable on appeal. See Bradley v. Sec'y of Health & Human Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

It is true that 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© (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 United States Supreme Court in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 594 (1993), "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), cert. denied, Terran v. Shalala, 531 U.S. 812 (2000). 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.

Special masters are guided by these considerations when evaluating the underlying support informing 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 epidemiologic 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) (citation omitted). 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.

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.

C. Proving Alternate Causation

By successfully satisfying the Althen factors, petitioners may have established a prima facie case. See Grant, 956 F.2d at 1149. Petitioners do not merit Program compensation, however, until the special master "also determine[s] that 'there is not a preponderance of the evidence that the . . . injury . . . is due to factors unrelated to the administration of the vaccine" or to "alternate etiologies." Id. (citing 42 U.S.C. § 300aa-13(a)(1)). The Federal Circuit has not spoken with a consistent voice regarding which party bears the burden of eliminating others possible causes for the sustained injury. In

Pafford, the Federal Circuit observed that as a practical matter, a petitioner may be required to eliminate potential alternate causes where the petitioner's other evidence on causation is insufficient. See Pafford, 451 F.3d at 1359; see also Althen, 418 F.3d at 1281 (stating that a claimant under the Vaccine Program bears the burden of eliminating other causes for the suffered injury).

But the Federal Circuit assigned the burden differently in Walther v. Sec'y of Health and Human Servs., 485 F.3d 1146, 1150 (Fed. Cir. 2007). In Walther, the Federal Circuit stated that the burden of proving alternative causation rests with respondent. Walther, 485 F.3d at 1150; see also Althen, 418 F.3d at 1278 (stating that the government bears the burden of establishing causation of the injury by factors unrelated to the vaccine); Knudsen v. Sec'y of Health and Human Servs., 35 F.3d 543, 547 (Fed. Cir. 1994) (citing Whitecotton v. Sec'y of Health and Human Servs., 17 F.3d 374, 376 (Fed. Cir. 1994), rev'd on other grounds sub nom., Shalala v. Whitecotton, 514 U.S. 268 (1995)). Respondent bears the burden of proving alternative causation by preponderant evidence, and respondent establishes alternative causation (a factor unrelated to the administration of the vaccination) by satisfying the Althen factors, specifically, a medical theory of causal connection, a logical sequence of cause and effect, and a proximate temporal relationship between the asserted injury and a factor unrelated to the received vaccination. See Walther, 485 F.3d at 1151; Althen, 418 F.3d at 1278; Knudsen, 35 F.3d at 547; Whitecotton, 17 F.3d at 376.

If petitioners fail to establish their prima facie case, however, the issue of alternate causation need not be reached.

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

The general causation theory that petitioners have advanced in the first three test cases has the following key components. Petitioners assert that the child who received the vaccines was developmentally normal prior to the receipt of the combination of thimerosal-containing vaccines and the MMR vaccine. See Cedillo Petitioners' Post-Hearing Brief (Cedillo Brief) at 21, 263; Hazlehurst Petitioners' Post-Hearing Brief (Hazlehurst Brief) at 6, 15; Snyder Petitioners' Post-Hearing Brief (Snyder Brief) at 9. Petitioners assert that the administered thimerosal-containing vaccines during the child's first year to year-and-one-half of life impaired the effective functioning of the child's immune system. See Cedillo Brief at 71-95, 207-217; Snyder Brief at 3-4, 9. Additionally, petitioners assert that the administered MMR vaccine also caused immunosuppression. Cedillo Brief at 71-95, Snyder Brief at 21; see Hazlehurst Brief at 15 (stating that the presence of immunologic problems "strengthen[s]" theory of causation but is "not . . . essential" to theory). It is the contention of petitioners that the combined immunosuppressive effects of the received vaccines, specifically the thimerosal-containing vaccines and the MMR vaccine, permitted the measles component of the MMR vaccine to persist in the child's body. Cedillo Brief at 217-229; Snyder Brief at 3; see also Hazlehurst Tr. at 372A (petitioners' expert neurologist Dr. Corbier opining that there is "possibly a synergistic effect" between the thimerosal-containing vaccines and the MMR vaccine). Petitioners contend that the persistence of the measles virus in the child's body caused chronic inflammation in the body's tissues, notably in the gastrointestinal system and in the brain. Cedillo Brief at 229-233; Hazlehurst Brief at 16; Hazlehurst Petitioners'

Reply Brief (Hazlehurst Reply Brief) at 19-23; Snyder Brief at 3-4. Petitioners contend that the persistent measles virus in the brain led to neurological injury that manifested as regressive autism. Cedillo Brief at 234-242, Hazlehurst Brief at 16, 19 (urging that the measles virus could "cause central nervous system injuries directly–by infecting the brain–or indirectly by triggering an autoimmune response"); Hazlehurst Reply Brief at 14-15; Snyder Brief at 4.

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.[21]

A. Examining Petitioner's Claimed Injury of Autism

1. Autism Spectrum Disorder

An autism spectrum disorder (ASD) is a neurological, developmental disorder. Cedillo Ex. DD at 1 (Dr. Wiznitzer's report); accord Cedillo Tr. at 1074 (Dr. Kinsbourne describing the disorder as a neurological one). An ASD is also described as a pervasive developmental disorder (PDD). Cedillo Tr. at 1263 (Dr. Fombonne). The term "autism" is used broadly to refer to ASDs or alternatively PDDs. Cedillo Ex. P at 6 (Dr. Fombonne's report). The term "autism" also is used more narrowly as a shorthand reference to autistic disorder, one of the five specific ASDs. Id. at 6, 7. Unless otherwise specified in this ruling, the undersigned uses the terms autism and ASD interchangeably.

There is some difference of opinion about whether the developmental disorder of autism has been recognized and described in writings for hundreds of years. Cedillo Ex. P at 6 (Dr. Fombonne's report); see also Cedillo Ex. P77 (2003 Frith book[22]). The disorder was not described as autism until 1943 when Dr. Leo Kanner, a psychiatrist at Johns Hopkins University, first used the term to describe his observations of 11 pediatric patients who manifested "significant social and language deficits and impairment of imaginative play." Cedillo Ex. P at 1, 7 (Dr. Fombonne's report).

There are currently two diagnostic classification systems for ASDs: (1) the Diagnostic & Statistical Manual, 4th Edition, Text Revision (DSM-IV) of the American Psychiatric Association, and (2) the International Classification of Diseases, 10th Edition (ICD-10) of the World Health Organization.[23] Cedillo Ex. P at 6 (Dr. Fombonne's report).

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[21] For ease of reference to the various sections of this decision, the undersigned has attached a table of contents at the conclusion of the decision.

[22] U. Frith, Autism: explaining the enigma (cognitive development), Blackwell Publishing (2d ed. 2003). Although Dr. Fombonne referenced the book, respondent did not file a copy of the book into the record.

[23] Unlike DSM-IV, ICD-10 covers "a whole range of medical disorders." Cedillo Tr. at 2616-2617A (Dr. Fombonne). It also provides "a common language to

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The DSM-IV provides the standard criteria used to diagnose ASDs in many parts of the world, including both the United States and Canada. Id. at 7. The DSM-IV classifies and sets forth the diagnostic criteria for five ASDs which are: (1) Rett disorder, (2) childhood disintegrative disorder (CDD), (3) Asperger's disorder, (4) autistic disorder, and (5) pervasive developmental disorder–not otherwise specified (PDD-NOS). Id.

a. The Categories of ASDs

ASDs are characterized by qualitative differences in the three core developmental areas: (1) behavior, (2) communication, and (3) social interaction. Cedillo Tr. at 1266 (Dr. Fombonne); Cedillo Ex. P at 7 (Dr. Fombonne's report); accord Hazlehurst Tr. at 267A (Dr. Corbier). The behavior of the affected individual characteristically involves repetitive and rigid patterns of play. Cedillo Tr. at 1264 (Dr. Fombonne). Moreover, the interests and activities of the affected individual are notably restricted. Cedillo Ex. DD at 1 (Dr. Wiznitzer's report); accord Cedillo Tr. at 1045A (Dr. Kinsbourne describing the repetition in play and in movement, whether a flapping movement or a whirling movement, that are characteristic habits of autistic children). The manner in which the affected individual communicates–with or without language–is different. Cedillo Tr. at 1263 (Dr. Fombonne); accord id. at 1044 (Dr. Kinsbourne explaining that the language difficulties in autistic children can present as either a lack of language or the use of language in peculiar ways). Additionally, the manner in which the affected individual interacts with others is different. Cedillo Tr. at 1263-1264A (Dr. Fombonne); accord id. at 1044-1045A (Dr. Kinsbourne describing the "disinterest in interacting with others" that autistic children manifest).

This disorder involves a "constellation of behaviors." Cedillo Tr. at 2588 (Dr. Fombonne). Some of the various behaviors observed in autistic children are: becoming upset with change–"even [changes in] what others would regard as trivial details;" fixing on the details or components of an object rather than the object as a whole; and exhibiting extreme sensitivity to certain sounds–like a vacuum cleaner–while appearing oblivious to other sounds–like being called by name. Id. at 1046A (Dr. Kinsbourne). Other noted behaviors include an aversion to being held, arching away from an embrace or a hug, and a disinterest in inviting others to interact with her or him. Id. at 1061. A diagnosis of the syndrome requires deficits in each of the three core developmental areas. Id. at 1263, 2588-2589A (Dr. Fombonne). There are, however, multiple indicators of deficits in each of the domains. Id. at 2589A. These indicators could number perhaps as many as 20 to 25 in each of the three domain areas. Id.

Children with the same diagnosis can present in very different ways. Cedillo Tr. at 1265A (Dr. Fombonne). The particular behaviors that implicate deficits in the three

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[23](...continued)
practitioners [and] common diagnostic systems . . . [that permit] a common reporting system for important vital statistics in many countries." Id. at 2616. Efforts were made, however, by the working groups responsible for revising the two classification systems to work together to make the two systems "more alike . . . in terms of the concepts, diagnostic criteria, algorithms and wording." Id. at 2619.

developmental domains vary from individual to individual. Cedillo Ex. P at 7 (Dr. Fombonne's report). Moreover, behaviors within a particular individual can vary based on the individual's age and level of intelligence or functioning. Id.; see also Hazlehurst Tr. at 457A (Dr. Rust) (stating that the manifestations of autism are highly age-dependent).

Onset of the disorder generally occurs before three years of age. Cedillo Tr. at 1264A (Dr. Fombonne); Cedillo Ex. DD1 at 889 (1998b Bailey article[24]). Early onset can occur in children under a year old, and in such cases, the symptoms are very subtle.[25] Hazlehurst Tr. at 267A (Dr. Corbier).

Petitioners' expert Dr. Corbier testified during the Hazlehurst hearing that differences in the timing of the onset of symptoms suggest different causes of the autistic condition. See Hazlehurst Tr. at 269A. He explained that when children manifest autistic symptoms in addition to seizures and other problems in early infancy, the cause of the autistic condition is more likely to be a prenatal one. Id. But, he opined that environmental factors "may have a greater role" in causing an autistic disorder in a genetically-predisposed child when the symptoms of the disorder develop after a period of apparently normal development (as in cases of regressive autism). Id. at 269A-270A. Dr. Corbier described the following clinical profile of the autistic child for whom vaccinations might be implicated as an environmental cause of the disorder: (1) a normally developing child; (2) who is vaccinated; (3) then starts to manifest "autistic symptomatology;" and (4) who also "has significant gastrointestinal . . . issues;" and (5) who is "sickly." Hazlehurst Tr. at 271A-272A (Dr. Corbier). Also important to Dr. Corbier's clinical profile is the timing of the appearance of the child's regression. When symptoms of regression appeared in a child within nine months after an MMR vaccination, Dr. Corbier attributed the development of the child's regressive autism to the vaccination. Id. at 306-307 (Dr. Corbier).

Autism occurs more commonly in males than in females. Cedillo Tr. at 1264A (Dr. Fombonne). "The prevalence of autistic disorder is approximately four times higher in males than in females, with an even higher ratio [for] milder forms of [autism spectrum disorder]." Cedillo Ex. N5 at 819 (2004 Veenstra-VanderWeele article[26]).

One in 160 children has an autism spectrum disorder. See Cedillo Tr. at 1490 (Dr. Cook). One in 500 children has autistic disorder. See Cedillo Tr. at 1489A (Dr. Cook).

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[24] A. Bailey et al., A clinicopathological study of autism, Brain 121: 889-905 (1998).

[25] Respondent's witness Dr. Wiznitzer testified that "[s]ymptoms may be subjective, dealing with the complaint that the person has. Sign[s] [are] the physical manifestations that [the person] show[s]." Snyder Tr. at 706.

[26] J. Veenstra-VanderWeele and E. H. Cook, Jr., Molecular Genetics of Autism Spectrum Disorder, Molecular Psychiatry 9: 819-832 (2004).

Autistic disorders fall within a spectrum of more severely affected cases to less severely affected cases. See Cedillo Tr. at 1053A-1054 (Dr. Kinsbourne). A brief description of each of the five ASDs follows.

I. Rett Disorder

Rett disorder or syndrome affects females primarily and is one of the most common causes of mental retardation in females. Cedillo Ex. P at 7 (Dr. Fombonne's report); Cedillo Ex. P2 at 185 (1999 Amir article[27]). The disorder is linked to a genetic defect, specifically a defect on the MECP2 gene on the X chromosome. Cedillo Ex. P at 7 (Dr. Fombonne's report); Cedillo Ex. P2 at 185 (1999 Amir article).

Development appears to be normal in patients with classic Rett syndrome until some time between six and 18 months of age. Cedillo Ex. P2 at 185 (1999 Amir article). At that time, the patients "gradually lose speech and purposeful hand use, and develop microcephaly [which is an abnormal smallness of the head], seizures, autism, ataxia, intermittent hyperventilation and stereotypic hand movements." Id. The condition stabilizes after this initial regression and patients "usually survive into adulthood." Id.

ii. Childhood Disintegrative Disorder

Childhood disintegrative disorder (CDD) is a severe and rare type of ASD. Cedillo Ex. P at 8 (Dr. Fombonne's report). The affected child appears developmentally normal during at least the first two years of life. Id. After the second year of life and typically during the third year of life, the child experiences a significant regression and loss of skills. Id. The profound loss of skills occurs "in at least two domains ([particularly,] language, social skills and adaptive behavior, bowel and bladder control, play, and motor skills)." Id.; see also Cedillo Ex. P62 at 149-150 (2002 Fombonne article[28]). Clinically, CDD resembles severe autistic disorder. Id.

iii. Autistic Disorder

A diagnosis of autistic disorder is appropriate when there are "deficits in each of the three domains of early development," which include social interaction, communication, and behavior.[29] Cedillo Ex. P at 8 (Dr. Fombonne's report). Deficits in

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[27] R. Amir et al., Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpGbinding protein, Nature Genet. 23(2): 185-188 (Oct. 1999).

[28] E. Fombonne, Prevalence of Childhood Disintegrative Disorder, Autism 6: 149 (2002).

[29] Under the diagnostic criteria for autistic disorder in the DSM-IV, there is a list of 12 possible symptoms. Cedillo Ex. P at 9. A child who shows at least six of the symptoms (of which two must be in the area of social development and "at least one symptom" must be in the area of communication and in the area of behavior or "abnormal

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the area of social interaction may present as "lack of eye contact, impaired peer relationships, lack of spontaneous seeking of shared experiences, and [lack] of social reciprocity." Cedillo Ex. P at 8 (Dr. Fombonne's report); Cedillo R's Trial Ex. 8 at 4 (Dr. Fombonne's trial slides). Deficits in the area of communication may present as "delay of spoken language, impairment of conversational skills, use of repetitive and idiosyncratic language, [and/or] lack of imaginative play." Cedillo Ex. P at 8 (Dr. Fombonne's report); Cedillo R's Trial Ex. 8 at 3 (Dr. Fombonne's trial slides). A young infant's limited babbling or self-directed babbling that is "not used with a communicative intent" may also be indicative of a qualitative communication deficit. Cedillo Tr. at 1267A (Dr. Fombonne). Moreover, the absence of pointing or gesturing may indicate abnormality in the communication domain. Cedillo R's Trial Ex. 8 at 3 (Dr. Fombonne's trial slides). Deficits in the area of behavior may present as "restricted patterns of interest, inflexible routines and rituals, stereotypical motor mannerisms, [and/or a] preoccupation with parts of objects." Cedillo Ex. P at 8 (Dr. Fombonne's report); Cedillo R's Trial Ex. 8 at 5 (Dr. Fombonne's trial slides).

The presentation of deficits in these areas and the onset of symptoms must occur prior to the third year of life. Cedillo Ex. P at 8 (Dr. Fombonne's report); see also Cedillo R's Trial Ex. 8 at 7 (Dr. Fombonne's trial slides); Hazlehurst R's Trial Ex. 1 at 2 (Dr. Rust's trial slides). When the child presents with all these typical symptoms of autism and the diagnoses of Rett syndrome and childhood disintegrative disorder have been ruled out, a clinician properly may diagnose a child as having an autistic disorder. Cedillo Ex. P at 8-9 (Dr. Fombonne's report).

On evaluation, nearly 70 percent of patients with autistic disorder score within the range of mental retardation (by scoring below 70) on standardized tests of intelligence. Cedillo Ex. P at 15 (Dr. Fombonne's report).

iv. Pervasive Developmental Disorder-Not Otherwise Specified

This diagnostic category of ASD is referred to as atypical autism. Cedillo Ex. P at 9 (Dr. Fombonne's report). Children who present with autistic abnormalities but do not satisfy the "full diagnostic criteria for autism" may receive this diagnosis. Cedillo Ex. P at 9 (Dr. Fombonne's report). A child receiving this diagnosis either exhibits deficits in only two of the three developmental areas or experiences the onset of symptoms later than the third year of life. Cedillo R's Trial Ex. 8 at 7 (Dr. Fombonne's trial slides).

The rates of mental retardation for children with pervasive development disorder-not otherwise specified (PDD-NOS) are slightly lower than the rates of mental retardation for children with autistic disorder. Cedillo Ex. P at 15 (Dr. Fombonne's report).

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[29](...continued)
pattern of play") meets the criteria for a diagnosis of autistic disorder. Cedillo Ex. P at 9.

v. Asperger's Disorder

Asperger's disorder presents with the same impairments in social interaction and the same restricted interests and play as in autistic disorder. Cedillo Ex. P at 8 (Dr. Fombonne's report). The difference between Asperger's disorder and autistic disorder is principally in the domain of language. Id. Language development in patients with Asperger's disorder is largely within normal limits. Id.; see also Cedillo R's Trial Ex. 8 at 7 (Dr. Fombonne's trial slides).

Another notable difference between Asperger's disorder and autistic disorder is in the area of mental capability. While nearly 70 percent of patients with autistic disorder score within the range of mental retardation on standardized intelligence tests, Cedillo Ex. P at 15 (Dr. Fombonne's report), patients with Asperger's disorder do not. Cedillo Ex. P at 8 (Dr. Fombonne's report); see also Cedillo R's Trial Ex. 8 at 7 (Dr. Fombonne's trial slides). Patients with Asperger's disorder are higher functioning.

2. The Phenomenon of Regressive Autism

In contrast to autistic children who, between the age of nine and 18 months, begin to display abnormal behavior skills or fail to acquire normal developmental skills, is a group of children with ASDs who appear to develop normally for a period of time and then begin to lose previously acquired skills. Cedillo Ex. P at 12 (Dr. Fombonne's report); Hazlehurst Tr. at 459A-460A (Dr. Rust) (describing the regressive or degenerative form of autism); accord Cedillo Tr. at 1054 (Dr. Kinsbourne) (stating that regression is characterized by the loss of skills that a child once had). This regressive pattern of development has not been reported in children with either non-autistic developmental delay or language delay. See Cedillo Ex. P at 12 (Dr. Fombonne's report).

Typically, the onset of symptoms signaling the regressive form of autism occurs between 15 and 24 months, but onset may occur within the broader interval of 12 months to 28 months. Hazlehurst Tr. at 470A-471A (Dr. Rust); see also Cedillo Ex. 61JJ at 239 (1987 Hoshino article[30]) (documenting the age at "setback" somewhere between 15 months and 30 months in a group of autistic children); accord Cedillo Tr. at 1055 (Dr. Kinsbourne) (explaining that regression "occurs typically, though not exclusively, in the second year of life"). Studies have shown the mean age of symptom onset in a child later diagnosed with an ASD, whether or not the regressive form, is within the five-month period following the child's first birthday. See Cedillo Ex. P at 12-13 (Dr. Fombonne's report).

The group of children exhibiting the regressive form of autism is estimated to be approximately 20 percent of the children with a diagnosis of either autistic disorder (autism) or pervasive developmental disorder otherwise not specified (PDD-NOS). See Cedillo Tr. at 1054-1055 (Dr. Kinsbourne). Because symptoms of the regressive form of

[30] Y. Hoshino et al., Clinical features of autistic children with setback course in their infancy, Jpn. J. Psychiatry Neurology 41: 237-246 (1987).

autism have been reported by parents to appear within a window of time that overlaps the period of time within which the MMR vaccination is administered in the United States (which is typically between the 12th and 15th month of life),[31] concern has grown about a possible causal association between the childhood immunization and the development of ASDs. See Cedillo Ex. 61RR at 195 (1985 Kurita article[32]); Cedillo Ex. P at 13 (Dr. Fombonne's report) (referring to the recommended age for MMR vaccination that pre-dated 1998).

Petitioners in the OAP litigation assert that regressive autism is a distinct phenotype that is distinguishable from classic autism which is characterized not by the loss of previously acquired skills, but rather by the failure to develop certain skills. 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 genetic and environmental influences on an individual. Underlying petitioners' argument that regressive autism is a distinct phenotype is their theory that this type of autism is caused, in part, by environmental factors that include childhood vaccines. As examined in much greater detail in the following sections of this decision, however, the evidence presented and considered in this litigation does not support a finding, under the applicable preponderance of the evidence legal standard, that postnatal exposure to the vaccines of interest leads to the development of autism of any type. Unpersuaded that childhood vaccines lead to the development of autism, the undersigned need not decide whether the evidence supports a finding that regressive autism is a separate phenotype.

3. Findings of Physical Abnormalities in Individuals with ASDs

Among the commonly found physical abnormalities in children with ASDs are malformed (dysmorphic) cranio-facial features and dysfunctional cranial nerves. Cedillo Ex. P at 20 (Dr. Fombonne's report); accord Cedillo Tr. at 1050A (Dr. Kinsbourne describing the "observable and measurable minor malformation of the arrangement of the [facial] features" of children with autism). Additionally, children with idiopathic ASDs have "higher rates of anomalies such as posteriorly rotated ears, small feet, and large hands" than do their unaffected siblings. Cedillo Ex. P at 20 (Dr. Fombonne's report); see also Cedillo Tr. at 1061 (Dr. Kinsbourne describing other minor congenital anomalies that may include "an abnormal crease across the palm of the hand or the eyes being wideset or slanting."). Because the observed minor physical abnormalities in children without ASDs do not occur at the same high rates in children with ASDs (whether siblings of the affected

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[31] As of 1998, the Advisory Committee on Immunization Practices has recommended administering the first dose of the MMR vaccine at 12 to 15 months of age. See Morb. Mortal. Wkly Rep. (MMWR) 55(22): 629-630 (2006). Prior to 1998, the recommendation was that the vaccine be administered at 15 months. See Morb. Mortal. Wkly Rep. (MMWR) 47(8):1-57 (1998).

[32] H. Kurita, Infantile autism with speech loss before the age of thirty months, J. of the Amer. Acad. of Child Psychiatry 24: 191-196 (1985).

children or not), investigators have attributed the physical abnormalities to abnormal fetal development. Cedillo Ex. P at 20 (Dr. Fombonne's report). Attributing the physical abnormalities observed in children with ASDs to "disturbances during embryonic development," and not to postnatal factors, investigators have considered whether an "early, prenatal, pathological process is involved in autism." Id. at 20, 21. Other evidence that points toward the involvement of an early, prenatal disturbance leading to the development of ASDs in children are the studies that have correlated brain abnormalities detected by magnetic resonance imaging (MRI) with the observed physical abnormalities in children with ASDs. See Cedillo Ex. P at 20 (Dr. Fombonne's report).

Additionally, there is evidence that abnormal brain development occurs during the first year of life of children with ASDs. Cedillo Ex. P at 15 (Dr. Fombonne's report). In particular, abnormal head growth that results in an enlarged head circumference (macrocephaly) occurs during the second half of the first year of life in some children with ASDs. Id.; see also Hazlehurst Ex. G4 at 488 (2006 Kern article[33]) (stating that increased brain volume is a "consistent neurological abnormality found in persons with autism"). Notably, this increased rate of head growth does not correlate to an increase in height. Cedillo Ex. P at 16 (Dr. Fombonne's report). This rate of head growth does decelerate, however, during the second year of life. Id. at 15-16.

Increased head circumference, which occurs in "about 25%" of autistics, appears to be a marker specific to autism because it is not seen in non-autistic patients with mental retardation or language disorders. Hazlehurst Ex. G51 at 109 (1999 Trottier article[34]). The increased head circumference observed in autistics who are also mentally retarded is distinguishable from the brain atrophy that frequently accompanies mental disorders that have a degenerative course. Id.; see also Cedillo Tr. at 1335-1337 (Dr. Fombonne) (noting that an abnormally large head circumference during the first year of life is typical in autistic subjects); Cedillo Ex. P at 15 (Dr. Fombonne's report)(same); Cedillo Ex. DD at 4 (Dr. Wiznitzer's report) (observing that the abnormal head size during the first year of life that is characteristic of autism generally pre-dates the administration of the MMR vaccine).

Particular neuroanatomical features are also present in individuals with ASDs. See Cedillo Ex. P at 20 (Dr. Fombonne's report). An understanding of these neuroanatomical findings is facilitated by an understanding of the structure of the brain and the observed abnormalities in the structure of the autistic brain.

During the Hazlehurst hearing, respondent's expert Dr. Rust described and compared the architectural structure of a non-autistic brain to the observed abnormalities in particular areas of the autistic brain. See Hazlehurst Tr. at 480A-501A (addressing the

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[33] J. Kern and A. Jones, Evidence of Toxicity, Oxidative Stress, and Neuronal Insult in Autism, Journal of Toxicology and Environmental Health, Part B 9: 485–499 (2006).

[34] G. Trottier et al., Etiology of infantile autism: a review of recent advances in genetic and neurobiological research, J. Psychiatry Neurosci. 24(2): 103-115 (1999).

pathophysiology or alteration in function noted in the brains of autistic patients); Hazlehurst R's Trial Ex. 1 at 5-10 (Dr. Rust's trial slides); see also Hazlehurst Ex. E7 at 95 (2007 Boylan article[35]) ("A number of structural abnormalities have been described in the brains of individuals with autism."). The observed abnormalities in the architecture of the autistic brain occur in a "characteristic" pattern in "particular areas" of the brain. See Hazlehurst Tr. at 493A-495A (Dr. Rust); see also Hazlehurst Ex. E23 at 103 (2007 Geschwind article[36]) ("presenting a synthesis of published data "support[ing] the emerging hypothesis that autism[] result[s] from disconnection of brain regions that are highly evolved in humans"). Dr. Rust testified that "the critical pathological change in autism is in [the] structure called the amygdala, which sits deep in the brain, and is a very . . . complex organ that connects . . . the limbic system."[37] Hazlehurst Tr. at 480 (Dr. Rust); see also Hazlehurst Ex. G24 at 86 (2007 Mueller article[38]) (There is direct evidence "of anatomical and functional compromise of the amygdala [an area in the brain known to affect social behavior] in autism."). The amygdala "is the part of [the] brain that has to do with fight and flight and strong emotions, sexual activity, [and] other kinds of things." Hazlehurst Tr. at 480A-481A. "It [also] connects with the thinking portions of the cortex." Id. at 481A. The cortex, which is the gray matter on the outside of the cerebrum, is the outer layer of the brain. See Dorland's at 424-425; Cedillo Tr. at 1088 (Dr. Kinsbourne).

The cortex of the brain consists of the thinking cells and their supportive cells, which include neuronal cells, astroglial cells, and other cells. Hazlehurst Tr. at 460A-461A (Dr. Rust). These cells "talk to each other" by sending impulses along axons (the fibrous extensions attached to the cells) and along dendrites (the branch-like fibrous extensions from the axons). See id. at 461A. The fibrous extensions between the cells (in the form of axons and dendrites) comprise the pathways or connections that permit the cells to communicate. See id. at 461A. These connections of fibers permit cells to communicate not only within the cortex of the brain but also between the cortical (or outer) layer of the brain and the subcortical layers of the brain. See id.

Dr. Rust explained that as cells develop in accordance with their genetic coding and are influenced by factors (including environmental factors) that affect the genetic

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[35] C. Boylan et al., Modeling early cortical serotonergic deficits in autism, Behav. Brain Res. 176(1): 94-108 (Jan. 10, 2007).

[36] D. Geschwind and P. Levitt, Autism spectrum disorders: developmental disconnection syndromes, Curr. Opin. Neurobiol. 17(1): 103-111 (Feb. 2007).

[37] The limbic system is a "set of forebrain structures" (including the hippocampus and the amygdala) that are associated with autonomic functions and certain aspects of emotion and memory. See Cedillo Ex. P at 20-21 (Dr. Fombonne's report); Hazlehurst Tr. at 480A (Dr. Rust); Dorland's at 1843.

[38] R. Mueller, The Study of Autism as a Distributed Disorder, Mental Retardation and Developmental Disabilities Research Reviews 13: 85-95 (2007).

expression of the cells,[39] the connections between the cells in the normal brain are expected to multiply, to become more specific, to become more sophisticated and to replace earlier connections that are less high-functioning and that developmentally "go[] offline." Id. at 472A, 474A-476A (Dr. Rust). The developmental process of circuit formation in the portion of the brain that affects communication and social behavior, in particular, is hierarchical in nature. Hazlehurst Ex. E23 at 107 (2007 Geschwind article). "[A] weakening of already formed connections[] or a failure of certain connections to establish correct organization" within particular regions of the brain is hypothesized by some investigators to produce the developmental disconnections that produce the core features that are characteristic of ASDs. Id. at 103-104. Investigators further hypothesize that genetic limitations in the early developing parts of the cellular communication system "greatly influence the subsequent range of possibilities for the development [of cellular] connectivity and, eventually, the level of function and degree of plasticity a particular circuit can exhibit." Id. at 107.

As Dr. Rust further explained, the amygdaloid region of the brain is comprised of "exceedingly complex connections through five layers of neurons," and all of the various connections "organize themselves into mini[-]columns." Hazlehurst Tr. at 481A-482A. The columnar structure of the cellular connections in the amygdaloid area of the brain has a distinct appearance and function. See Hazlehurst R's Trial Ex. 1 at 9 (Dr. Rust's trial slides). The columns are arranged at right angles to the surface so the columnar arrangement is "very orderly." See Cedillo Tr. at 1088-1089A (Dr. Kinsbourne). In the normal brain, the columnar structure in the amygdaloid region of the brain regulates cellular communication "[with]in [that] particular portion of the brain[,] . . . and to other parts of the brain." Hazlehurst Tr. at 482A (Dr. Rust). In the autistic brain, however, "selective changes [occur] in what the amygdala connects to." Id. at 481A. Defective development (or dysgenesis) "is found in [this particular area of the] brains of people with autism." Id. At 482A; accord Cedillo Tr. at 1089A (Dr. Kinsbourne describing the columnar disorganization that has been found in the autopsies of autistic brains). The brains of autistic patients have been described to contain "[a]n excessive number of minicolumns" that "are generated early in gestation" by the division of cells lining the embryonic ventricles. See also Cedillo Ex. P at 21 (Dr. Fombonne's report).

Dr. Rust elaborated on the defective development observed in the brains of autistic patients:

> We see not only the column itself being abnormal and its connections being abnormal, but [the] thickness of the cortex over it . . . may be larger than it ou[gh]t to be. . . . [T]he abnormal tissue is actually thicker than it ought to be. [In contrast,] [w]hen we cause injury to a tissue, we make it smaller because we cause cellular elements to be disrupted and killed.
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> In th[e] [circumstance involving an autistic brain, however,] it's larger, and during brain development in the first year and a half of life, lots of areas of

[39] Such factors that affect genetic expression but do not alter genetic structure are known as epigenetic factors. Stedman's Medical Dictionary at 654-655 (28th ed. 2006).

> the brain become larger than they will be in time because they've got all those recruited neurons that are excited about doing something and are not yet connected with each other, and once they do connect, some are eliminated, and so this enlargement becomes something that [becomes] smaller and more compact . . . .
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> [Specifically] what we see in the [autistic] brain . . . underneath the cortical margin [that] is the outside of the brain . . . are the inner layer[s] that become[] too large and . . . too unwieldy, . . . , so th[e brain] volume increases.
>
> This is a characteristic thing . . . [in] particular brain regions [of autistics]. . . .

Hazlehurst Tr. at 482A-484A (Dr. Rust); Hazlehurst R's Trial Ex. 1 at 6-8 (Dr. Rust's trial slides); accord Cedillo Tr. at 1089A (Dr. Kinsbourne testifying that the white matter of the brain is "more voluminous than it should be").

Specifically, "[y]ou lose large [pyramidal] neurons, and I'll emphasize it's the large ones, . . . the very large ones, and you lose some small neurons in the limbic system, . . . [which is the area] I told you about that has to do with emotions and connection with our surroundings in an emotional way. You [also] lose . . . GABA[40] projections." Hazlehurst Tr. at 488A-489A (Dr. Rust) (footnote added); Hazlehurst R's Trial Ex. 1 at 7 (Dr. Rust's trial slides). GABAergic connections are part of the system in the brain that controls matters "like epilepsy and convulsions and abnormal electrical surges in the brain." Hazlehurst Tr. at 483A (Dr. Rust); Hazlehurst R's Trial Ex. 1 at 7 (Dr. Rust's trial slides). There is also evidence of a significant loss of Purkinje cells, which are located in the back of the brain (in the cerebellum) and are important for coordination and language. See Hazlehurst Tr. at 489A (Dr. Rust); Hazlehurst R's Trial Ex. 1 at 7 (Dr. Rust's trial slides); accord Cedillo Tr. at 1088 (Dr. Kinsbourne stating that the Purkinje cells are "deficient" and "impaired"in the autistic brain). The brains on autopsy of autistic patients have revealed observable losses of particular cells in highly selected areas of the brain, including a significant loss of Purkinje cells in the cerebellum of the brain that are "not what you see" after mercury toxicity, encephalitis, or an acquired brain injury. See Hazlehurst Tr. at 486A, 488A (Dr. Rust). The absence of Purkinje cells in the cerebellum in the brain observed on autopsy of individuals with autism as well as the absence of any scarring in the area where the Purkinje cells are missing suggest that the losses of the Purkinje cells occurred prior to birth "before the scarring system is in place in the brain" and were not later-occurring cell deaths. Snyder Tr. at 695 (Dr. Wiznitzer).

The effect of the loss of these particular cells in the autistic brain is a reduction in the "functional boundaries" of columnar connections in the brain that permit certain parts of the brain to communicate with other parts of the brain. See Hazlehurst Tr. at 490A (Dr.

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[40] GABA is the abbreviation for gamma(γ)-aminobutyric acid. Stedman's at 781. The secretion of this substance is important for neural structures. See Dorland's at 747 (defining "GABAergic"). GABA is the primary inhibitory neurotransmitter in the brain. See Cedillo Tr. at 1634A-1635A (Dr. Wiznitzer); Snyder Tr. at 691A (Dr. Wiznitzer).

Rust). These alterations in the structural organization of the brain that are characteristic of the autistic brain result in the loss of the brain's "integrative capacity" that exists in a person with preserved brain architecture. Id. Accordingly, what is missing in autistic patients is an ability to lose interest in an activity and move to another activity; rather than moving to another activity, an autistic patient exhibits a keen interest in a restricted area. Id. 490A-491A. Additionally, autistics may demonstrate an "[a]bnormal sensitivity to certain stimuli," such as loud noises and mixed textures in foods. Id. at 492A-493A.

The cellular connections that form the architecture of the brain develop in the womb. Id. at 493A. In the autistic brain, the connections do not continue to develop as elaborately as in non-autistic brains. See Hazlehurst Tr. at 493A (Dr. Rust). Because studies indicate that "the total number of minicolumns is attained in the first 40 days of gestation in primate species," there is some support for the suggestion that the differences in the minicolumn structure in the brains of autistic patients develop early in the prenatal environment. See Cedillo Ex. P at 21 (Dr. Fombonne's report) (citing 2002a Casanova article, 2002b Casanova article and 2003 Casanova article[41]).

4. Diagnosing an ASD

An evaluation to determine whether a child has an ASD requires a review of the child's developmental history and behaviors. See Cedillo Ex. P at 9 (Dr. Fombonne's report). The assessment tools used to evaluate ASDs include specialized checklists of behaviors and symptoms, standardized instruments for conducting a detailed interview of the parents concerning the child's past and current development, and standardized activities and tasks that permit a clinician to observe the child.[42] Cedillo R's Trial Ex. 8 at 6 (Dr. Fombonne's trial slides); Cedillo Ex. P at 9 (Dr. Fombonne's report). A "high [degree of] consensus" exists among clinicians that the use of these tools permits a proper evaluation of whether or not a subject has an ASD. Cedillo Ex. P at 10.

An evaluating clinician may select the method of assessing a child's symptoms, choosing either a clinical examination or one of the standardized checklists that afford a

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[41] The full cites for these three articles are: (1) M. Casanova et al., Minicolumnar pathology in autism, Neurology 58(3): 428-32 (Feb. 2002); (2) M. Casanova et al., Neuronal density and architecture (gray level index) in the brains of autistic patients, J. Child Neurol. 17(7): 515-21 (Jul. 2002); and (3) M. Casanova et al., Disruption in the inhibitory architecture of the cell minicolumn: implications for autism, Neuroscientist 9(6): 496–507 (Dec. 2003). The articles were filed respectively as Cedillo Exs. P20, P21, and P22.

[42] Among the specialized checklists used in evaluating ASDs is the Childhood Autism Rating Scale known as CARS. Cedillo R's Trial Ex. 8 at 6 (Dr. Fombonne's trial slides). Among the standardized instruments used to evaluate ASDs are the Autism Diagnostic Interview-Revised (or ADI-R) and the Autism Diagnostic Observational Schedule-Generic (ADOS-G). Id.

more standardized observation or measure, or a developmental interview that guides the clinician in the collection of informative symptoms and then can be used to apply DSM-IV criteria in an algorithmic manner to reach a diagnostic conclusion. Cedillo Tr. at 2615A (Dr. Fombonne).

The diagnosis of an ASD is based entirely on abnormalities in behavior and development observed by clinicians and reported by parents. Cedillo Ex. P at 9 (Dr. Fombonne's report). There are no biological markers or medical tests that are diagnostic of an ASD. See id.

Early manifestations of autism may become apparent when clinicians analyze home videotapes of the child's first year of life or first birthday party. See Cedillo Ex. P at 11 (Dr. Fombonne's report); see also Hazlehurst Tr. At 453A (Dr. Rust) (stating that "videos can be very helpful" in diagnosing autism). Additionally, parents tend to recognize symptoms of an autistic child earlier when the child in question is not the first born because the parents' prior experience with childhood development alerts the parents to developmental delay or abnormality in a subsequent child. Cedillo Ex. P at 11 (Dr. Fombonne's report). The first diagnosis of an ASD is likely to occur either during infancy or early childhood because the symptoms marking the onset of an ASD generally occur within the first three years of life. See Cedillo Ex. P at 9 (Dr. Fombonne's report).

Among the questions now asked of parents when evaluating children for autism is whether there are any gastrointestinal symptoms, including either diarrhea or constipation. Cedillo Tr. at 2716A (Dr. Fombonne). Respondent's expert Dr. Fombonne estimates that between 10 and 20 percent of his clinical load of autistic children report gastrointestinal problems for which he refers the children to the pediatrician within the clinic who addresses the children's medical difficulties. Id. Among the responses by physicians to the parents' reports of gastrointestinal problems is dietary advice. Id. at 2716A-2717A. Diet is an important aspect of managing the reported gastrointestinal problems because many of the observed children have a poor diet due to their behavioral restrictions, and some of the children have pica.[43] Id. at 2716A-2717A.

5. The Underlying Cause of ASDs

While the underlying cause of the condition is unknown (idiopathic) in 90 to 95 percent of cases, the biological underpinning of a child's autism spectrum disorder is identifiable in the remaining cases. See Cedillo Ex. P at 16-17 (Dr. Fombonne's report); accord Cedillo Tr. at 1050A (Dr. Kinsbourne estimating that "the actual genetic abnormality has been identified" in 10 to 20 percent of autism cases). Among the known causes of ASDs to date are the genetic disorders involving "marker chromosome 15

[43] Pica is "a perverted appetite for substances not fit as food or of no nutritional value, e.g., clay, dried paint, starch, ice." Stedman's at 1495.

syndrome, fragile X syndrome,[44] tuberous sclerosis,[45] and certain inborn errors of metabolism."[46] Cedillo Ex. DD at 1 (Dr. Wiznitzer's report); Cedillo Ex. P at 17 (Dr. Fombonne's report); see also Cedillo Tr. at 1485 (Dr. Cook).

Additionally, the medical disorder of congenital rubella, which is caused by a prenatal rubella infection, is associated with autistic syndromes. Cedillo Ex. P at 17 (Dr. Fombonne's report). Other identified prenatal environmental risk factors that appear to increase the risk of autistic-like symptoms in children include in utero exposure to thalidomide,[47] valproic acid,[48] misoprostol,[49] and rubella virus infection.[50] Cedillo Ex. P at 20 (Dr. Fombonne's report); see also Cedillo Tr. at 2725A (Dr. Fombonne), Cedillo Ex. P22 at 505 (2003 Casanova article) (noting the "observation of a high incidence of pervasive developmental disorders in children with prenatal exposure to thalidomide). The malformations found in patients exposed to thalidomide or valproic acid "indicate that developmental interference occurs between 20 and 24 days after conception." Cedillo Ex. P at 20 (Dr. Fombonne's report). Moreover, there is scientific evidence that the "window of vulnerability" for exposures to misoprostol or rubella virus infection "occurs during the first 12 weeks of gestation." Id. What is known about environmental exposures that may increase the risk of autism is "entirely confined to the pregnancy or the post-conception weeks." Cedillo Tr. at 2725A-2726A (Dr. Fombonne). "[T]here is not much evidence of postnatal environmental factors." Id. at 2725A.

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[44] Fragile X syndrome is caused by an abnormality on the X chromosome that results in mental retardation. See Stedman's at 1898. Twenty-five to 50 percent of the people with the fragile X gene have autism. Cedillo Tr. at 1485 (Dr. Cook).

[45] Tuberous sclerosis is a condition caused by a genetic mutation that produces seizures and mental retardation in the affected individual. See Stedman's at 1733-1734.

[46] The condition known as phenylketonuria (or PKU) involves inborn errors of metabolism "which can produce brain damage resulting in severe mental retardation" that is accompanied commonly by seizures. See Stedman's at 1480.

[47] Thalidomide was commonly used as "a sedative and hypnotic" in the 1950s and 1960s. Dorland's at 1891. Upon the discovery that it caused serious congenital abnormalities in a fetus when taken by a woman during the early stages of pregnancy, its use was discontinued. Id.

[48] Valproic acid is an orally administered anticonvulsant used to treat epileptic seizures. Dorland's at 2004.

[49] Misoprostol is an orally administered synthetic substance used to prevent the development of gastric ulcers in persons who have had long-term treatment with nonsteroidal anti-inflammatory drugs. See Dorland's at 1161.

[50] Rubella is "[a]n acute but mild exanthematous disease caused by rubella virus . . . with little enlargement of lymph nodes, but usually with little fever or constitutional reaction." Stedman's at 1708.

Although the specific cause for most cases of autism is unknown, there is strong evidence that the principal cause of the condition is genetic.

I. Strong genetic basis for ASDs

Studies of twins and siblings indicate that autism spectrum disorder is a strongly genetic disorder. Cedillo Ex. N at 1 (Dr. Cook's report); Cedillo Ex. N1 at 63 (1995 Bailey article[51]); Cedillo Tr. at 1510-1530 (Dr. Cook) (addressing his own research of genetic bases for autism); Cedillo Ex. P at 17 (Dr. Fombonne's report); Hazlehurst R's Trial Ex. 1 at 3 (Dr. Rust's trial slides) (noting that the results of twin and sibling studies indicate that "[a]utism is . . . among the most heritable of all neurological conditions"). But, autism spectrum disorder is not exclusively genetic. Cedillo Ex. N at 1 (Dr. Cook's report); Cedillo Ex. N1 at 63 (1995 Bailey article); Cedillo Tr. at 1535A-1536 (Dr. Cook) (describing the cause of the condition in identical twins as ninety-two percent genetic and "8 percent [unknown] other").

The relative risk of recurrence of autism in families that has been observed in studies of different family members provides compelling evidence of a strong genetic predisposition to the condition. See Cedillo Ex. N at 1-2 (Dr. Cook's report); Cedillo Tr. at 1490-1491 (Dr. Cook); see also Cedillo Ex. 61D at 63 (1995 Bailey article) (observations of an elevated recurrence risk for autism in siblings and reports of concordance for autism in monozygotic (identical) twins point to the strong influence of familial and genetic factors in autism). When a particular pattern of recurrence of a disorder in family members emerges, that pattern is "distinctive . . . of a disorder with [a] strong genetic influence and relatively little environmental influence." Cedillo Ex. N at 2 (Dr. Cook's report). The pattern of recurrence of a genetically-based disorder expected to occur in a family is as follows:

> If a child has disorder X, the risk of the identical twin having disorder X is much higher than the risk of the fraternal (non-identical) twin having disorder X. . . . [T]he risk to the fraternal twin would be no more than the risk to siblings.

Cedillo Ex. N at 1-2 (Dr. Cook's report).

If, however, there were a significant environmental influence or a significant environmental interaction with genetic factors that contributed to the development of a disorder, the risk of recurrence for a fraternal twin would be expected to be higher than that for a sibling. Cedillo Ex. N at 2 (Dr. Cook's report). The reasoning underlying this thinking is that if environmental factors were a significant causal factor in the development of a disorder, the recurrence risks for fraternal twins and for non-twin siblings would be different because "fraternal twin pairs share environment more strongly than sibling pairs." Cedillo Ex. N at 2 (Dr. Cook's report). However, as respondent's

[51] A. Bailey et al., Autism as a strongly genetic disorder: Evidence from a British twin study, Psychological Medicine 25: 63-77 (1995).

expert Dr. Cook pointed out, the risk to fraternal twins is no more than the risk to siblings for autism. Cedillo Ex. N at 2 (Dr. Cook's report); Cedillo R's Trial Ex. 10 at 1 (Dr. Cook's trial slides). The chance that the next child in a family will have autism if one child (who is not an identical twin) has autism is "approximately 5%" or a 25-fold increased risk. Cedillo R's Trial Ex. 10 at 1.

But studies show that identical twins, who "share 100% of their [genetic code, as determined by their] DNA," have a higher risk of having an autism spectrum disorder than do non-identical twins or non-twin siblings. Cedillo Ex. N at 1-2 (Dr. Cook's report); Cedillo Tr. at 1490-1492A (Dr. Cook); Cedillo Ex. N1 at 68 (1995 Bailey article) (study found 60% concordance rate for autism in monozygotic (identical) twin pairs and 0% concordance rate for autism in dizygotic (fraternal) twin; also found 92% concordance rate for cognitive and social deficits in monozygotic twin pairs and 10% concordance rate for cognitive and social deficits in dizygotic twins). The risk of an identical twin having autism is more than 60% if the other twin has the condition. Cedillo Ex. N at 2 (Dr. Cook's report); Cedillo Tr. at 1491 (Dr. Cook); Cedillo Ex. N1 at 68 (1995 Bailey article). The 60 percent chance that the other twin will have autism if the condition is present in an identical twin represents "a 300-fold increase [of risk] over [that of] the general population." Cedillo Tr. at 1491 (Dr. Cook); Cedillo R's Trial Ex. 10 at 1 (Dr. Cook's trial slides). Moreover, the risk is nearly 90% for an autism spectrum disorder in an identical twin if the other twin has autism. Cedillo Ex. N at 2 (Dr. Cook's report); Cedillo R's Trial Ex. 10 at 1 (Dr. Cook's trial slides); Cedillo Ex. N1 at 68 (1995 Bailey article). Dr. Cook described this increased risk in twins as a "multiplying of risk" that is "a strong signature of . . . multiple genes interacting together." Cedillo Tr. at 1491-1492A (Dr. Cook).

For fraternal (non-identical) twins as well as non-twin siblings, who share 50% of their genetic code, the risks are different. Cedillo Ex. N at 2 (Dr. Cook's report); Cedillo Tr. at 1493A (Dr. Cook). The risk of recurrence for fraternal twins is approximately the same as the risk of recurrence for siblings. Cedillo Ex. N at 2 (Dr. Cook's report); Cedillo Ex. N2 at 935 (1991 Jorde article[52]) (finding a sibling recurrence risk of 4.5%). These findings point to the strength of the genetic predisposition. See Cedillo Ex. N at 2 (Dr. Cook's report); see also Cedillo Ex. P at 17-18 (Dr. Fombonne's report).

A person's susceptibility to autism is likely to be determined by multiple genes rather than a single gene. Cedillo Tr. at 1501, 1523, 1530 (Dr. Cook); see also Hazlehurst Tr. at 457 (Dr. Rust) ("[A]utism is likely the result of a number of different genetic problems."); Cedillo Ex. N2 at 935 (1991 Jorde article) (segregation analysis performed on families with autism does not reveal a single major genetic locus for the inheritance of autism); Cedillo Ex. N5 at 819 (2004 Veenstra-VanderWeele article) ("A[utism] S[pectrum] D[isorder] has a large genetic component with complex inheritance."); Cedillo Ex. P at 19 (Dr. Fombonne's report). A combination of inherited genes as well as individual genetic mutations and chromosomal disorders is suspected to be responsible for

[52] L. Jorde et al., Complex segregation analysis of autism, American Journal of Human Genetics, 49: 932–938 (1991).

causing autism.[53] See Cedillo Tr. at 1503-1505, 1510, 1531 (Dr. Cook); Cedillo Ex. 117 (2007 Beaudet article[54]).

Not all of the implicated genes are represented or expressed in every individual. See Hazlehurst Tr. at 457A (Dr. Rust). Gene expression may be affected by epigenetics, the environmental influences (particularly, the intrauterine influences) that play a role in determining or altering the activity of genes without changing the structure of the genes. Id. at 463A-464A; see also Dorland's at 627. The different genetic abnormalities that occur "may provide some subtle differences between patients and certainly provide differences that are not subtle, . . [such as] the time of onset of disease." Hazlehurst Tr. at 457A (Dr. Rust).

Dr. Cook likened the preprogrammed timing for gene expression (which is the turning on and off of genes) to "genes constantly getting green lights and red lights and some are getting yellow lights to be only partially expressed." Cedillo Tr. at 1499. "[A]ll the genes that we have in any given cell in the body at any given time . . . [have] a completely different sort of toggling what's on and what's off." Id. A classic example of a genetic disorder that does not express symptomatically until much later in life is Huntington's Disease.[55] Id. at 1499-1500 (Dr. Cook).

Dr. Cook testified that "storage diseases"[56] rather than a specific triggering event or

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[53] Dr. Cook testified that a portion of children with autism have elevated levels of serotonin measured in their blood. Cedillo Tr. at 1473A. Serotonin is a naturally occurring vasoconstrictor found in high concentrations in many body tissues, including the intestinal mucosa and the central nervous system. Dorland's at 1686. While investigators have not "tied [the elevated level of serotonin in the blood] sufficiently cleanly to exactly what's happening in the brain yet," id., investigators have discovered that "certain people with autism have specific mutations in the serotonin transporter," a finding consistent with earlier chemistry findings of an "increased serotonin transport function" in some autism patients. Cedillo Tr. at 1479A. Of note, Dr. Cook's discussion of the elevated levels of serotonin discovered in the blood of autistic children illustrated a cautious discussion of scientific findings for which the proper interpretation and understanding is evolving.

[54] A. Beaudet, Autism: highly heritable but not inherited, Nature Medicine 13(5): 534-36 (2007).

[55] 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.

[56] A storage disease is "[a] metabolic disorder in which some substance accumulates or is stored in certain cells in unusually large amounts; the stored substances (continued...)

factor cause "most classic genetic syndromes [involving] normal development and [then] regression." Cedillo Tr. at 1495-1496 (Dr. Cook); see also Cedillo Ex. P at 14 (Dr. Fombonne's report) (stating that the "delayed onset of a disorder does not mean that the disorder is not genetic in origin"). He stated that the genetic disorder "is present from birth" but does not manifest symptomatically until a later date, [and] sometimes a fairly sudden or precipitous date." Cedillo Tr. at 1496 (Dr. Cook). Rett syndrome is an example of a genetic storage disease allowing relatively normal development for the first six to 12 months, followed by a regression at 12 to 18 months in the areas of social interaction and language. Cedillo Tr. at 1496 (Dr. Cook). Approximately 80 percent of the classic cases of Rett syndrome are due to mutations in MECP2. Cedillo Tr. at 1496 (Dr. Cook); see Cedillo Ex. N3 at 1 (2000 Kim article[57]) (Rett syndrome, which is believed to result from mutations on the MECP2 protein, "is a severe neurodevelopmental disorder affecting females almost exclusively.").

Petitioners' expert Dr. Kinsbourne testified that although the genetic predisposition to becoming autistic is very powerful, the genetic element indicates a susceptibility rather than a predestination. Cedillo Tr. at 1049A-1051A. Dr. Kinsbourne added that the medical literature suggests that certain cases of autism require an environmental trigger to potentiate the genetic predisposition, an interaction known as a gene-environment interaction. See id. at 1051A-1052A. Acknowledging "that the term environmental is used in a very broad sense," Dr. Kinsbourne identified the prenatal environment and the postnatal environment as the "temporal domains" in which "possib[le]" environmental causes for autism might exist. See id. at 1052A. Among the environmental factors that Dr. Kinsbourne posited might trigger the development of autism are viral infections and vaccines. Id. at 1052A-1053A.

Respondent's expert Dr. Cook acknowledged that because environmental factors can influence changes in genetic expression, environmental factors are likely to play a role in the development of autism. Cedillo Tr. at 1552A (Dr. Cook); see also Cedillo Ex. N2 at 935 (1991 Jorde article) (attributing the observed familial clustering to a "combination of both polygenic and shared environmental effects"). Dr. Cook explained, however, that "when we think of environment and gene interaction, particularly in very early child onset, we're very typically focusing in on what happens before birth." Cedillo Tr. at 1494 (Dr. Cook). Dr. Cook elaborated that references to the interaction between genes and the environment in scientific literature "[m]ost commonly" refer to prenatal environmental risks and conditions and to peri-natal (obstetrical) conditions or risks. Id. at 1494-1495. Among the potential environmental factors implicated in the development of autism are also "preconception" environmental factors such as the ages of the parents at the time of conception. Cedillo Tr. at 1540A-1541A (Dr. Cook). Dr. Cook observed, however, that in a series of reported cases of autism in Tanzania, it appeared that the postnatal impact of

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[56](...continued)
may be lipids, proteins, carbohydrates or other substances." Dorland's at 542.

[57] S. J. Kim, and E. H. Cook, Jr., Novel de novo nonsense mutation of MECP2 in a patient with Rett syndrome, Human Mutation 15: 382-383 (2000).

infectious disease, specifically, malaria, was a contributing factor in the development of the condition. Cedillo Tr. at 1541A.

Dr. Cook cautioned against reliance on articles such as the 2002 Purcell article[58], filed as Cedillo Ex. N4, for the proposition that autism is caused by environmental influences. Cedillo Tr. at 1501-1502A (Dr. Cook). Dr. Cook explained that the 2002 Purcell article is a mathematical modeling paper addressing the gene-environment interaction for conditions like major depression "where there are known environmental influences." Id. at 1502A. The 2002 Purcell article does not address autism at all. Id. at 1502A.

The presented evidence on the genetic influences underlying autism supports a finding that the genetic basis for autism is very strong. Petitioners did not disagree that genetic influences are a significant factor contributing to the development of autism. Petitioners urge, however, that because autism is not an exclusively genetic condition, environmental factors must be considered also. Petitioners posit that thimerosal-containing vaccines and the MMR vaccine are among the environmental factors that can contribute to the development of autism.

Petitioners' theory of vaccine-related causation has been the subject of a number of epidemiologic studies, which are studies of the factors that cause disease and that influence the distribution of disease in human populations. See Cedillo Tr. at 2501 (Dr. Fombonne) (defining epidemiology as "the study of the distribution of disease in human populations and the study of [the] factors which influence that distribution"); see also Dorland's at 626 (defining epidemiology as "the science concerned with the study of the factors determining and influencing the frequency and distribution of disease, injury, and other health-related events and their causes"); Cedillo Ex. P76 at 150-171 (2007 Fombonne book excerpt[59]). The undersigned turns now to examine the conducted epidemiologic studies of autism and childhood vaccines.

ii. The epidemiologic studies show no causal association between autism and administered childhood vaccines

Epidemiology does not decide the question of causation. Cedillo Tr. at 1058 (Dr. Kinsbourne). But it does detect associations "and then other scientific methods can further explore those associations to determine whether [they are] causal or coincidental." Id. at 1058-1059A.

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[58] S. Purcell, Variance component models for gene-environment interaction in twin analysis, Twin Research 5(6): 554-571 (2002).

[59] E. Fombonne, Epidemiology chapter in Lewis's Child and Adolescent Psychiatry: A Comprehensive Textbook, A. Martin et al., eds. (Lippincott Williams & Wilkins 4th ed. 2007).

There are different types of epidemiologic study designs. Cedillo Tr. at 2501 (Dr. Fombonne); see also Cedillo R's Trial Ex. 21 at 2 (Dr. Fombonne's trial slides). The two major study designs are the cohort study (a prospective study) and the case-control study (a retrospective study). Cedillo Tr. at 2501-2502 (Dr. Fombonne); see also Cedillo R's Trial Ex. 21 at 2 (Dr. Fombonne's trial slides); Cedillo Ex. P76 at 152-153 (2007 Fombonne book excerpt).

The cohort study, also known as an incidence study, compares the onset of a disease in two different groups of subjects. Cedillo Tr. at 2501. One group is comprised of subjects that had been unexposed to a particular substance of interest prior to the exposure. Id. The other group is comprised of subjects that remain unexposed to the substance of interest. Id. The incidence of a developing disease is measured in both groups over time and compared. Id. If the incidence of the developing disease is comparable or equal in the two groups, the exposure of interest is deemed to have no effect on the incidence of the disease. Id. at 2502.

With a case-control study, the initial group of subjects selected has a disease of interest. Cedillo Tr. at 2502. Then a control group of subjects is selected (a group that is free of the disease of interest). Id. Past exposures and retrospectively-determined biological problems are evaluated for both groups and then compared to assess whether the past exposures and biological problems were greater in the group of cases than in the controls. Id. This comparison yields information about the relative risk for the disease in the two groups. Id.

In addition to the two major study designs are two additional types of epidemiological studies, the prevalence study and the ecological study. A brief description of those study designs follows.

The third type of epidemiologic study design is the prevalence study or the cross-sectional study. Id. For this study design, a given population is assessed at a single point in time to determine who has the disease of interest, who does not have the disease, and who has the characteristic of interest that may be related to the disease. Id. at 2502-2503A.

The fourth type of epidemiologic study design is the ecological study. Id. at 2503A. The purpose of the ecological study is to relate rates of exposure over the same time period. Id. For example, one might examine whether there is a relationship between unemployment rates and suicide rates over time. Id. The type of inference to be made from ecological studies is much less strong than the inferences to be made from either a cohort study or a case-control study. Id.

The described epidemiologic studies measure either the prevalence rate of disease or the incidence rate of disease. Id. at 2504A-2505A. The prevalence rate is the simple proportion of subjects in a given study who have the disease of interest. Id. at 2505A. There is no passage of time with this measurement, and the measurement does not inform about the onset of new cases of the disease of interest. Id. at 2505A.

The incidence rate may be calculated in two different ways. The first calculation is

of cumulative incidence, and it measures the new onset of a disease over a given period of time. Id. at 2505A-2506A. The second calculation of incidence determines incidence rate. This calculation is derived from studies of dynamic populations where "people . . . come in, people . . . come out, people. . . die." Id. at 2506A-2507. The numerator of the calculation is expressed as the number of new onsets of disease over a period of time. Id. at 2507. The denominator of the calculation is the number of persons observed during a period of time and is often expressed in person years. Id. As an example of this incidence rate calculation, consider that the suicide rate in the United States for males between the ages of 15 and 24 is 20 per 100,000 persons observed in this age group for one year. Id. at 2507-2508A.

Dr. Fombonne testified that most of the epidemiologic studies of autism have been prevalence studies. Since the year 2000, at least 12 published studies performed by different investigators using different methods and variously located in the United States, Canada, the United Kingdom, Scandinavia and the Faroe Islands have reported consistently that autism rates are around 60 to 70 children per 10,000. Id. at 2512. Compared to the recorded rates of four or five children per 10,000 in earlier epidemiologic studies performed in the 1960s and in the early 1970s, the prevalence rates are now much higher. Id. Nonetheless, Dr. Fombonne explained that higher prevalence rates is not necessarily evidence that the disorder is increasing in the population. See id. at 2512-2513A. Moreover, current referral data maintained by health care providers or educational providers offer information about the numbers of people accessing services, but that data can be misleading with respect to trends in the incidence rate of autism. Cedillo Tr. at 2519A.

Among the explanations studied and offered for why prevalence rates are higher than they were previously is the change in diagnostic concepts and criteria during the past 40 years. Id. at 2513A (Dr. Fombonne); accord id. at 1057A (Dr. Kinsbourne) (acknowledging some improvement in case ascertainment and diagnosis). The disorders of pervasive developmental delay and Asperger's disorder were added to the spectrum of autistic disorders. See id. at 2513A-2514A (Dr. Fombonne). Additionally, the criteria in the diagnostic instruments were reorganized. See id. at 2514A-2516. There is strong evidence that changes in diagnostic practices have contributed to the higher number of diagnoses of autism spectrum disorder.[60] Cedillo Tr. at 2523, 2530; see also Cedillo Ex. P134 (2006 Shattuck commentary[61]) (referencing the 2006 Shattuck study reporting that diagnostic substitution, specifically a decrease in the classification of children as either

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[60] The initial criteria for autism were developed in 1970 in England by Michael Rutter. Cedillo Tr. at 2513A. The criteria were reorganized and simplified in the DSM-III in 1980, and the term pervasive development disorder was coined. Id. at 2513A-2514A. Subsequently, the diagnostic criteria for autistic disorders were reorganized in the DSM-IV, and the diagnosis of Asperger's disorder was introduced. Id. at 2514A.

[61] P.T. Shattuck, Diagnostic substitution and changing autism prevalence, Pediatrics 17(4): 1438-1439 (2006). This filing is a published commentary by Dr. Shattuck responding to criticism of his conducted study. Although Dr. Fombonne referenced the report, respondent did not file a copy of the 2006 Shattuck study.

learning disabled or mentally retarded and a correlative increase in the classification of children as autistic, accounts for the increase in the number of children who currently have a diagnosis of autism). As one study in Finland reflects, simply changing the diagnostic criteria from what Dr. Kanner used when he first identified a group of autistic children in 1943 to the criteria contained in the more modern ICD-10 criteria, resulted in a threefold increase in the prevalence rate. Id. at 2514B-2515A; Cedillo R's Trial Ex 21 at 7 (Dr. Fombonne's trial slides); see also Cedillo Ex. P97 (2000 Kielinen article[62]).

Studies examining whether an association exists between the MMR vaccine and the development of autism have found no association. Cedillo Tr. at 2530-2559 (Dr. Fombonne); see also Cedillo Ex. P145 (1999 Taylor article[63]) (study in the United Kingdom finding no difference in autism rates between children who were never exposed to MMR and children who were); Cedillo Ex. P38 (2004 DeStefano article[64]) (a case-control study conducted in Atlanta, GA looking at immunized and unimmunized children with autism spectrum disorders); Cedillo Ex. P105 (2002 Madsen article[65]) (a retrospective cohort study of Danish children finding no association between MMR exposure and development of ASD[66]); Cedillo Ex. P137 (2004 Smeeth article[67]) (a case-control study in the United Kingdom finding no association between autism and past exposure to MMR); Cedillo Ex. P40 (2001 DeWilde article[68]) (testing hypothesis that a behavioral decline in children follows the administration of the MMR and finding no increased consultations with doctors in autism group than in the non-autism group during the six months after the

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[62] M. Kielinen et al., Autism in Northern Finland, Eur. Child Adolesc. Psychiatry 9(3): 162-7 (Sep. 2000).

[63] B. Taylor et al., Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal connection, Lancet 353: 2026-2029 (1999).

[64] F. DeStefano et al., Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta, Pediatrics 113(2): 257-266 (Feb. 2004).

[65] K. M. Madsen et al., A population-based study of measles, mumps, and rubella vaccination and autism, N. Engl. J. Med. 347(19): 1477-1482 (Nov. 7, 2002).

[66] According to the Danish investigators, children who received the MMR vaccine had received thimerosal-containing vaccines prior to the receipt of the MMR vaccine until 1995 or 1996 when thimerosal-containing vaccines were no longer administered as part of the Danish immunization schedule. See Cedillo Tr. at 2646A-2651 (Dr. Fombonne).

[67] L. Smeeth et al., MMR vaccination and pervasive developmental disorders: a case control study, Lancet 364(9438): 963-969 (Sep. 11-17, 2004).

[68] S. DeWilde et al., Do children who become autistic consult more often after MMR vaccination? Br. J. Gen. Pract. 51(464): 226-227 (Mar. 2001).

MMR immunization); Cedillo Ex. P33 (2001 Dales article[69]) (showing no correlation between the increase in the number of children diagnosed with autism and shift in the age of receipt of the vaccination from 17 months to 24 four months; Cedillo Ex. P74 (2006 Fombonne article[70]) (a Canadian study examining the rates of autism after the first MMR dose at 12 months and the second MMR dose at 18 months and finding no increased risk of autism after the second dose); Cedillo Ex. P87 (2005 Honda article[71]) (finding that discontinued MMR exposure had no effect on increasing autism rates in Japan). A number of controlled epidemiologic studies has been conducted employing different designs. Cedillo Tr. at 2576 (Dr. Fombonne). The results of the studies are consistent, showing no association between MMR and autism. Id.

To the extent that the claim precipitated by the work of Dr. Andrew Wakefield viewed regressive autism as a relatively new phenotype of the disorder, that claim is undercut by evidence of an epidemiologic study conducted in 1966, more than 40 years ago, that documents a loss of skills in about 30 percent of the studied children. See Cedillo Tr. at 2562-2563. That percentage is comparable to other more recent studies that have found rates of regression that range from 25 to 40 percent in autistic children. Id. at 2563-2564A. Additionally, the 2007 Uchiyama article,[72] filed as Cedillo Ex. P149, "showed absolutely no effect of MMR on the proportion of regressive autism." Cedillo Tr. at 2566-2567 (Dr. Fombonne); see also Cedillo Ex. P149 at 215 (2007 Uchiyama article) (analysis of study results "disconfirm[s] the hypothesis that the MMR vaccination causes regression in ASD"). Moreover, the 2006 Richler article, filed as Cedillo Ex. P124,[73] examined autistic children with regression and autistic children without regression and the timing of the receipt of the MMR vaccination and found no association between the development of regressive autism and the timing for receipt of the MMR vaccine. See Cedillo Ex. P124 at 299-300, 314 (2006 Richler article).

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[69] L. Dales et al., Time trends in autism and in MMR immunization coverage in California, JAMA 285(9): 1183-1185 (Mar 7, 2001).

[70] E. Fombonne, Pervasive developmental disorders in Montreal, Quebec, Canada: prevalence and links with immunizations, Pediatrics 118(1): e139-e150 (2006).

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

[72] T. Uchiyama, et al., MMR-vaccine and regression in autism spectrum disorders: negative results presented from Japan, J. Autism Dev. Disord. 37(2): 210-7 (Feb. 2007) (finding that the rate of regressive autism in Japanese subjects who received the MMR vaccine was no higher than the rate of regressive autism in Japanese subjects who did not receive the vaccine).

[73] 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 (Apr. 2006).

Petitioners have argued that autistic enterocolitis is a regressive form of autism that is accompanied by gastrointestinal symptoms and that occurs in a previously normal child within days after the receipt of the MMR vaccine. Studies have examined whether there is any association between inflammatory bowel conditions, the MMR vaccine and autism, and have found no association among the three factors. See Cedillo Tr. at 1425A-1429A; see also Cedillo Ex. P36 (1998 DeGiacomo article[74]) (study of incidence of inflammatory bowel disorders in two large samples of British children who were referred to a specialized clinic for pervasive developmental disorders at Maudsley Hospital in London); Cedillo Ex. P37 (2005 Demicheli article[75]) (review of prospective and retrospective studies conducted worldwide to assess the occurrence of adverse events, including inflammatory bowel disease, following exposure to MMR); Cedillo Ex. P12 (2002 Black article[76]) (a study in the United Kingdom finding no association between inflammatory bowel disease and autism). The epidemiologic studies do not show that there is a separate phenotype of autism that can be described as autistic enterocolitis. Cedillo Tr. at 2724-2725A.

Other studies have looked at whether there is a causal association between thimerosal-containing vaccinations and the development of autism. See id. at 2576-2586; see also Cedillo Ex. P88 (2003 Hviid article[77]) (a Danish study comparing 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 and finding no increased risk in the subjects with thimerosal exposure); Cedillo Ex. P106 (2003 Madsen article[78]) (an ecological study looking at the effect of discontinuing the use of thimerosal in vaccines in 1992 in Denmark and finding that autism rates continued to increase after the removal of thimerosal from vaccines); Cedillo Ex. P150 (2003 Verstraeten article[79]);

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[74] A. DeGiacomo and E. Fombonne, Parental recognition of developmental abnormalities in autism, Eur. Child Adolesc. Psychiatry 7(3): 131-136 (1998).

[75] V. Demicheli et al., Vaccines for measles, mumps and rubella in children, Cochrane Database Syst. Rev. (4): CD004407 (Oct. 19, 2005).

[76] C. Black et al., Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database, BMJ 325(7361): 419-21 (Aug. 24, 2002).

[77] A. Hviid et al., Association between thimerosal-containing vaccine and autism, JAMA 290(13): 1763-1766 (Oct. 1, 2003).

[78] K. M. Madsen, Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data, Pediatrics 112(3Pt1): 604-606 (Sep. 2003).

[79] T. Verstraeten et al., Vaccine Safety Datalink Team. Safety of thimerosal containing vaccines: a two-phased study of computerized health maintenance organization databases, Pediatrics 112(5): 1039-1048 (Nov. 2003).

Cedillo R's Ex. P3 (2004 Andrews article[80]); Cedillo Ex. P86 (2004 Heron article[81]); R's Ex. P141 (2003 Stehr-Green article[82]). The studies showed no association. Cedillo Tr. at 2585.

Dr. Fombonne noted that the claims that there is an epidemic of autism "have been made in the context of th[e] vaccination hypothesis." Id. at 2703A-2704. But there is a large body of evidence from studies that have been replicated across countries showing that the exposure of particular children to either MMR or thimerosal-containing vaccines does not increase the risk of autism. Id. at 2705A-2706A. Moreover, the continued rise in the rates of autism after the discontinuation of certain vaccine exposures is "quite convincing" that the rise "has nothing to do with vaccination[s]." Id. at 2704A.

A statistically significant association, or the lack thereof, between an exposure and a disease detected in an epidemiologic study does not decide whether or not the association is a causal one. Cedillo Ex. P76 at 156 (2007 Fombonne book excerpt). But when the findings of multiple studies are consistent, the assessment of causality is strengthened. See id. Importantly, "the substantive findings of epidemiologic studies . . . inform public health activities." Id.

The testimonial and documentary evidence presented by the parties indicate that the conducted epidemiological studies are not without their respective design flaws. Petitioners assert that, for purposes of this litigation, the most critical flaw in the studies is the failure to examine whether there is an association between the onset of the regressive form of autism, the receipt of the MMR vaccine and thimerosal-containing vaccines, and the development of gastrointestinal problems. Petitioners argue that because the body of epidemiological evidence to date has focused on autism in general and not on the regressive form of autism in particular, the conclusions of the discussed and cited studies have limited relevance to petitioners' OAP claims.

The undersigned finds petitioners' contention unavailing. Epidemiological evidence cannot establish causation, but can show an association between factors that, after further study, may be causally related. As introduced into evidence here, multiple epidemiological studies of different populations by different researchers using different study designs have failed to show an association between the MMR vaccine, thimerosal-containing vaccines, the onset of autism, and the development of gastrointestinal

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[80] 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 (Sep. 2004).

[81] J. Heron et al., ALSPAC Study Team. 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 (Sep. 2004).

[82] P. Stehr-Green et al., Autism and thimerosal-containing vaccines: lack of consistent evidence for an association, Am. J. Prev. Med. 25(2): 101-106 (Aug. 2003).

symptoms. That the collective body of epidemiological evidence has consistently failed to show any association makes petitioners' claims of a causal relationship less likely. Moreover, even if many of the conducted studies were not designed to examine whether an association exists between regressive autism and the vaccines of interest in this litigation, at least two of the conducted studies specifically looked for an association between the MMR vaccine and the development of regressive autism and found none. See Cedillo Ex. P149 at 210-211, 214 (2007 Uchiyama article) (finding that the rate of regressive autism in Japanese subjects who received the MMR vaccine was no higher than the rate of regressive autism in Japanese subjects who did not receive the vaccine); Cedillo Ex. P124 (2006 Richler article) (examining autistic children with regression and autistic children without regression and the timing of the receipt of the MMR vaccination and finding no association between the development of regressive autism and the timing for receipt of the MMR vaccine). Petitioners are not required to present epidemiological evidence in support of their vaccine claims. See Capizzano, 440 F.3d at 1325. But when the existing epidemiological evidence introduced into the record fails to show an association between autism and the MMR vaccine or thimerosal-containing vaccines, the undersigned properly may consider that the epidemiological evidence does not militate in favor of a finding urged by petitioners that certain cases of regressive autism are vaccine-related. See 42 U.S.C. § 300aa-13(b)(1) (requiring that a special master "consider[] the entire record").

The undersigned turns now to address the first aspect of petitioners' general causation theory pertaining to thimerosal-containing vaccines.

B. Examining Petitioners' Claim that the Mercury Component of Thimerosal-Containing Vaccinations Causes Immune Dysfunction and Neurological Injury that Contributes to the Development of Autism

As the first aspect of their general causation theory, petitioners assert that the thimerosal content in the prescribed schedule of childhood vaccinations received during the first year of life increases the mercury body burden in a genetically-predisposed child who is hypersusceptible to mercury exposure and has difficulty excreting mercury. Cedillo Post-Hearing Brief at 64-66; Hazlehurst Supp. Post-Hearing Brief at 4-5; Snyder Post-Hearing Brief at 20-21. Petitioners contend that the increased mercury body burden in such a child leads to immune dysfunction in the child that impairs the child's ability to fight viral infections. Cedillo Post-Hearing Brief at 207-217; Hazlehurst Supp. Post-Hearing Brief at 9; Snyder Post-Hearing Brief at 20-21. Additionally, the increased mercury body burden in such a child can lead to a deposition of mercury in the brain that causes neurological injury that presents as autism. See id.

In support of their arguments regarding the neurotoxic properties of the mercury component of thimerosal, petitioners offered the expert opinion of Dr. Aposhian. Dr. Aposhian asserted that complex diseases such as autism result from the interplay of three factors: a person's genetic susceptibility, exposure to environmental factors, and the stage of a person's development at the time of certain environmental exposures. See Cedillo Tr.

at 109 (Dr. Aposhian) (citing 2003 Kalada article[83]); Cedillo Ps' Trial Ex. 1 at 37 (Dr. Aposhian's trial slides). One of the critical environmental factors in the development of autism, according to Dr. Aposhian, is mercury exposure through thimerosal-containing childhood vaccinations. See Cedillo Ps' Trial Ex. 1 at 13, 31, 38 (Dr. Aposhian's trial slides). Dr. Aposhian contends that this exposure is particularly problematic in autistic children because autistic children may be hypersusceptible to the effects of mercury. See Cedillo Tr. at 129A-129B (Dr. Aposhian). Additionally, Dr. Aposhian posits, autistic children cannot properly excrete mercury, a condition Dr. Aposhian describes as a mercury efflux disorder. See Cedillo Ps' Trial Ex. 1 at 26, 28, 31 (Dr. Aposhian's trial slides). Dr. Aposhian, who is not a medical doctor, based his opinions on his asserted expertise as an environmental toxicologist.

Respondent's expert Dr. Brent asserted that the proper method for evaluating the effects of a chemical exposure, or more specifically in this case, the effect of the mercury exposure, is to consider: (1) what was the form of the mercury and the amount of the exposure; (2) whether such exposure could cause the condition at issue; and (3) whether the exposure did cause the condition at issue. See Cedillo R's Trial Ex. 17 at 5 (Dr. Brent's trial slides). Dr. Brent contends that there is no evidence to support the hypothesis that the doses of thimerosal given in vaccines cause adverse neurotoxic or immunological effects, other than allergic reactions. See Cedillo R's Trial Ex. 17 at 17 (Dr. Brent's trial slides). Moreover, Dr. Brent contends that there is no reliable scientific support for the hypothesis that autistics have an efflux disorder that causes them to excrete mercury differently than non-autistics. See Cedillo R's Trial Ex. 17 at 31, 40-41 (Dr. Brent's trial slides).

In his practice as a medical toxicologist, Dr. Brent has treated children suffering from mercury poisoning and has treated children with ASDs for whom a toxicological examination and treatment are sought. Cedillo Ex. L at 3 (Dr. Brent's report). He maintains that mercury poisoning is a "clinically distinct" syndrome from an ASD. Id. at 4. Dr. Brent asserts that each of the conditions presents "its own characteristic signs, symptoms, and laboratory findings." Id. at 4.

Before addressing the opinions of the parties' experts and the evidence offered in support of their opinions in further detail, the undersigned first examines what the mercury content is in thimerosal-containing vaccinations and then examines what are the factors that determine the toxicity of mercury. These principles are useful in understanding why the undersigned finds that petitioners' reliance is misplaced on literature that involves dosages of mercury that far exceed the mercury content in the vaccines of interest and that involves forms of mercury that have different toxicological properties from the properties of the mercury component in childhood vaccines. This literature does not support petitioners' theory of vaccine-related causation.

[83] Although Dr. Aposhian cited this article in his testimony, petitioners never filed a copy of the article into the record.

1. Thimerosal-Containing Vaccines have a Mercury Component

Thimerosal is the trade name for ethylmercury thiosalicylate. Cedillo Ex. 55H (2006 Clarkson article[84]); see also Hazlehurst Tr. at 373A. Ethylmercury thiosalicylate is a mercury-containing compound that "was introduced as a preservative in many medicinal preparations and vaccines" in the 1930s.[85] Id.; see also Cedillo Tr. at 2312 (Dr. Brent). Use of thimerosal as a preservative is particularly important in multiple-use vaccine vials, which are vials from which the vaccine fluid is extracted multiple times by a syringe needle for multiple vaccine administrations. See Cedillo Ex. 55H at 645 (2006 Clarkson article); see also Cedillo Ex. L8 at 1147 (2001 Ball article)[86] (noting that, consistent with Food and Drug Administration (FDA) regulations, preservatives must be added to multi-use vials of vaccine).

Prior to the year 2000, children could receive up to 185.5 mcg of ethylmercury from thimerosal-containing vaccines during the first 14 weeks of life under the prescribed immunization schedule for children.[87] See Cedillo Ex. 55 at 9 (Dr. Aposhian's report)

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[84] T. W. Clarkson and L. Magos, The Toxicology of Mercury and Its Chemical Compounds, Critical Reviews in Toxicology 36: 609, 645 (2006).

[85] A number of substances, including thimerosal, enjoyed widespread medicinal use well before modern regulatory measures were implemented. Accordingly, due to thimerosal's long history of medicinal use, it has never been the subject of a new drug application review process by the United States Food and Drug Agency (FDA), which was established about the same time that the use of thimerosal as a medicinal preservative began. See R's Trial Ex. 19 (Dr. Brent's slides) (containing a copy of Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses, 21 C.F.R. § 310.545 (Apr. 11, 2007) (listing drug products containing certain active ingredients that are offered over-the-counter for certain uses even though "there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses")). Other commonly used substances that were never subjected to the FDA's new drug application process and thus, are identified as lacking "adequate data to establish . . . the safety and effectiveness of [the substances] for the specified uses" are aspirin, honey, caffeine, and codeine." Id.; Cedillo Tr. at 2317 (Dr. Brent); Cedillo Tr. Ex. 17 at 4 (Dr. Brent's trial slides).

[86] L. K. Ball et al., An assessment of thimerosal use in childhood vaccines, Pediatrics 107(5):1147-1154 (May 2001).

[87] The immunization schedule included nine doses of thimerosal-containing vaccines: three doses of which were DtaP (diphtheria, tetanus and acellular pertussis) vaccines, three doses of which were Hep B (hepatitis B) vaccines, and three doses of which were HIB (hemophilus influenzae B) vaccines. See Cedillo Ex. II at 28 (Institute of Medicine, Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders, K. Stratton et al., eds. (National Academy Press 2001)).

(continued...)

(citing 2001 Clements article[88]). The amount of ethylmercury contained in a pediatric dose of vaccine for anti-microbial purposes typically ranged from 12.5 to 25 mcg.[89] Cedillo Ex. 55NN at 1737 (2002 Pichichero article[90]).

Petitioners argue that the vaccine doses of mercury-content administered in accordance with the prescribed immunization schedule are effectively bolus injections of mercury at one time. Cedillo Ex. 55 at 9 (Dr. Aposhian's report). Petitioners contend that these vaccine dosages are sufficient to suppress the immune systems of children and have neurotoxic effects on the bodies of the children who subsequently develop autism as a result of having received the mercury-containing vaccinations. See Cedillo Ex. 55 at 9-11 (Dr. Aposhian's report).

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 Cedillo L8 at 1147 (2001 Ball article). The evaluation included an assessment of the exposure dose at which toxicity occurs. Id. The FDA observed that "[d]epending on the immunization schedule, vaccine formulation, and infant weight, cumulative exposure of infants to mercury from thimerosal during the first six months of life may exceed EPA guidelines" for exposure to methylmercury, a form of mercury other than ethylmercury (the form of mercury into which thimerosal dissociates after vaccination).[91] Id. 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). Id. The FDA concluded, however, that the doses of thimerosal in vaccines administered to children in accordance with the prescribed immunization schedule "revealed no evidence of harm." Id.

Subsequently, on July 7, 1999, the American Academy of Pediatrics and the United

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[87](...continued)
The other administered childhood vaccines, specifically, the inactivated polio vaccine and the live viral vaccines (which include MMR, varicella, and oral polio) never contained any thimerosal. Id. at 27.

[88] Dr Aposhian addressed this article in his report but petitioners did not file a copy into the record.

[89] The abbreviation for a microgram, a unit measure of weight, is either mcg or µg. See Stedman's at 1207. Citations to this unit of measure appear in this decision as mcg.

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

[91] The FDA used the EPA's guidelines for exposure to methylmercury because no EPA guidelines existed for ethylmercury. See Section III.B.2.c of the decision.

States Public Health Service issued a joint statement, which was followed by an interim report from the American Academy of Pediatrics to clinicians recommending, as a precautionary measure, the prompt removal of thimerosal from childhood vaccines. See Cedillo Ex. L8 at 1147, 1153 (2001 Ball article); Hazlehurst Ex. 37L (1999 Joint Public Health Statement[92]). In September 1999, the American Academy of Pediatrics and the United States Public Health Service issued a joint public health statement recommending that the use of thimerosal as a preservative in childhood vaccinations be discontinued. See Hazlehurst Ex. 37L (1999 Joint Public Health Statement). In response, vaccine manufacturers discontinued the use of thimerosal as a preservative in most childhood vaccines currently administered in the United States.[93] See Cedillo Ex. L8 at 1147 (2001 Ball article); see also Cedillo Ex. 55H at 645 (2006 Clarkson article).

Chemically, thimerosal is approximately 50 percent ethylmercury. See Cedillo Ex. 55H at 645-647 (2006 Clarkson article); see also Cedillo Ex. 55G at 15 (2002 Clarkson article[94]). The "relatively weak" chemical bond between the ethylmercury and the thiosalicylate components in thimerosal facilitates the disassociation of thimerosal into ethylmercury and thiosalicylate during an injection of vaccine fluid into the body. Cedillo Tr. at 2114 (Dr. Brent). Some of that disassociation may occur in the vaccine vial prior to an administration of vaccine. Cedillo Tr. at 2314A (Dr. Brent).

An evaluation of petitioners' arguments concerning the effect of the thimerosal content in childhood vaccines requires an examination of the factors that determine the toxicity of mercury. Among the factors to be considered are the properties of mercury, in general, and the properties of ethylmercury, the mercury component in thimerosal, in particular.

2. Factors that Determine the Toxicity of Mercury

A poison may be defined "as any agent capable of producing a deleterious response in a biological system, seriously injuring [the] function [of the biological system,] or producing death." Cedillo Tr. at 2337-2338 (Dr. Brent) (quoting Cedillo Ex. L35 (2001

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[92] Joint Statement of the American Academy of Pediatrics (AAP) and the United States Public Health Service (USPHS), Pediatrics 104(3): 568-569 (Sep. 1999).

[93] Trace amounts of thimerosal left from the manufacturing process remained in vaccines produced after the 1999 recommendation to discontinue the use of thimerosal in vaccines. Cedillo Ex. II at 30 (Institute of Medicine, Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders, K. Stratton et al., eds. (National Academy Press 2001)). Additionally, previously produced lots of thimerosal-containing vaccines remained available. Id. The use of thimerosal as a preservative has continued, however, in the influenza vaccine routinely administered to children. Id.

[94] T. W. Clarkson, The three modern faces of mercury, Environ. Health Perspect. 110: 11-23 (2002).

Klaassen toxicology book excerpt[95]). When an agent "becomes capable of producing a deleterious response," and thereby becomes poisonous, is determined by the amount or dose of the agent to which an individual is exposed. Cedillo Tr. at 2338 (Dr. Brent) (conversely, what determines "that the thing is not a poison" is the dose). As the potential toxicity of mercury was described in the early 16th century by Paracelsus, a Swiss physician, it is "[t]he dosage [that] makes it either a poison or a remedy." Cedillo R's Trial Ex. 17 at 19 (Dr. Brent's trial slides).

The toxicological concept that informs what impact a particular exposure might have on an individual is referred to as the dose/response relationship. The dose/response relationship is the relationship between an exposure to an amount of an agent that has particular characteristics and the spectrum of observed or measured responses in an individual following that exposure. See Cedillo Ex. L1 at 1 (1999 ATSDR Mercury Profile[96]); Cedillo Ex. L35 at 834 (2001 Klaassen toxicology book excerpt). During the Cedillo hearing, petitioners' expert Dr. Aposhian concurred that "[e]ssentially, we take dose in[to] consideration." Cedillo Tr. at 130. But, he asserted, "[d]ose is not the only factor that determines toxicity." Id. Dr. Aposhian posited that toxicologists must now consider "the genetics and hyper[]susceptibility of some people." Id. at 129A-129B.

Among the recognized factors that determine whether an individual who has been exposed to mercury will be harmed are: (1) the form of mercury to which the individual is exposed (the type of mercury involved), (2) the amount of mercury to which the individual is exposed (the exposure dose), (3) the duration of the exposure, and (4) the method of the exposure (whether by inhalation, ingestion, or skin contact). See Cedillo Ex. L1 at 1 (1999 ATSDR Mercury Profile). Additional factors to consider are other sources of chemical exposure, age, sex, diet, family traits, and the state of one's health. Id. Although the pharmacokinetics of mercury exposure are different for children, "there are no [identified] special metabolites or metabolic pathways that are unique to children." Cedillo Ex. L1 at 355 (1999 ATSDR Mercury Profile).

a. The Properties of Mercury in Its Different Forms and the Observed Effects of Exposures

Mercury, the chemical symbol for which is Hg, is a heavy metal.[97] Cedillo Ex. 55H at 612. The history of its use in medical preparations exceeds 300 years. See Cedillo Ex.

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[95] C. D. Klaassen, Casarett & Doull's Toxicology - The Basic Science of Poisons (6th ed. 2001).

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

[97] The atomic number of mercury is 80 and its atomic weight is 200.59. Cedillo Ex. 55 at 2 (Dr. Aposhian's report).

55H at 612 (2006 Clarkson article[98]). An examination of the various forms of mercury is a predicate to understanding the known biological effects of mercury exposure and to evaluating petitioners' claim regarding the role of mercury exposure in the development of autism.

Mercury occurs in several forms: (1) elemental or metallic, (2) inorganic or ionic, and (3) organic. See Cedillo Ex. 55H at 612 (2006 Clarkson article); Cedillo Ex. L1 at 1 (1999 ATSDR Mercury Profile); Cedillo Tr. at 70-74 (Dr. Aposhian); Cedillo Tr. Ex. 1 at 4 (Dr. Aposhian's trial slides). Although these mercury compounds are chemically similar, it is well-recognized that the differences in the chemical structures of these compounds reflect "markedly different" toxicological properties. See Cedillo Ex. 55 at 2, 9 (Dr. Aposhian's report); Cedillo Ex. L at 10 (Dr. Brent's report); Cedillo Ex. L35 at 834 (2001 Klaassen toxicology book excerpt); Cedillo Tr. at 123A (Dr. Aposhian); see also Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1087-1090 (Fed. Cir. 2008) (stating, in a patent infringement case, that changes in the structure of a chemical compound causes changes in the properties of that compound, including the level of toxicity). For this reason, petitioners' expert Dr. Aposhian expressed a dislike for the "use [of] the term mercury without specifying what form of mercury we're talking about." Cedillo Tr. at 128A.

Specificity is imperative in any discussion about mercury. As the ATSDR, a component of the United States Centers for Disease Control and Prevention (CDC), has stated in its toxicological profile on mercury:

> Exposure to mercury . . . does not necessarily mean that adverse health effects will result. Health effects depend on the amount of exposure, the form of mercury, and the route of exposure. Each form and route leads to different effects.

Cedillo Ex. L at 10 (Dr. Brent's report) (citing Cedillo Ex. L1 at 29-30 (1999 ATSDR Mercury Profile)). The form of mercury involved in an exposure is as important as the amount of mercury involved in the exposure. See Cedillo Ex. 55H at 612 (2006 Clarkson article).

Among the notable differences between the various forms of mercury is the difference in their relative toxicity. See Cedillo Tr. at 144 (Dr. Aposhian) ("[D]ifferent forms of mercury have different toxicological properties."). The relative toxicity of mercury in its various forms differs according to the method of exposure, whether by ingestion, inhalation, injection, or skin absorption. See Cedillo Ex. L at 6 (Dr. Brent's report). Additionally, the biological effects of mercury differ depending on the form of mercury. Cedillo Ex. 55 at 3-4 (Dr. Aposhian's report).

Each form of mercury is capable of converting into other forms of mercury. Cedillo Ex. 55 at 3 (Dr. Aposhian's report). The rates of conversion between the different

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[98] T. W. Clarkson and L. Magos, The toxicology of mercury and its chemical compounds, Critical Reviews in Toxicology 36: 609-622 (2006).

forms of mercury vary according to the type of mercury undergoing conversion. Cedillo Ex. 55 at 3 (Dr. Aposhian's report).

b. The Half-Life of Mercury in the Body Depends on the Form of Mercury

The half-life or half-time[99] of mercury in the body differs depending on its form. Studies indicate that the half-life required for clearing mercuric mercury, an inorganic form of mercury, from different areas of the body differs depending on the pathway of exposure, specifically, whether orally ingested or inhaled. Cedillo Ex. 55H at 614-615 (2006 Clarkson article). Orally ingested mercuric mercury by adult volunteers had an approximate half-life of two days in the gastrointestinal tract and an average half-life of 25 days in red blood cells and plasma (although the range for the half-life in the blood spanned from two days to 40 days). But, the ingested mercuric mercury produced no significant radioactivity in the head region in the first 58 days. Id.

Comparing the half-life of mercuric mercury, an inorganic form of mercury, to the half-life of the organic forms of mercury illustrates another area in which the form of the mercury involved makes a difference. The half-life of methylmercury, an organic form of mercury, as measured in the blood of adults and in breast-feeding infants, has been estimated to range from 40 to 50 days. See Cedillo Ex. 55NN at 1740 (2002 Pichichero article). But, the half-life of ethylmercury, another organic form of mercury and the type of mercury present in thimerosal-containing vaccines, as measured in the blood serum of babies two to three weeks after vaccination, has been estimated to be less than 10 days. Cedillo Ex. 55 at 10 (Dr. Aposhian's report); Cedillo Ex. 55NN at 1740 (2002 Pichichero article); see also Cedillo Ex 55F at (2005 Burbacher article[100]) (describing conversion rates in infant monkeys). Blood mercury concentrations may be indicative of the mercury concentrations in other organs as well. Cedillo Ex. 55NN at 1740 (2002 Pichichero article). With an anticipated half-life of less than 10 days, ethylmercury is present in the body for a much shorter time than is methylmercury, and organic mercury remains in the body for a shorter time period than inorganic mercury.

c. The Limits for Human Exposure to Mercury Established by Public Health Agencies

Human exposure to mercury primarily comes from consumption of fish, emissions from dental amalgams, and vaccines containing thimerosal. See Cedillo Tr. at 74A-76 (Dr. Aposhian). Based on the assessed risks to the general population from the ingestion

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[99] 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.

[100] T. M. Burbacher et al., Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing thimerosal, Environ. Health Perspect. 113: 1015-1021 (2005).

of methylmercury, which is the type of mercury present in fish, various public health agencies have made efforts to determine safe levels of methylmercury exposure. Based on data from the Japanese public health disasters involving the ingestion of fish contaminated by industrial sources, the WHO "established [in 1972] a tolerable weekly intake" of 3.3 mcg/kg (or 0.47 mcg/kg/day) of methylmercury in the human diet. Cedillo Ex. 55II at 4 (2000 Myers article[101]). Based on data from Iraq's experience in the 1970s with methylmercury-contaminated grain, the EPA subsequently proposed an oral reference dose (RfD) of 0.1 mcg/kg/day. Cedillo Ex. 55II at 4 (2000 Myers article). Based on data from the studies in the Faroe Islands and the Seychelles Islands of methylmercury exposure from dietary fish consumption, the ATSDR recommended the setting of a minimal risk level (MRL) of 0.3 mcg/kg/day. Cedillo Ex. 55II at 4 (2000 Myers article). In 2005, the FDA issued a statement agreeing with the EPA's proposed RfD of 0.1 mcg/kg/day of methylmercury. Cedillo Tr. at 69A (Dr. Aposhian).

An established RfD is the dosage of a substance of interest per kilogram of body weight per day to which a person can be exposed every day for the rest of the person's life without harmful effects. See Cedillo Tr. at 84A (Dr. Aposhian). An established RfD assumes a steady state of exposure. See id. The mercury exposure limits set by the various public health agencies address methylmercury exposures only. The public health agencies have not established exposure limits for ethylmercury, the mercury form of interest in the OAP litigation.

d. The Primary Routes for Eliminating Mercury from the Human Body

The excretion of mercury from the body occurs primarily through fecal elimination and urinary excretion. Cedillo Ex. 55H at 617 (2006 Clarkson article). Urinary concentrations of mercury assist in quantifying a person's exposure to mercury during the past several months. Snyder Ex. T5 at 159-160 (2006 Heyer article[102]). But, urinary concentrations of mercury may not provide a reliable measure of longer term exposure (in particular, an exposure of more than several months). Snyder Ex. T5 at 159-160 (2006 Heyer article). One of the described biomarkers of prolonged exposure to all forms of mercury is an increase in specific urinary porphyrins.[103] Snyder Ex. T5 at 160 (2006 Heyer article).

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[101] G. J. Myers and P. W. Davidson, Does methylmercury have a role in causing developmental disabilities in children? Environ. Health Perspect. 108(53): 413-420 (June 2000). The pagination of this document refers to the pagination of the electronic filing.

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

[103] Porphyrins are the chemicals in the body that assist in "making the hem[e] [component] of hemoglobin." Cedillo Tr. at 93 (Dr. Aposhian).

e. The Symptoms of Mercury Toxicity

Signs and symptoms of toxic levels of ethylmercury exposure, the form of mercury exposure attributable to thimerosal-containing vaccines, characteristically include a constricted visual field, ataxia (uncoordinated movement), dysarthria (poor articulation, specifically, slurred speech due to poor motor control of speech-related muscles), peripheral neuropathy (abnormal sensation in the extremities due to damage of the peripheral nerves), kidney function abnormalities, and tremors. Cedillo Ex. L at 4 (Dr. Brent's report); Cedillo Ex. 55H at 619 (2006 Clarkson article). These symptoms of mercury toxicity are not the characteristic symptoms of an ASD. See Cedillo Ex. L at 4 (Dr. Brent's report) (citing 2003 Nelson article[104]).

3. Sources of the Three Different Forms of Mercury

a. Elemental Mercury

One of the several forms of mercury is elemental mercury. Elemental mercury is commonly referred to as liquid silver. In its liquid form, elemental mercury "is relatively nontoxic." See Cedillo Ex. 55 at 3 (Dr. Aposhian's report); Cedillo Tr. at 70 (Dr. Aposhian). At room temperature, however, elemental mercury "emits a vapor . . . that . . . is very, very toxic." Cedillo Tr. at 70 (Dr. Aposhian); Cedillo Ex. 55 at 4 (Dr. Aposhian's report); accord Cedillo Ex. 55H (2006 Clarkson article) at 612 (stating that a long history of use of liquid metallic mercury teaches that mercury "vapor can be highly toxic when inhaled but the ingestion of the liquid form offers a minuscule hazard"). Mercury vapors are odorless and colorless. Cedillo Ex. L1 at 2 (Agency for Toxic Substances and Disease Registry, Toxicological Profile for Mercury (1999)).

Elemental mercury may be found in silver tooth fillings, which are known as dental amalgams. Petitioners' expert Dr. Aposhian asserted that dental amalgams are a source of exposure to mercury vapor, Cedillo Tr. at 74 (Dr. Aposhian), because silver tooth fillings emit elemental mercury, Cedillo Ex. 55 at 5 (Dr. Aposhian's report) (citing Cedillo 55PP (1994 Skare article[105])). Dr Aposhian further asserted that the target organ in the body for mercury vapor is the brain. Cedillo Tr. at 74 (Dr. Aposhian). Mercury vapor, however, is not the form of mercury present in thimerosal-containing vaccines.

b. Inorganic Mercury

Another form of mercury is inorganic mercury. "Inorganic mercury compounds occur when mercury combines with elements such as chlorine, sulfur, or oxygen." Cedillo

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[104] K. Nelson and M. Bauman, Thimerosal and Autism? Pediatrics 111: 674-679 (2003).

[105] I. Skare and A. Engqvist, Human exposure to mercury and silver released from dental amalgam restorations, Arch. Environ. Health 49:384-394 (1994). Dental fillings are also called restorations. See Dorland's at 701.

Ex. L1 at 2 (1999 ATSDR Mercury Profile). Also called mercury salts, the inorganic or ionic forms of mercury include mercurous mercury and mercuric mercury. Id.; Cedillo Tr. at 73A (Dr. Aposhian); Cedillo Ex. L at 2 (Dr. Brent's report). Most inorganic mercury compounds are white crystals or powders.[106] Cedillo Ex. L1 at 2 (Agency for Toxic Substances and Disease Registry, Toxicological Profile for Mercury (1999)). Through the process of global cycling, inorganic mercury is deposited in the sediment of various bodies of water. See Cedillo Ex. 55H at 625-626 (2006 Clarkson article).

Human exposure to inorganic mercury has occurred primarily in controlled occupational settings. Cedillo Ex. 55 at 4 (Dr. Aposhian's report); Cedillo Tr. at 129A (Dr. Aposhian). Other sources of inorganic mercury historically have included antibacteriostatic compounds (such as the topically applied tincture merthiolate), teething powders, skin bleaching creams, and laxatives. Cedillo Ex. 55H at 614 (2006 Clarkson article). See also Cedillo Ex. 55GG at 5 (2000 McRill article[107]) (users of a mercury-containing beauty cream that had been manufactured in Mexico reported a variety of symptoms, including headaches, dizziness, fatigue, irritability, joint pain, eye irritation and decreased concentration; upon examination, the cream users had elevated levels of mercury in their urine); Cedillo Ex. 55P at 962-963 (1977 Fagan article[108]) (10 of the 13 infants whose umbilical hernias were treated with a thimerosal tincture died, and a post-mortem analysis of their tissues revealed elevated mercury levels).

There is evidence that once in the body, the mercuric form of mercury is unable to pass through the blood-brain barrier, which is the system of proteins that separates the blood in the body from the essential elements of the central nervous system, but can accumulate in the brain "as the metabolic end product" of other forms of mercury that do pass through the blood-brain barrier,. Cedillo Ex. 55 at 7 (Dr. Aposhian's report) (citing Cedillo Ex. 55WW (1994 Vahter article[109])). Exposure to inorganic mercury primarily affects the kidneys, but can also affect the stomach, gastrointestinal system, and the lungs. See Cedillo Ex. 55H at 616 (2006 Clarkson article); see also Cedillo Tr. at 74 (Dr. Aposhian) ("The target organ[] . . . for . . . mercuric mercury [is] the kidney."). Other reports link mercuric mercury exposure to the development of systemic autoimmunity in animals and possibly humans. See Cedillo Ex. 55H at 616 (2006 Clarkson article). This form of mercury, although addressed by petitioners' expert Dr. Aposhian both in his report and in his testimony at the Cedillo hearing, is not the form of mercury at issue in the OAP

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[106] Mercury sulfide, however, is red, and the compound turns black after exposure to light. Cedillo Ex. L1 at 2 (ATSDR Mercury Profile).

[107] C. McRill & L. Boyer, Mercury Toxicity Due to Use of a Cosmetic Cream, J. Occupational Environ. Med. 42: 4-7 (2000).

[108] D. Fagan et al., Organ mercury levels in infants with omphaloceles treated with organic mercurial antiseptic, Arch. Dis. Childhood 52: 962-965 (1977)).

[109] 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).

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c. Organic Mercury

When mercury combines with carbon, the formed compounds are called "organic" mercury compounds or organomercurials. Cedillo Ex. L1 at 2 (1999 ATSDR Mercury Profile). The organic forms of mercury include: (1) ethylmercury (CH_3CH_2Hg+), which is the mercury component in thimerosal; (2) methylmercury (CH_3Hg+); and (3) dimethylmercury. See Cedillo Tr. at 71 (Dr. Aposhian); Cedillo Trial Ex. 1 at 4 (Dr. Aposhian's trial slides).

Sources of exposure to thimerosal (and to ethylmercury, once thimerosal disassociates) include those medicinal preparations to which thimerosal has been added as a preservative. See Cedillo Ex. 55 at 5 (Dr. Aposhian's report). Dr. Aposhian testified during the Cedillo hearing that in 1982, a panel convened by the FDA concluded that "thimerosal is not safe for over-the-counter topical use because of its potential for cell damage if applied to broken skin and its allergy potential." Cedillo Tr. at 88A (citing 1982 Federal Register[110]). Moreover, the FDA-convened panel found that thimerosal was not an effective topical antimicrobial "because its bacteriostatic action can be reversed." Id. Because the method of exposure to mercury is one of the factors that affects the toxicity of mercury, see Cedillo Ex. L at 6 (Dr. Brent's report), findings pertaining to the topical use of thimerosal are not directly applicable to thimerosal-containing vaccines, which are injected.

Other sources of ethylmercury have included childhood vaccines. Cedillo Ex. 55 at 5 (Dr. Aposhian's report). Prior to the removal of thimerosal from most childhood vaccines in the year 2000, children could receive, during the first 14 weeks of life, up to 185.5 mcg of ethylmercury from thimerosal-containing vaccines. Cedillo Ex. 55 at 9 (Dr. Aposhian's report) (citing 2001 Clements article). The prescribed childhood vaccination schedule for the first six months of life involved the administration of repeated doses of thimerosal-containing vaccines, which doses were equivalent to 5 to 20 mcg of ethylmercury. Cedillo Ex. 55 at 10 (Dr. Aposhian's report) (citing Cedillo Ex. 55U at 2 (1999 Halsey article[111])). It is the impact, if any, of this exposure on the development of ASDs that is one of the foci of the OAP litigation.

The most common organic mercury compound in the environment is not ethylmercury, but methylmercury (or monomethylmercury). Cedillo Ex. L1 at 2 (1999 ATSDR Toxicological Profile for Mercury). Human exposure to methylmercury occurs primarily through the consumption of fish or seafood containing mercury. Although "no

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[110] Mercury-containing drug products for topical antimicrobial over-the-counter human use: establishment of a monograph, 47 Fed. Reg. 436, 441 (Jan. 5, 1982) (Statement of Advisory Review Panel).

[111] N. Halsey, Limiting infant exposure to thimerosal in vaccines and other sources of mercury, JAMA 282: 1763-1766 (1999).

clinical cases of methylmercury poisoning have ever been reported from [the] consumption of fish where the source of methylmercury was the natural biomethylation process,"[112] reports of poisoning have occurred when "uniquely high levels of methylmercury [have been] produced in fish" following a chemical discharge. Cedillo Ex. 55H at 631 (2006 Clarkson article).

Petitioners' toxicologist Dr. Aposhian acknowledged in his report that with respect to the mercury exposure of the general population, "the evidence to date indicates that exposure to methyl mercury causes the most toxic responses." Cedillo Ex. 55 at 8 (Dr. Aposhian's report)(emphasis added). Dr. Aposhian stated that "almost all of the exposure to methyl mercury is retained. The methyl mercury stays in the body." Cedillo Tr. at 87A (emphasis added).

Of the organic forms of mercury, dimethylmercury is the most toxic. This form of mercury is "so toxic it's called the super toxic form of mercury." Cedillo Ex. 55 at 4 (Dr. Aposhian's report); Cedillo Tr. at 71 (Dr. Aposhian) (describing dimethylmercury as "extremely toxic"). Recorded exposures to dimethylmercury have occurred primarily in chemical laboratories. See Cedillo Ex. 55H at 630 (2006 Clarkson article). The general population is not ordinarily exposed to dimethylmercury.

Notably, exposure to the organic mercury compound of dimethylmercury results in a delayed biological response. Cedillo Ex 55 at 4 (Dr. Aposhian's report); Cedillo Tr. at 71 (Dr. Aposhian). The delay in response has no generally accepted explanation. Cedillo Ex 55 at 4 (Dr. Aposhian's report) (citing Cedillo Ex. 55ZZ at 854 (2002 Weiss article[113]) (examination of "different patterns of delayed neurotoxicity between exposure and the onset of detectable signs")).

In the human body, each of the forms of organic mercury is converted to inorganic mercury. See Cedillo Ex. 55 at 4 (Dr. Aposhian's report); Cedillo Tr. at 73 (Dr. Aposhian). The rates of conversion from the organic form to the inorganic form in the body differ for the different organomercurials. See Cedillo Ex. 55 at 5 (Dr. Aposhian's

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[112] The natural biomethylation process occurs when mercury (in the form of mercury vapor or the inorganic form of mercuric mercury): (1) becomes airborne through emissions from soil, mountains, and fossil-fuel burning utility plants; (2) enters rivers, bays, and oceans after rainfall or as a result of leaching from soil; and (3) encounters bacteria in the water that cause methylation. Cedillo Ex. 55 at 6 (Dr. Aposhian's report); see also Cedillo Tr. at 79A-80A (Dr. Aposhian). Organisms absorb the methylmercury, and through the process of biomagnification, small fish with low methylmercury concentrations are consumed by larger fish, who in turn, have higher mercury content. Cedillo Ex. 55 at 6 (Dr. Aposhian's report); see also Cedillo Tr. at 79A-80A (Dr. Aposhian). Among the fish with higher mercury content that humans typically consume are shark, swordfish, tuna, and tilefish. Cedillo Ex. 55 at 6 (Dr. Aposhian's report).

[113] B. Weiss et al., Silent latency periods in methylmercury poisoning and in neurodegenerative disease, Environ Health Perspectives 110: 851-854 (2002).

report). Ethyl compounds are converted more quickly to inorganic mercury in the brain. See Cedillo Ex. 55 at 5 (Dr. Aposhian's report); Cedillo Ex. 55H at 624 (2006 Clarkson article); Cedillo Ex. 55F at 1018 (2005 Burbacher article[114]). Methyl compounds convert to inorganic mercury more slowly than ethyl compounds. See Cedillo Ex. 55 at 5 (Dr. Aposhian's report).

Dr. Aposhian testified during the Cedillo hearing that the organic mercury compounds "methyl mercury and ethyl mercury have some similar properties, but their toxicokinetics are different." Cedillo Tr. at 88A. In particular, methylmercury is selectively toxic to the central nervous system. Cedillo Ex 55JJ at 1686 (2003 Myers article[115]). Methylmercury also inhibits processes that are important to brain development such as neuronal cell division and migration. Cedillo Ex 55JJ at 1686 (2003 Myers article); see also Cedillo Tr. at 74A (Dr. Aposhian) (target organ for methylmercury is the brain). Moreover, methylmercury ions exhibit an affinity for hydrogen and sulfur compounds (known as thiols) that is greater than the ions' affinity for other molecules (or ligands). Cedillo Ex. 55VV at 26 (1977 Tsubaki article[116]). Because the health effects of methylmercury have been studied more widely than the health effects of ethylmercury, the testimony of petitioners' experts and the filed medical literature focused more on methylmercury than on ethylmercury.

The recognized properties of the different forms of mercury inform the analysis of the various assertions petitioners regarding their theory of vaccine causation.

4. Petitioners' Claim that Mercury Exposure can Cause Neurological Damage

Petitioners assert that mercury exposure can cause neurological damage. In support of this assertion, petitioners point to documented neurological injuries that have occurred after various exposures to mercury. The reported neurological injuries have occurred after both prenatal and postnatal exposures to mercury. Petitioners contend that the reported injuries support their claim that mercury exposure (through thimerosal-containing vaccines) is an environmental factor that can cause neurological injury that, in turn, can lead to the development of an autism spectrum disorder. See Hazlehurst Tr. at 284A-285A (Dr. Corbier). Petitioners argue that consideration of the offered evidence "as a whole" supports their claim regarding the neurotoxic effects of mercury exposure.

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[114] T. Burbacher et al., Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing thimerosal, Environ. Health Perspect. 113: 1015-1021 (2005).

[115] G. Myers, Prenatal ethylmercury exposure from ocean fish consumption in the Seychelles child development study, Lancet 361: 1686-1692 (2003).

[116] T. Tsubaki and K. Iruayama, eds., Minamata disease: methylmercury poisoning in Minamata and Niigata, Japan, New York: Elsevier (1977).

a. Reported Poisonings Resulting from Significant Methylmercury Exposures

During the Cedillo hearing, Dr. Aposhian pointed to several public health studies of mass poisonings that resulted from the consumption of food contaminated by significant levels of methylmercury. See Cedillo Tr. at 81-83A. He asserted that the studies of the effects of significant methylmercury exposures have raised concerns about the effect of low levels of methylmercury exposure from fish consumption by "children in this country" because fish consumption is the primary source of human exposure to methylmercury. Cedillo Tr. at 83A.

Among the first reports of a public health problem arising from methylmercury exposure occurred in Japan between the 1950s and 1970s following a mass, accidental poisoning that resulted in the appearance of the condition now known as "Minamata disease." See Cedillo Ex. 55H at 631 (2006 Clarkson article); see also Cedillo Tr. at 83 (Dr. Aposhian addressing the observed condition in Japan referred to as "Minamata disease"). Dr. Aposhian asserted that reports of this condition as an observable effect of the significant methylmercury exposure by area residents and their children support petitioners' claim that both prenatal and postnatal exposures to mercury can produce neurological injuries. See Cedillo Tr. at 81A-82A (Dr. Aposhian).

The condition described as "Minimata disease" began to appear after discharges from a chemical plant into the Minamata Bay and neighboring seas caused significant methylmercury-contamination of the fish consumed by area fishermen and their families. Cedillo Ex. 55VV at 2 (1977 Tsubaki article). Multiple reports of patients presenting "with clinical symptoms that coincided with those of organomercury poisoning" led to the determination by the public health officials that the causative agent of "Minamata disease" was the methylmercury contained in the waste from an area chemical plant. See Cedillo Ex. 55VV at 2-6 (1977 Tsubaki article).

In the 1960s, an additional case of mass methylmercury poisoning, which is commonly referred to as the Niigata case, occurred in Japan affecting the residents along the Agano River. Cedillo Ex. 55VV at 57-59 (1977 Tsubaki article). The identified source of the river's methylmercury contamination was an acetaldehyde chemical plant located along the Agano River. Id. at 94. The affected residents had consumed "large volumes" of fish caught from the contaminated water. Id. at 64.

The noted symptoms of Minamata disease were ataxia,[117] impaired speech, and a constricted visual field. Cedillo Ex. 55VV at 146 (1977 Tsubaki article). These symptoms were "very often accompanied by impaired hearing and sensory disturbance." Id. The symptoms could progress to neuropsychiatric disorders, see id. at 111, and death, id. at 106. Among women who delivered babies or were pregnant at the time of the mass poisoning, one case of congenital disease was reported. Id. at 68; see also Cedillo Tr. at

[117] Ataxia is a "failure of muscular coordination." Dorland's at 170.

82A (Dr. Aposhian). One of the noted injuries among the babies was cerebral palsy[118] with mental retardation and brain atrophy. Cedillo Ex. 55VV at 67-68 (1977 Tsubaki article); see also Cedillo Tr. at 82A, 156 (Dr. Aposhian).

Among the living patients suffering from methylmercury poisoning, an increase in hair mercury levels and blood mercury levels was measured. Cedillo Ex. 55VV at 73-74. The mercury content measured in hair samples collected from exposed persons two to three months after the onset of their symptoms had mercury content between 280-700 mcg/g. Id. at 52. By comparison, the level of mercury content in the hair samples of Japanese inhabitants living away from the contaminated areas (control samples) was between 1-7 mcg/g. Id. at 52-53. The mercury levels in both the blood and the hair of the persons affected by the methylmercury poisoning decreased "gradually with the lapse of time." Id. at 74.

Additionally, the examined organs during the autopsies of those who died from Minamata disease revealed "[a]bnormal mercury levels," and those levels "decreased with increasing time after the onset of symptoms." Id. at 51. An examination of the organs of patients who died of acute poisoning showed lower mercury accumulation in the brain than in other organs, such as the kidney and the liver. See id. at 74. The detected mercury level in the grey matter of the brain was higher than in the white matter of the brain. Id. at 76.

On autopsy, the brains of those who died less than a month after the onset of symptoms revealed some neuronal loss. Id. at 104. The most severely affected brains exhibited a macroscopic spongy state with cystic cavities easily visible to the naked eye. Id. at 106. On microscopic review, the cavities were composed of vascular and glial tissue lacking neurons.[119] Id. The cerebellar hemispheres "showed remarkable disintegration," and in the central portion of the cerebellum, the Purkinje cells had completely disappeared.[120] Id. at 106-108. Even in the mildest cases, a reduction in brain weight (by atrophy) of less than 10 to 15 percent occurred. Id. at 115. Other noted pathological

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[118] Cerebral palsy is a neurological condition involving abnormality in muscle tone (whether "very tight" or "very floppy"). See Hazlehurst Tr. at 395A (Dr. Corbier).

[119] Glial or neuroglial cells form the structure of nervous tissue. Dorland's at 1254. The branched cells form a fine web that appears to play a role in the formation of myelin (the cylindrical sheath covering neuronal axons that speeds the conduction of nerve impulses), the transport of material to neurons, and the maintenance of the neuronal environment. Id. at 1254, 1689 (myelin).

[120] The cerebellum is the portion of the brain that occupies the "posterior cranial fossa behind the brain stem" and is involved in the coordination of movements. See Dorland's at 336. Purkinje cells are the large cells in the cerebellar cortex of the brain. See Dorland's at 325. Within the Purkinje cells, threadlike extensions called dendrites branch out in a tree-like formation toward the surface of the cell. See Dorland's at 488. The dendrites "compose most of the receptive surface of a neuron." Id.

changes included the erosive inflammation of the digestive tract, underdevelopment (or hypoplasia)[121] of the bone marrow, lymph node atrophy, and fatty degeneration in the liver and kidneys. Id. at 126.

Although the brains on autopsy of those who died as a consequence of the mass methylmercury poisoning revealed disintegration and nearly complete Purkinje cell loss in the cerebellum of the brain, the decedents' clinical and pathological presentation did not resemble the clinical and pathological presentation of those who are afflicted with autism. The brains on autopsy of autistic patients have revealed observable losses of particular cells in highly selected areas of the brain, including a significant loss of Purkinje cells in the cerebellum of the brain that are "not what you see" after mercury toxicity, encephalitis, or an acquired brain injury. See Hazlehurst Tr. at 486A, 488A (Dr. Rust). Additionally, the impairments in areas of communication, behavior, and social interaction that are distinctive in and diagnostic of ASDs are not the types of neurological problems with which persons exposed to excess mercury through fish consumption have presented.

Dr. Aposhian also discussed during the Cedillo hearing various reports of neurological injuries following the ingestion, either directly or indirectly, of mercury-contaminated grain. See Cedillo Tr. at 82B-83A. One of the reports involved an epidemic of methylmercury poisoning in Iraqi farmers and their families in the early 1970s. See Cedillo Ex. 55D at 231-232 (1973 Bakir article[122]). The distribution of wheat seed that had been treated with a methylmercurial fungicide to Iraqi farmers began in 1971. Id. at 232. The farmers and their families who consumed homemade bread that had been prepared from the contaminated wheat seed began to present to area hospitals with signs of methylmercury poisoning. Id. Of the 6350 cases of diagnosable poisonings on hospital admission, 459 deaths were recorded. Id. at 234. The nature and severity of the observed signs and symptoms were dose-dependent. Id. at 236. Those patients who had consumed contaminated bread for a shorter period of time exhibited only parasthesia; but those who had consumed bread for a longer period of time presented with other clinical manifestations, including speech and hearing difficulties. Id. Moreover, the severity of the presenting patients' ataxia ranged from gait unsteadiness to gross lack of coordination, and the severity of visual effects ranged from blurred vision to blindness. Id.

Another reported case of methylmercury poisoning following the indirect ingestion of contaminated grain involved the family of a farmer in New Mexico who inadvertently fed mercury-treated grain to a pig that the family subsequently killed and ate. See Cedillo Ex. 55N at 680 (1994 Davis article[123]); Cedillo Tr. at 77A (Dr. Aposhian). The family, which included the farmer, his pregnant wife, and four children, ate the pig over a period

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[121] See Dorland's at 897 (defining hypoplasia).

[122] F. Bakir et al., Methylmercury Poisoning in Iraq, Science 181: 230-241 (1973).

[123] L. E. Davis et al., Methylmercury poisoning: long term clinical, radiological, toxicological, and pathological effects on an affected family, Annals of Neurology 35: 680-688 (1994).

of three months, from September 1969 to December 1969. Cedillo Ex. 55N at 680-681 (1994 Davis article). The two youngest children, including a child with congenital poisoning based on intrauterine methylmercury exposure and a girl who was eight years of age when she ate the contaminated pig, developed severe neurological problems, including dementia, severe mental retardation, blindness, muteness, quadriparesis (or slight paralysis of the four limbs),[124] and seizures. Id. at 681 (Table 1), 686. While both died, the elder of the two youngest children survived for nearly 20 years. Id. An autopsy of the brain of the elder of the two siblings who died showed mercury levels more than 50 times the mercury level in a control patient (that is, a patient without the same significant methylmercury exposure). Id. at 681, 685. The two oldest children at the time of exposure survived and showed some improvement over time. Id. at 686. Neither parent developed any symptoms. Id. Petitioners assert that this study shows that mercury that reaches the brain remains in the brain a long time. See Cedillo Tr. at 76-77A, 145A (Dr. Aposhian). Petitioners' expert Dr. Aposhian conceded during the Cedillo hearing, however, that the family's exposure to methylmercury was at a much higher dose than the exposure dose of ethylmercury that is received through thimerosal-containing vaccines. See Cedillo Tr. at 146-147A (Dr. Aposhian).

As petitioner's own expert conceded, the difficulty with petitioners' reliance on these reported poisonings as evidence of an environmental exposure causing neurological injury is the large doses of methylmercury involved in the poisonings. The exposure doses involved in the methylmercury mass poisonings are substantially larger than the cumulative exposure dose of ethylmercury attributable to the thimerosal-containing vaccines prescribed by the childhood vaccination schedule. Not only are the exposure doses between the documented mass poisonings and the administered childhood vaccines vastly different, but the reported poisonings involve a different form of mercury, specifically, methylmercury rather than ethylmercury, the form of mercury in vaccines. Additionally, as documented, the neurological injuries from the methylmercury mass poisonings do not resemble autism.

b. Risks Associated with Dietary Fish Consumption

Petitioners also point to the studies of two different island populations with significant dietary seafood consumption as evidence of the risks associated with environmental exposure, both prenatally and postnatally, to methylmercury. See Cedillo Ex. 55S (1997a Grandjean article[125]); Cedillo Ex. 55R (1999 Grandjean article[126]); see also

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[124] See Dorland's at 1371, 1556 (defining "paresis" and "quadri").

[125] P. Grandjean et al., Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury, Neurotoxicol. Teratol. 19:417-428 (1997a).

[126] P. Grandjean, Mercury risks: controversy or just uncertainty? Public Health Rep. 114:512-515 (1999).

Cedillo Ex 55JJ (2003 Myers article[127]); Cedillo Ex. 55II (2000 Myers article[128]); Cedillo Ex. 55AA at 75 (1989 Kjellstrom article[129]) (a New Zealand study finding "an apparent association between prenatal methylmercury exposure in fish and a decreased performance in the [administered] psychological tests" that petitioners cited, see Cedillo Brief at 208; Cedillo Ex 55 at 8 (Dr. Aposhian's report), as confirmation of the findings from the study in the Faroe Islands) (emphasis added). One of the studies examined children in the Faroe Islands. Cedillo Ex. 55R at 513 (1999 Grandjean article). The 18 islands known as the Faroe Islands are located "in the North Atlantic Ocean, about 250 miles . . . directly north of Scotland."[130] See http://www.worldatlas.com/webimage/countrys/europe/faeroe.htm. (last visited on 2/9/09). The residents of the Faroe Islands consume mostly imported food, other than their indigenous seafood and lamb. Id. The primary source of methylmercury exposure among the Faroese comes from the consumption of pilot whale meat. Cedillo Ex. 55S at 418 (1997a Grandjean article).

The other study examined children on the Seychelles Islands. Cedillo Ex 55JJ (2003 Myers article). A collection of nearly 100 tropical islands, the Seychelles Islands are located in the Indian Ocean, northeast of Madagascar. Id.; see also http://www.infoplease.com/ipa/A0107955.html (last visited on 2/1/09). Like the residents of the Faroe Islands, the residents of the Seychelles Islands also enjoy a fish diet. Cedillo Ex 55JJ (2003 Myers article). On the Seychelles Islands, however, residents have ready access to fruits and vegetables, too. Cedillo Ex 55JJ (2003 Myers article); see also Cedillo Tr. at 85A-85B (Dr. Aposhian).

Dr. Aposhian testified that the two studies, in the Faroe Islands and in the Seychelles Islands, were designed "to test the intelligence of the children" borne to mothers who had consumed fish containing methylmercury. Cedillo Tr. at 68A (Dr. Aposhian). He further testified that the results of the Faroe Islands study showed "harmful effects on the intelligence" of the examined children. Id. He added that a subsequent

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[127] G. J. Myers et al., Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study, Lancet 361:1686-1692 (2003). This article references the originally reported findings from the Seychelles Islands study. See also P. W. Clarkson et al., Longitudinal neurodevelopment study of Seychelles children following in utero exposure to methylmercury from fish ingestion occurrences at 19 and 29 months, Neurotoxicology 16: 677-688 (1995).

[128] G. J. Myers et al., Does methylmercury have a role in causing developmental disabilities in children? Environ. Health Perspect. 108: 413-420 (2000).

[129] 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).

[130] The Faroe Islands are an autonomous territory belonging to the Kingdom of Denmark. See https://www.cia.gov/library/publications/the-world-factbook/geos/fo.html (last visited on 2/1/09).

study of the children in the Seychelles Islands at age seven indicated that the boys had "certain intelligence deficits at age 7 that did not show up at age 5." Id. at 68A.

Dr. Aposhian's testimony that the Faroe Islands study showed that the consumption of methylmercury-containing fish had "harmful effects on the intelligence" of the studied children overstates the findings of the investigators. Cedillo Tr. at 68A. The investigators did not address the effect of the exposure on the intelligence of the children. Rather, the investigators indicated that they had detected "subtle" dysfunction in the areas of language, attention, and memory, and in the area of visuospatial and motor functions. See Cedillo Ex. 55S at 423-424, 426 (1997a Grandjean article). The investigators attributed the detected "subtle" dysfunction to higher prenatal (not postnatal) mercury exposure levels. See id. The risks associated with prenatal mercury exposure are distinguishable from–and are of limited value in the evaluation of–the risks associated with postnatal mercury exposure from administered vaccines.

The population of the Faroe Islands had been selected for study based on the substantial variations in seafood intake and limited social variations (which minimized the confounding factors).[131] Id. at 418. The maternal hair mercury levels varied widely and were most closely associated with cord blood levels at birth. See id. at 418, 426. No obvious cases of congenital methylmercury poisoning were detected. Id. at 418. The investigators concluded that the results of the study suggested that several domains of brain function were affected by prenatal exposure to methylmercury. Id. at 426. The investigators' analyses "almost uniformly indicated decreased function with increased prenatal mercury exposure levels." Id. at 423. Although the investigators noted that the effects of postnatal exposure could not be excluded, their observations were consistent "with the particular neurotoxic potential of prenatal exposure." Id. at 426.

In the Seychelles Islands study, investigators examined 779 mother-infant pairs (reflecting half of the live births on the islands) in 1990. Cedillo Ex. 55JJ at 1686 (2003 Myers[132]). The mothers had eaten fish containing methylmercury concentrations similar to the methylmercury concentrations in the fish consumed in the United States; but the average maternal fish consumption during 12 meals a week in the Seychelles Islands was higher than correlative fish consumption in the United States. Id. at 1686. Prenatal mercury exposure was determined from maternal hair samples. Id. at 1687. The children were assessed for neurocognitive, language, memory, motor, perceptual motor, and behavioral functions. Id. The initial study examined children up to the age of five and one-half years (or 66 months) of age in the Seychelles Islands and found no "evident" association between the deficits measured by testing for development and the mercury concentrations in the hair of the children's mothers. See id. at 1692.

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[131] A confounding factor is a factor that make it difficult to evaluate whether a causal association exists between two or more factors because the effects of the individual factors cannot be determined. See Dorland's at 407; Stedman's at 429.

[132] G. Myers et al., Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study, Lancet 361: 1686-1692 (2003).

Based on the suggestion of Dr. Philippe Grandjean, the researcher most closely associated with the Faroe Islands study, that the different outcomes between the study in the Faroe Islands and the initial study in the Seychelles Islands might be attributable to the different methods employed in the studies for assessing methylmercury exposures and the different ages of the children at the time of the performed evaluations, the investigators in the Seychelles Islands conducted a subsequent study. See Cedillo Ex. 55R at 513 (1999 Grandjean article[133]). This subsequent study in the Seychelles Islands addressed the age differences between the children studied in the Faroe Islands (up to seven years of age) and the children initially studied in the Seychelles Islands (up to five and one-half years). Cedillo Ex. 55JJ at 1692 (2003 Myers article). The subsequent Seychelles Islands study examined children up to nine years of age. Id. at 1686. The investigators tested 643 mother-child pairs in the Seychelles Islands after some of the initial study participants refused to continue and other mother-infant pairs were excluded from the study that had neurodevelopmental disorders resulting from traumatic brain injury, meningitis, epilepsy, or severe neonatal illnesses. Id. at 1686-1687. Testing of the children revealed that only two functions–specifically, a markedly decreased performance on the grooved pegboard using the non-dominant hand in males, and a significant improvement in the assessed scores on the hyperactivity index–were associated with prenatal methylmercury exposure. Id. at 1690. The investigators concluded that both associations were attributable to chance. Id. at 1691. The authors interpreted the study as demonstrating no support for the hypothesis that there is a neurodevelopmental risk from prenatal methylmercury exposure as the result of consuming ocean fish. Id. at 1692. The investigators found that the previously reported results for the Seychelles Islands were not disturbed. Id. The investigators suggested that the difference in findings between the Faroe Islands study and the Seychelles Islands study may have been attributable to the type of fish ingested in the Faroe Islands (primarily whale meat), which may have increased the likelihood that those studied in the Faroe Islands had consumed bolus doses of methylmercury. See id. at 1691; see also Cedillo Tr. at 86A (Dr. Aposhian testifying that the availability of citrus fruit in the Seychelles Islands was "one reason for the Seychelles Islands study not showing the effects that the Faroe Islands study did"). The investigators further noted that the concentration of mercury in the hair of the examined mothers correlated with the concentration of mercury found in the brains of infants who died of natural causes. Cedillo Ex. 55JJ at 1687 (2003 Myers article). Contrary to Dr. Aposhian's representations, the investigators did not point to any impact on the intelligence of the studied children as a result of their prenatal methylmercury exposure.

Also offered in support of their claim that environmental exposures to mercury, through fish consumption for example, can cause neurological injuries, petitioners point to a year-long study evaluating 720 patients at a general internal medicine practice in San Francisco, California, for mercury excess from eating fish. Cedillo Ex. 55W at 604-605 (2003 Hightower article[134]). The investigators asked the patients to estimate their weekly

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[133] P. Grandjean, Mercury risks: controversy or just uncertainty? Public Health Rep. 55: 512-515 (1999).

[134] J. Hightower and D. Moore, Mercury levels in high-end consumers of fish, (continued...)

dietary consumption of fish with high mercury content. Id. at 604. The investigators also investigated the patients' other sources of mercury exposure, including thimerosal-containing vaccines and dental amalgams with mercury content. Id. at 605. Patients with high estimates of weekly consumption and patients who presented with symptoms that are consistent with methylmercury excess, such as fatigue, headache, decreased memory, decreased concentration, and muscle or joint pain, were tested for mercury excess. Id. Patients with unexplained symptoms or with blood mercury levels greater than 5.0 mcg/L or with hair mercury levels greater than 1.0 mcg/g were advised to stop eating all fish for a six-month period or to select fish with low mercury content such as salmon, tilapia, sole, sardines or small shellfish. Id. at 605. Although the investigators "identified a subpopulation at risk for mercury excess," id. at 606, the investigators did not "fully address[]" the cause and effect regarding the patients' observed symptoms because, as the investigators acknowledged, "a chart review of symptomatology on all patients presenting to the office during the 1-year study was not done" and thus, control subjects were not available for comparative review, id. at 607. Additionally, the investigators noted the difficulty in determining whether patients were presenting with symptoms that were caused or aggravated by the excess mercury or whether the symptoms were, in fact, caused by another condition. Id. The article offers very little to inform the question of cause and effect with respect to the mercury content in vaccines and the development of autism.

Petitioners allege that "low level" environmental exposure to mercury can cause neurological injury that leads to the development of autism. However, petitioners' reliance on the studies of dietary fish consumption as support for the proposition is problematic. Among the problems with petitioners' reliance on these studies is the fact that the reported neurological injuries associated with dietary fish consumption result from exposure to methylmercury, not ethylmercury. It is ethylmercury, however, that is present in thimerosal-containing vaccines and is of particular interest in this case.

Moreover, the reported neurological symptoms associated with excess fish consumption (which variously include fatigue, headache, decreased memory, decreased concentration, and muscle or joint pain) are not consistent with the types of impairment that are characteristic in and diagnostic of ASDs. The types of impairment that signal autism occur in the areas of behavior, communication, and social interaction.

c. Neurological Impairment Reported after Laboratory Exposures

Petitioners cite the recorded neurological impairments that have followed exposures to dimethylmercury as further evidence in support of their claim that mercury exposure can cause neurological injury. Petitioners also contend that the reports of the toxic effects of exposure to dimethylmercury in particular support their claim that the neurological effects of mercury exposure may not be immediate.

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[134](...continued)
Environ. Health Perspect. 111: 604-608 (2003).

The supplied scientific literature in this case indicates that a recorded exposure to dimethylmercury by two chemists in a laboratory in London, England, in the 1860s, whether by inhalation or by skin contact, was fatal. See Cedillo Ex. 55H at 630 (2006 Clarkson article). Prior to their deaths, the chemists manifested signs of central nervous system damage that began initially as numbness of the hands and feet, followed by a lack of coordination, and a loss of vision and hearing. Id.

Petitioners in the OAP litigation also urge the undersigned to consider two subsequently reported cases of exposure to dimethylmercury that also involved chemists at work in their laboratories. In the early 1970s, a chemist who had synthesized dimethylmercury over a three-month period died 50 days after the exposure. Id. Prior to his death, he experienced numbness and tingling in his fingertips and lips, suffered insomnia, ataxia, slurred speech, impaired hearing, and an inability to recognize his relatives. Id.

More recently, in August 1997, a chemistry professor at Dartmouth College in New Hampshire wrote in her lab notebook that she accidentally spilled a few drops of dimethylmercury on her latex gloves in a fume cupboard while calibrating a scientific instrument. See Cedillo Ex. 55LL (1998 Nierenberg article[135]); see also Cedillo Ex. 55H at 630 (2006 Clarkson article). On hospital admission five months later, she presented with a five-day history of "progressive deterioration in balance, gait, and speech," a 15-pound loss over a two-month period, and several brief episodes of nausea, diarrhea, and abdominal discomfort. Cedillo Ex. 55H at 630 (2006 Clarkson article). She experienced progressive difficulty with speech, walking, hearing, and vision, and, within 22 days of her first neurological symptoms, she became "unresponsive to all visual, verbal, and light touch stimuli." Id. She died several months later. Id. Based on an analysis of her hair and blood levels, her absorption of liquid dimethylmercury was calculated to have been "no more than 0.44 ml." Id. The latency period of five months between her dimethylmercury exposure and the onset of her symptoms "is the longest ever reported." Id.; see also Cedillo Tr. at 71-72A (Dr. Aposhian).

Petitioners point to the severe effects of dimethylmercury exposure to illustrate the toxicity of mercury and to show that a period of time may elapse between an exposure and the appearance of symptoms. Cedillo Tr. at 71-72 (Dr. Aposhian). The difficulty, however, with petitioners' reliance on dimethylmercury exposure for illustrative purposes is that dimethylmercury exposure in small doses is substantially more toxic than is ethylmercury in equivalent doses. There is no question that the toxicity of ethylmercury, the mercury form of concern in vaccines, does not compare to the extreme toxicity of dimethylmercury in comparable doses. Moreover, the neurological impairments caused by dimethylmercury exposure, which include progressive difficulty with speech, hearing, vision, and coordination, are distinguishable from the characteristic deficits in social interaction, range of interests, and communication that define an autism spectrum disorder.

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[135] D. Nierenberg, at al, Delayed cerebellar disease and death after accidental exposure to dimethylmercury, New England J. of Med. 338: 1672-1676 (1998).

d. Evidence of the Impact of Mercury Exposure on the Brain

Petitioners assert that there is evidence that mercury can remain in the brain for a long time and that its presence in the brain can produce neurological problems. Petitioners' expert Dr. Aposhian opined that "[o]nce any form of mercury enters the brain and is converted to mercuric mercury, it is not easily eliminated from the brain, despite estimates of brain mercury half-life data appearing in scientific literature." Cedillo Ex. 55 at 5-6 (Dr. Aposhian's report). He posited that the "elimination of . . . mercury from the brain is extremely slow if it occurs at all" after a conversion to mercuric mercury takes place in the brain. Id. at 6. He stated that "[t]he brain is the primary target organ of mercury vapor, methyl mercury, and ethyl mercury." Id.; see also Cedillo Tr. at 74A (Dr. Aposhian) (asserting that the target organ in the human body for mercury vapor is the brain).

In support of his position that mercury which reaches the brain is not eliminated quickly from the brain, Dr. Aposhian pointed to the 1996 Opitz article. In the 1996 Opitz article, Dr. Aposhian asserted, the investigators found "exceedingly high levels of mercury . . . in the human brain and other organs 17 years after metallic mercury exposure." Cedillo Ex. 55 at 6 (Dr. Aposhian's report) (citing Cedillo Ex. 55MM at 142-143 (1996 Opitz article[136]) (case report noting the mercury concentration in the brain, kidney, liver, lung, and thyroid gland measured on autopsy of male patient exposed to high concentrations of metallic mercury vapor during 13 years of work recycling mercury from dental amalgams); Cedillo Tr. at 152A (Dr. Aposhian). The 1996 Opitz article reported findings on autopsy of a man who had been exposed "to . . . metallic mercury vapor" that resulted in nerve damage, but the patient had never developed the typical clinical signs of mercurialism (mercury poisoning). Cedillo Tr. at 151A (Dr. Aposhian); see also Cedillo Ex. 55MM at 139, 142-143 (1996 Opitz article). Dr. Aposhian acknowledged during his testimony, however, that the "exceedingly high level[] of mercury" found in the man's brain was "approximately 2,000 micrograms per kilogram," and was indicative of an exposure dose that could not be compared to the thimerosal content in vaccines. See Cedillo Tr. at 152A, 154A (Dr. Aposhian); Cedillo Ex. 55MM at 143 (1996 Opitz article) (mercury concentrations in different brain tissues set forth in Table 21).

Dr. Aposhian also pointed to the 1994 Vahter article as further support for the proposition that mercury which reaches the brain remains in the brain for a long time. Cedillo Ex. 55 at 6 (citing Cedillo Ex. 55WW (1994 Vahter article[137])). The investigators in the 1994 Vahter article measured the species of mercury found, on autopsy, in the blood and brains of Macaca monkeys after 18 months of daily oral ingestion of methylmercury in apple juice. See Cedillo Ex. 55WW at 222 (1994 Vahter article).

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[136] H. Opitz et al., Demonstration of mercury in the human brain and other organs 17 years after metallic mercury exposure, Clin. Neuropathology 15: 139-144 (1996).

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

Although the presence of inorganic mercury was confirmed in the brains of the studied monkeys in the 1994 Vahter article at a time later than the initial mercury exposure, the neurological impact of the inorganic mercury in the brain appeared to have been somewhat contained. After examining the monkeys on autopsy, the investigators reported that the gross lesions which are characteristic of mercury toxicity were not present in the liver, kidney, or gastrointestinal tube. Id. at 223. Moreover, on examination of the different areas of the brain, the investigators found no evidence that long-term exposure to methylmercury affected the function of the blood-brain barrier. Id. at 227. In addition, the investigators noted that contrary to earlier assumptions that methylmercury "is lipid soluble" and able to diffuse passively across membranes, "it has been shown that [methylmercury] is associated with water soluble molecules such as cysteine or glutathione in blood and tissues. . . which would limit its access to lipoidal tissues," and thereby would limit methylmercury's ability to cross the blood-brain barrier and deposit mercuric mercury, an inorganic form of mercury, in the brain. Id. at 228.

Other research to which Dr. Aposhian referred provided evidence that when infant monkeys were administered thimerosal, the ethylmercury component of that thimerosal (the organic form of mercury of interest in theory number one of the OAP litigation) was converted to inorganic mercury "at a rate seven times faster than methyl mercury." Cedillo Ex. 55 at 9-10 (Dr. Aposhian's report); Cedillo 55F at 1020 (2005 Burbacher article) (noting "a much higher proportion of inorganic Hg in the brain of thimerosal monkeys than in the brains of MeHg monkeys (up to 71% vs. 10%)"). Dr. Aposhian testified that the target organs for thimerosal are the brain and the kidney. Cedillo Tr. at 74A (Dr. Aposhian).

Dr. Aposhian addressed the potential sources of mercury that reach the brain. He stated that 95 to 99% of the methylmercury contained in fish is absorbed by the gastrointestinal system after the fish is consumed. Cedillo Tr. at 75A. From the gastrointestinal system, the methylmercury is transported to the blood. Id. When methylmercury comes into contact with blood, a methylmercury protein complex is formed that carries the amino acid methionine from the blood into the brain across the blood-brain barrier. Id. In the brain cells, methylmercury is slowly demethylated into the inorganic form of mercury, mercuric mercury. Id. at 75A-76.

Dr. Aposhian added that mercury vapor emitted from dental fillings in the mouth travels to the lungs, is absorbed "quickly into the lungs," and then is transported "very quickly to the blood-brain barrier and to other body tissues." Cedillo Tr. at 74A-75. He explained that the blood-brain barrier "protect[s] the brain from noxious substances." Id. at 75A. But because "mercury vapor is lipid soluble," the vapor can diffuse across the blood-brain barrier (the system of proteins that separates the blood in the body from the key components of the central nervous system) and oxidize to mercuric mercury that, in turn, binds to proteins in the brain. Id. at 75A. Dr. Aposhian testified that mercuric mercury, an inorganic form of mercury "is a standard enzyme inhibitor used in the laboratory." Cedillo Tr. at 73A. An enzyme inhibitor is "[a]ny substance that interferes with" the chemical reactions initiated by certain protein molecules. Dorland's at 623, 933 (defining "enzyme" and "inhibitor").

Although petitioners presented evidence concerning the conversion from the

organic forms of mercury, both methylmercury and ethylmercury, to the inorganic form of mercury in the brain, and the neurological impact on the body resulting from the deposition of inorganic mercury in the brain, the undersigned considered the evidence for the limited proposition in this litigation that the inorganic form of mercury can remain in the brain for a period of time and that elevated levels of mercury exposure can produce neurological effects. Petitioners' second theory of general causation, which was heard in three test cases during proceedings held in May 2008 and in July 2008,[138] involved a much more comprehensive examination of the neurological effects of the deposition of inorganic mercury into the brain after the body converts all of its organic mercury content, including the ethylmercury derived from thimerosal-containing vaccines, to inorganic mercury. Accordingly, the undersigned declines to address here this aspect of petitioners' claim in the same detail as will be required in the opinion addressing the second theory of general causation, specifically, the theory that the receipt of thimerosal-containing vaccines can lead to the development of autism spectrum disorder. Instead, the undersigned focuses on the aspect of petitioners' claim (asserted during the hearings on the first general theory of causation) that the mercury exposure from administered thimerosal-containing vaccines has an immunosuppressive effect on the vaccinee.

5. Petitioners Assert that There is a Subgroup of the Population that Responds to Mercury Exposure Differently than the Rest of the Population

a. The Claim that Certain Individuals are Genetically Hypersusceptible to Injury following Mercury Exposure

Dr. Aposhian posited that certain persons who have a genetic hypersusceptibility to mercury have developed neurological injuries after mercury exposure while other persons who do not possess that same hypersusceptibility have not developed neurological injuries. See Cedillo Ex. 55 at 9 (Dr. Aposhian's report); Cedillo Tr. at 70, 73A-74A (Dr. Aposhian); Cedillo Trial Ex. 1 at 18 (Dr. Aposhian's trial slides). As support for this claim, Dr. Aposhian relied on reports of persons within exposed populations who responded differently to mercury exposures.

Dr. Aposhian first described a percentage of the population that he asserted was hypersensitive to the mercury in dental amalgams. Cedillo Tr. at 77A-79A. He based his opinion of hypersusceptibility in part on the observed resistance to antibiotics four months after the insertion of mercury-containing dental amalgams into the teeth of monkeys, as

[138] The three test cases heard on petitioners' second theory of general causation are King v. Secretary of Health and Human Services, No. 03-584V, assigned to Special Master Hastings, Dwyer v. Secretary of Health and Human Services, No. 03-1202V, assigned to Special Master Vowell, and Mead v. Secretary of Health and Human Services, No. 03-215V, assigned to the undersigned.

was reported in the 1993 Summers article.[139] Id. at 77A-78A (referencing Cedillo Ex. 55RR at 832 (1993 Summers article) (a study showing that over a period of 16 weeks, the bacteria in the gastrointestinal tracts of monkey, who had mercury-containing amalgams inserted into their teeth became increasingly resistant to antibiotics)). The inserted fillings contained nearly 100 mg of mercury. See Cedillo Ex. 55RR at 826 (1993 Summers article). The mercury content of the inserted fillings was nearly 540 times more than the total mercury content (up to 185.5 mcg) in the prescribed childhood vaccination schedule.[140] In Dr. Aposhian's view, however, the observed increased resistance to antibiotics within four months of a known mercury exposure is suggestive evidence that there is a hypersusceptibility to mercury exposure in a certain segment of the population.

Dr. Aposhian also pointed to published reports describing the development of "pink disease," a condition presenting in children who were given an inorganic form of mercury (specifically, mercurous mercury, in the form of mercurous chloride or calomel) in teething powders during the first half of the 20th century. Cedillo Ex. 55 at 8-9 (Dr. Aposhian's report); Cedillo Tr. at 90A, 159 (Dr. Aposhian); Cedillo Ex. 55H at 613 (2006 Clarkson article). The teething powder was topically applied to the gums of the teething children. Cedillo Tr. at 159 (Dr. Aposhian). The manifested condition was known as acrodynia or "pink disease." Cedillo Ex. 55 at 8 (Dr. Aposhian's report); Cedillo Tr. at 90A (Dr. Aposhian); Cedillo Ex. 55H at 613 (2006 Clarkson article); see also Cedillo Ex. 55L at 291 (1997 Dally article[141]) (describing pink disease as a "serious disease that was common, at least in children's clinics, during the first half of the [20th century]").

The described signs and symptoms of pink disease included "profuse sweating, swollen red feet and hands, which were cold, clammy, desquamating [or peeling], and painfully sensitive to touch." Cedillo Ex. 55H at 614 (2006 Clarkson article); see also Cedillo Tr. at 90A (Dr. Aposhian describing same cluster of symptoms). The affected children also exhibited a body rash and a rash on the legs and arms. Cedillo Ex. 55H at 614 (2006 Clarkson article). "Progressive weight loss, marked weakness, . . apathy[,] [i]nsomnia, and photophobia" were other noted symptoms of the condition. Id. Anecdotally, the affected children were described as "too miserable to acknowledge their mothers" or "behav[ing] like [] mad dog[s]." Cedillo Ex. 55L at 292 (1997 Dally article). Not all of the children who were given the teething powder developed the condition. See Cedillo Ex. 55H at 614 (2006 Clarkson article). Rather, only a small fraction of the children who were given the teething powder were reported to have developed pink

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[139] A. Summers et al., Mercury released from dental "silver" fillings provokes an increase in mercury and antibiotic-resistant bacteria in oral and intestinal floras of primates, Antimicrob. Agents Chemother. 37: 825-834 (1993).

[140] One milligram (mg) is equal to 1000 micrograms (mcg).

[141] Ann Dally, The rise and fall of pink disease, Soc. Hist. Med. 10: 291-304 (1997).

disease. Id.[142] The adverse publicity generated by describing the observed ill-effects of pink disease as "mercury poisoning" prompted manufacturers to remove mercury "from most teething powders after 1954." Cedillo Ex. 55L at 302 (1997 Dally article). Following the removal of mercury from teething powders, "[p]ink disease almost disappeared." Id.

Petitioners argue that the children who developed pink disease from the use of teething powder provide evidence of a segment of the population that is genetically hypersusceptible to mercury exposure. Cedillo Tr. at 73A, 91A (Dr. Aposhian); Cedillo Trial Ex. 1 at 4 (Dr. Aposhian's trial slides); see also Hazlehurst Tr. at 382A-383A (Dr. Corbier). Respondent's expert Dr. Brent counters that in the absence of other scientific evidence pointing to a hypersusceptibility to mercury, the more likely explanation for why some but not all of the children were affected by the mercury content in the teething powder is a dose-response relationship. See Cedillo Tr. at 2366A-2367 (Dr. Brent) (pointing to a study finding "exceedingly high" mercury levels in the urine of persons suffering from acrodynia). Petitioners' expert Dr. Aposhian acknowledged during the Cedillo hearing that the scientific literature does not contain information about the dose of mercurous salts that children were administered, and the amount of teething powder given to the children who did develop the "pink disease" is not known. Cedillo Tr. at 163A-164 (Dr. Aposhian).

As additional support for their proposition that there is a population subgroup that is genetically hypersusceptible to mercury exposure, petitioners rely on a study of urinary porphyrin profiles of dentists and dental assistants who had occupational exposures to mercury in a dental practice for five consecutive years. See Snyder Ex. T5 at 160-161 (2006 Heyer article[143]). Urinary porphyrin profiles are profiles of certain compounds measured in urine that could serve as a biomarker for the presence of mercury in the body. See Snyder Ex. T3 at 465 (1991 Woods article[144]) (positing that the "urinary porphyrin excretion pattern elicited during prolonged exposure to . . . methyl mercury hydroxide . . . in rats . . . reflects both dose- and time-dependent effects of mercury in the kidney . . . and might serve as a useful biomarker of mercury concentration and effects over a prolonged course of mercury exposure"); see also Dorland's at 1488. Of the tested dentists and

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[142] The oft-cited fraction is one in 500 children exposed to mercury in teething powder developed pink disease. The fraction was first provided in a 1953 study, see Court Tr. Ex. 1 (J. Warkany and D. Hubbard, Acrodynia and Mercury, 42 J. Pediatrics 365 (1953)), and has been regularly cited. But the basis for that determination is unclear. Cedillo Ex. 55H at 614 (2006 Clarkson article).

[143] 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).

[144] The citation for this article is J. Woods et al., Urinary porphyrin profiles as biomarkers of trace metal exposure and toxicity: studies on urinary porphyrin excretion patterns in rats during prolonged exposure to methyl mercury, Toxicol. Appl. Pharmacol. 110: 464-476 (1991).

dental assistants, 85% were reported to have had urinary porphyrin levels that were within the normal range based on the predicted pattern of dose- and time-related porphyrins among human subjects occupationally exposed to mercury. Cedillo Trial Ex. 1 at 18 (Dr. Aposhian's slides); Cedillo Tr. at 93 (Dr. Aposhian); Snyder Ex. T5 at 160 (2006 Heyer article). But 15% of the occupationally exposed had "an atypical porphyrinogenic response." Cedillo Trial Ex. 1 at 18 (Dr. Aposhian's slides); Cedillo Tr. at 93A (Dr. Aposhian); Snyder Ex. T5 at 160 (2006 Heyer article). Dr. Aposhian asserted that the atypical response was attributed to a polymorphism in the human gene (identified as coporphyrinogen oxidase) that is suspected to modify the biological effects of mercury. Cedillo Trial Ex. 1 at 18 (Dr. Aposhian's slides); Cedillo Tr. at 93A-94A (Dr. Aposhian); Snyder Ex. T5 at 165 (2006 Heyer article) (describing the discovered polymorphism as the only one identified to modify the effect of mercury on porphyrin metabolism in humans). But the authors of the 2006 Heyer article were more reserved in their interpretation of their own study's findings than was Dr. Aposhian. The authors of the 2006 Heyer article stated that the "consequences of th[e] effect [of the polymorphism] on mercury toxicity in human subjects"–whether through modification of mercury toxicokinetics or through changes in porphyrin metabolism–are now under study. Snyder Ex. T5 at 166 (2006 Heyer article).

Additionally, respondent's expert Dr. Michael McCabe asserted that the article has limited applicability when evaluating the effects of thimerosal-containing vaccines because the study subjects in the 2006 Heyer article had high levels of mercury exposure. Snyder Tr. at 813-814. He indicated that the mercury exposure of the study's subjects was much higher than the mercury exposure attributable to thimerosal-containing vaccines. See id. at 814. Dr. McCabe pointed out that the findings from the porphyrin studies of the occupationally exposed in dental practices, studies performed by Dr. Woods, have not been adopted by the vast majority of metal toxicologists. Snyder Ex. T at 2 (Dr. McCabe's report). Respondent's expert Dr. Cook concurred that petitioners' experts' theory that certain persons are genetically predisposed to have adverse reactions to the thimerosal content in vaccines is speculative. See Cedillo Tr. at 1505 (Dr. Cook).

Nonetheless, Dr. Aposhian posited that children are more susceptible to the effects of mercury exposure because "[c]hildren are not small adults." Cedillo Tr. at 87A. They have different metabolisms. Id. They "absorb metals from their guts at a faster rate," and their brains and central nervous systems "are the most sensitive to methyl mercury." Id.

Respondent's expert Dr. Brent testified that there is "a formal toxicological concept of hypersusceptibility." Cedillo Tr. at 2481. Toxicologists can identify as a hypersusceptible population the group of people who manifest toxic responses to a dose of an agent that does not produce any response in the general population. See id. Dr. Brent testified that a hypersusceptible population has not been found in the autistic population "with regard to mercury." Id. at 2481-2482.

The difficulty with the theory of hypersusceptibility to mercury exposure that petitioners advance is twofold. First, the route of exposure involved in the studies on which petitioners rely is different from route of mercury exposure at issue in this litigation. Both dental amalgams and teething powders to be applied to the gums of children involve oral exposures rather than intramuscular exposures. Additionally, the Heyer study involving occupationally-exposed dentists and dental assistants did not involve

intramuscular exposure but rather exposure by inhalation and skin contact.

Second, the referenced studies involved elevated levels of mercury exposure. The 2006 Heyer study involved exposures to very high levels of mercury. The levels of occupational exposure in dental offices are grossly disproportionate to the exposure levels of vaccinated children. The 1993 Summers study also involved a level of exposure greater than the level of exposure for vaccinated children. Although the specific exposure levels for the children suffering from pink disease were not known, the amount of mercury to which teething children were exposed varied according to the frequency and liberality of use of the teething powder. Users of the teething powder had been advised to use the powder as often as necessary. That the observed symptoms of pink disease largely disappeared after the removal of the mercury content from the powder is quite consistent with what has been discovered about mercury in the more than 300 years of its use as a medicinal preparation–that is, dose determines the toxicity of the exposure. As discussed in Section III.B.2 of this decision, factors that affect the toxicity of mercury include the route (or method) of exposure and the exposure dose.

That a certain population of autistic children may be hypersusceptible to mercury exposure has not been established scientifically. And the evidence on which petitioners rely to support their hypersusceptibility theory is at best suggestive, but when the exposure routes and the exposure levels involved in the studies cited by petitioners are viewed in the proper context, the likelihood of the presented hypersusceptibility theory is diminished.

b. The Claim that Autistic Children have a Mercury Efflux Disorder

Dr. Aposhian further posited that there are autistic children who are unable to excrete mercury effectively and thus are affected by mercury exposures differently than children without a mercury excretion problem or efflux disorder. See Cedillo Tr. at 206A, 209A-209B. He testified that "normally" mercury efflux prevents the "accumulation of toxic levels of th[e] metal[]" in the human body through "a transport system that takes the mercury out of the cell[s]" of the body. Id. at 95A. When an efflux disorder exists, however, there is "a problem with getting . . . mercury[] out of a cell." Id. Dr. Aposhian asserted that "there is now considerable evidence" for the theory that "autism is a mercury efflux disorder." Id. at 70.

Dr. Aposhian described the process of normal mercury efflux and described the impairment in the process in autistic children. He testified that in a "normal individual," mercury moves from tissues to the blood and then moves from the blood to hair, before moving to urine or feces for excretion, but in an autistic child, mercury efflux is inhibited "so that the mercury stays in the tissue, the blood level is low and the hair level is low." Cedillo Tr. at 103 (Dr. Aposhian).

Dr. Aposhian urged that the medically-recognized efflux disorder of the heavy metal copper, known as Wilson's Disease, provides a model for the hypothesis he advances, specifically that a mercury efflux disorder exists. See Cedillo Petitioners' Trial Ex. 1 at 21 (Dr. Aposhian's trial slides); Cedillo Tr. at 95A, 97, 206A-207A (Dr. Aposhian); see also Hazlehurst Tr. at 377A (Dr. Corbier). Wilson's Disease is a disorder

of copper metabolism. Stedman's Medical Dictionary at 565 (28th ed. 2006). The disorder is caused by a mutation in the copper transporting gene (ATP7B). Stedman's at 566; Cedillo Ps' Trial Ex. 1 at 21 (Dr. Aposhian's trial slides); Cedillo Tr. at 95A-97 (Dr. Aposhian testifying that it is a disorder caused by "a mutation in . . . the ATP7B gene" and is "characterized by a large amount of copper in the tissues"). The disorder is characterized by the accumulation of copper in the brain stem and in the liver, in particular. Cedillo Tr. at 95A (Dr. Aposhian); see also Stedman's at 565-566.[145] The neurological complications involve the central nervous system. Cedillo Petitioners' Trial Ex. 1 at 21 (Dr. Aposhian's trial slides). This genetic disorder is treatable by administration of a chelating agent. Cedillo Petitioners' Trial Ex. 1 at 21 (Dr. Aposhian's trial slides); Cedillo Tr. at 96A (Dr. Aposhian).

In furtherance of the theory that autistic children potentially have a mercury efflux disorder, Dr. Aposhian pointed to various studies showing increased levels of mercury measured in the blood, hair, and teeth of autistic children. See Cedillo Tr. at 98A-99A. It was Dr. Aposhian's view that these studies lend support to a finding that autistic children have difficulty excreting mercury, a finding that would be consistent with a mercury efflux disorder. See Cedillo Tr. at 99A.

The four studies on which petitioners relied most heavily were the 2003 Holmes article,[146] see Cedillo Ex. 55X, the 2003 Bradstreet article,[147] see Cedillo Ex. 55E, the 2007 Adams article,[148] see Cedillo Ex. 82, and the 2002 Pichichero article, see Cedillo Ex 55NN. See also Cedillo Petitioners' Trial Ex. 1 at 22-26 (Dr. Aposhian's trial slides); Cedillo Tr. at 98A-105A, 199 (Dr. Aposhian); Hazlehurst Tr. at 377A, 379A-382A (Dr. Corbier).

The 2003 Holmes article summarizes the findings of an analysis of the mercury content of first-haircut hair clippings from 94 children diagnosed with various severities of autism and the comparison of the results with the clipping analyses from non-autistic children. See Cedillo Ex. 55X at 278-279 (2003 Holmes article); Cedillo Tr. at 98A (Dr.

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[145] The disorder of copper metabolism is marked by a decrease in plasma levels of copper and an increase in urinary excretion of copper. Stedman's at 565-566. The disorder is characteristically accompanied by liver cirrhosis, basal ganglia degeneration, green or golden pigmentation in the periphery of the cornea, and neurologic manifestations. Id.

[146] A.S. Holmes et al., Reduced levels of mercury in first baby haircuts of autistic children, Int'l J. of Toxicology 22: 277-285 (2003).

[147] J. Bradstreet, A case-control study of mercury burden in children with autistic spectrum disorders, J. Am. Physicians and Surgeons 8: 76-79 (2003).

[148] J. B. Adams, et al., Mercury, lead, and zinc in baby teeth of children with autism versus controls, Journal of Toxicology and Environmental Health Part A, 70: 1046-1051 (2007).

Aposhian). The investigators found that the "[a]utistic infants released dramatically lower levels of mercury into hair than control infants." Cedillo Ex. 55X at 283 (2003 Holmes article). But the reduced mercury hair levels were not associated with lower levels of overall mercury exposure. Id. Among the mercury exposures considered by the investigators were the number of maternal dental amalgams during pregnancy, any Rho D immunoglobulin injections received by the mother during pregnancy,[149] maternal fish consumption during pregnancy, and childhood vaccination exposures. Id. at 279. The investigators found that the autistic infants had higher exposures in many, but not all, of the exposure categories. Id. at 283. The investigators concluded, and petitioners here have argued, that measurements of mercury levels in the first haircuts of autistic infants that are lower than non-autistic controls suggest that autistic children have difficulty excreting mercury. Cedillo Ex. 55X at 284 (2003 Holmes article); Cedillo Petitioners' Trial Ex. 1 at 22-23 (Dr. Aposhian's trial slides); see also Cedillo Ex. 55Y at 1-2 (2003 Hu article[150]) (initial study to test hypothesis that autistics have difficulty excreting mercury by comparing the mercury-zinc concentrations in hair samples from three persons with autism spectrum disorder to the mercury-zinc concentrations in hair samples from non-autistic controls through the use of a scientific process--specifically, instrumental neutron activation analysis--that measures the heavy metal concentrations of interest, mercury, and zinc in the hair; the concentration of zinc is of interest because it may play a role in promoting mercury excretion); Cedillo Tr. at 98A-99A (Dr. Aposhian referring to the 2003 Hu article).

Dr. Aposhian explained the significance of his reliance on the 2003 Holmes article:

> [H]air is an excretory organ and . . . hair is reflective of the mercury or the metal in the blood, and the blood is a reflection of the mercury in the tissues, and so the fact that the autistic children had less mercury in their hair was a hint or indication that perhaps there was [a] mercury efflux disorder.

Cedillo Tr. at 99A; see also Snyder Tr. at 759 (respondent's expert Dr. McCabe explaining that "the measurement of mercury in the hair is a measure of exposure to an organic form of mercury, either methyl mercury or ethyl mercury"). But, respondent's expert Dr. McCabe explained that the measure of mercury in the hair is not a measure of excretion of mercury into the hair, but rather is a snapshot of or "a proxy" for the amount of mercury that could have been found in the blood of a person at a particular time. Snyder Tr. at 764. It is a measurement that is "reflective of what we have already seen in the blood data." Id.

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[149] 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.

[150] L. Hu et al., Neutron activation analysis of hair samples for the identification of autism, Transactions Amer. Nuclear Soc. 89: 681-682 (2003).

Dr. McCabe stated that measurements taken from hair closest to the scalp reflects mercury exposure within the last month. Id. at 761.

Additionally, respondent's expert Dr. Brent testified that hair is not a "normal excretory organ for mercury." Cedillo Tr. at 2468. As discussed in Section III.B.3.d of the decision, mercury is eliminated from the body primarily through feces and urine. See Cedillo Ex. 55H at 617 (2006 Clarkson article).

Dr. Brent also urged a closer look at certain irregularities in the 2003 Holmes study. He testified that the levels of mercury detected in the autistic subjects examined in the Holmes study were levels that fall within the range of normal for mercury hair levels reported in a random survey of children in the United States. Cedillo Tr. at 2352 (Dr. Brent) (discussing the mercury hair levels reported as normal in the federally funded National Health and Nutrition Exposure Survey). Dr. Brent further testified that as compared to the federally funded national survey of the mercury hair levels in children, the normal or control subject in the Holmes study had "very, very, very elevated hair levels." Id. at 2353. Dr. Brent stated that because the data obtained from the Holmes study "doesn't make any sense," the study does not provide a reliable scientific basis for concluding that autistic children are not able to excrete mercury. Id. at 2353. Petitioners have not refuted the irregularities in the Holmes study involving the reporting of normal mercury hair levels in autistic subjects as low because the mercury hair levels in the control subjects were extremely elevated.

A subsequent effort to replicate the hair study reported in the 2003 Holmes article was not successful. See Cedillo L32 (2004 Ip article[151]); Cedillo Tr. at 199-200A (Dr. Aposhian). In a case-control study of 82 children with ASDs and 55 children without ASDs in which blood and hair mercury levels were measured over a five-month period, the investigators found no statistically significant difference in the mean mercury levels between the two groups, with similar environmental exposures. Cedillo Ex. L32 at 432 (2004 Ip article).

The undersigned determines that the reported findings in the 2003 Holmes study are of questionable reliability based on the irregularities in the study that respondent's expert Dr. Brent described and petitioners did not rebut. The inability of other investigators to replicate the Holmes findings speaks further to the questionable reliability of the study.

The second of the four articles on which Dr. Aposhian relied heavily is the 2003 Bradstreet article that detailed the findings of a retrospective study comparing mercury excretion in urine from 221 children with ASDs with the urinary mercury excretion from a non-autistic control population of 18 children after three days of treatment with the oral chelating agent known as DMSA (or meso-2,3-dimercaptosuccinic acid). Cedillo Ex. E at 76 (2003 Bradstreet article); Cedillo Tr. at 99A-100A (Dr. Aposhian). The control children involved in the study had presented for an elective determination of their "levels of environmental mercury exposure at the request of their families." Cedillo Ex. 55E at 76

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

(2003 Bradstreet article). The investigators determined that when autistic children are chelated, they excrete far more mercury than the controls excrete. Cedillo Ex. 55E at 79 (2003 Bradstreet article). Dr. Aposhian explained that because the chelating agent "has a greater affinity for th[e] metal than [for] the protein to which the metal is attached in the cell," the chelating agent binds to the mercury in the body's cells and permits the urinary excretion of mercury. Cedillo Tr. at 100A. He reasoned that the increased mercury excretion from autistic children was an indication of an increased body burden and a possible efflux disorder. Id. at 100A (Dr. Aposhian).

Dr. Aposhian gave testimony that the "best way" to assess the effect of a chelator is establish a pre-chelation baseline for comparison with a post-chelation measurement. Cedillo Tr. at 166 (Dr. Aposhian). But, the 2003 Bradstreet study provides no information about the mercury levels measured in the children prior to chelation. In the absence of pre-chelation measurements of urinary mercury levels, the effectiveness of the administered chelator is difficult to assess. The inability to evaluate the effectiveness of the administered chelator significantly limits the usefulness of the 2003 Bradstreet article in evaluating petitioners' mercury efflux theory.

The usefulness of the article is diminished further by the acknowledgment of the study's investigators that they are unable to determine from their study whether the higher urinary excretion of mercury in the autistic children is due to exposure to higher mercury levels or to an inability to excrete mercury or to a combination of these factors. Cedillo Ex. 55E at 79 (2003 Bradstreet article). The undersigned cannot accept this article as support that petitioners' claim of mercury efflux disorder is more likely than not when the authors of the article do not express that same level of confidence that the study supports a finding of an inability to excrete mercury.

Respondent's expert Dr. Brent identified additional problems with the 2003 Bradstreet article. He testified that there was a failure to control for dietary mercury sources (which introduced a confounding factor), there was a "huge amount of variance" in the standard deviations of the study, and "[t]here was a large amount of overlap between the values in the autistics and the control population." Cedillo Tr. at 2357-2358. Moreover, Dr. Brent stated that using "the statistical methodology that [the investigators] describe in their paper[,] [he] could not come up with a statistically significant result which [the investigators] said that they had." Id. at 2358. Dr. Brent observed that the results of the 2003 Bradstreet article could not be replicated in a subsequent reported effort by investigators who administered a chelating agent to the patients (both autistic and normal) coming to their clinic. Id. at 2360-2361 (Dr. Brent referring to the 2007 Soden article, filed as Cedillo Ex. OO[152]). The investigators in the 2007 Soden study attempted to replicate the 2003 Bradstreet study but found no difference between the two groups (autistic and control) in the amount of heavy metal, including mercury, that was excreted. Id. at 2361 (Dr. Brent still referring to the 2007 Soden article); see also Cedillo Ex. OO at

[152] S. Soden et al., 24-Hour provoked urine excretion test for heavy metals in children with autism and typically developing controls, a pilot study, Clinical Toxicology 45: 476–481 (2007).

479-480 (2007 Soden article). Dr. Brent further observed that multiple studies have shown that urinary excretion following chelation with the chelating agent DMSA "is not an accurate or reliable measure of mercury body burden." Cedillo Ex. L at 22 (Dr. Brent's report). Petitioners did not rebut Dr. Brent's testimony.

Having found that the usefulness of the study's findings is limited due to the lack of pre-chelation data and to the inability of the study's investigators to attribute the post-chelation mercury levels in the urine to difficulty in excreting mercury, and informed by the unrebutted testimony of Dr. Brent that the reported findings in the study were not statistically significant, the undersigned determines that the 2003 Bradstreet article offers little or no support for petitioners' claim of mercury efflux disorder.

The third of the four articles on which petitioners' expert Dr. Aposhian relied is the 2007 Adams article that described a study investigating the body burden of mercury and lead in autistic children compared to controls by evaluating the amount of mercury and lead in the children's baby teeth. Cedillo Tr. at 101A-102A (Dr. Aposhian); Cedillo Ex. 82 at 1047 (2007 Adams article). The investigators examined baby teeth because the teeth, which are formed in utero and during the first few years of life, "provide a measure of cumulative exposure during that critical period of development." Cedillo Ex. 82 at 1047 (2007 Adams article); see Cedillo Tr. at 101A (Dr. Aposhian testifying that teeth are "tissues or [nonexcretory] organs of [the] body"). The investigators found that the mercury levels measured in the teeth of autistic children were twice the amount measured in the teeth of controls. Cedillo Ex. 82 at 1048-1049 (2007 Adams article); Cedillo Tr. at 101. In the study, no statistically significant difference was detected in the levels of zinc and lead measured in the autistic children and measured in the controls. Cedillo Ex. 82 at 1048-1049 (2007 Adams article); Cedillo Tr. at 102 (Dr. Aposhian). The measured mercury levels, however, were markedly different. Cedillo Ex. 82 at 1048-1049 (2007 Adams article); Cedillo Tr. at 102A. 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. Cedillo Tr. at 102A, 198.

Dr. Brent addressed the 2007 Adams article, stating that teeth, which are "basically bone," are not a "normal excretory organ for mercury." Cedillo Tr. at 2468-2469. He added that "[w]e don't incorporate mercury very much into bone" or "usually get mercury in bone." Id. He expressed uncertainty about "exactly . . . what" the investigators wanted to study. Id. Noting that the mercury levels of children are readily ascertainable from blood or urinary mercury levels, Dr. Brent stated that:

> There's not one single study in the peer-reviewed English language literature that reports a difference in blood mercury level in autistic children [compared to controls] or [a difference] in urine levels in autistic children compared to controls, and so I don't know what to make of . . . . [t]eeth. It doesn't make any sense.

Cedillo Tr. at 2469. Based on the small size of the sampled group in the 2007 Adams article and based on what is known about the lack of a statistically significant difference between the mercury levels in the blood and in the urine of autistic children as compared to control children, Dr. Brent questioned whether the reported results in the 2007 Adams

article were actually statistically significant. Id. Petitioners have not rebutted Dr. Brent's testimony about the 2007 Adams article.

The difficulty with petitioners' reliance on the 2007 Adams article as supportive evidence of the claim that autistic children have a mercury efflux disorder is twofold. First, because teeth are not an excretory organ for mercury, the premise for the study is scientifically questionable. Second, the reported findings of the 2007 Adams article are inconsistent with what is known about the comparative blood mercury levels and urinary mercury levels in autistic children and in control children. Unlike teeth, blood and urine provide easily ascertainable measurements of mercury. For these reasons, the undersigned is not persuaded that the 2007 Adams article offers reliable information about the mercury body burden of autistic children as compared to control children.

The fourth of the four articles on which petitioners' expert Dr. Aposhian relied most heavily in support of the mercury efflux disorder theory is the 2002 Pichichero article. Cedillo Ex 55 at 9 (Dr. Aposhian's report). The 2002 Pichichero article reported the results of a study of the blood mercury levels in 40 infants who received thimerosal-containing vaccines as compared to the blood mercury levels in 21 infants who received thimerosal-free vaccines. Cedillo Ex. 55NN at 1738 (2002 Pichichero article). The infants were aged two months to six months. Cedillo Ex. 55NN at 1738 (2002 Pichichero article). The "very low concentrations" of mercury detected in the blood of the infants who had received the thimerosal-containing vaccines (that delivered up to 62.5 micrograms of mercury) were found to be lower than the concentration of mercury thought to be safe in cord blood. Cedillo Ex 55NN at 1740 (2002 Pichichero article); see also Cedillo Tr. at 2342A (Dr. Brent). The concentration of mercury thought to be safe in cord blood had been determined to be that concentration of mercury that is "ten times below the lower 95% CI [(confidence interval)][153] limit of the minimal cord blood concentration [of mercury] associated with an increase in the prevalence of abnormal scores on the cognitive function tests in children." Cedillo Ex. 55NN at 1740 (2002 Pichichero article) (emphasis added). Dr. Aposhian criticized the article on the ground that it did not involve the study of autistic children, but he nonetheless pointed to the measured mercury blood levels in the vaccinated children studied as support for his mercury efflux theory. Cedillo Ps' Trial Ex. 1 at 30.

Although unable to provide the range of normal mercury blood levels for children without consulting a reference book, Dr. Aposhian did testify that in an adult, a mercury blood level of "under five micrograms per liter is [not] considered to be . . . of clinical concern." Cedillo Tr. at 131 (Dr. Aposhian); accord id. at 2329A (Dr. Brent testifying that "[m]ost people in this country are walking around with blood mercury levels less than five micrograms per liter"). None of the children whose mercury blood levels were measured in the 2002 Pichichero article had levels greater than 29 nmol/L (or 5.817

[153] A confidence interval is an estimated "range of values believed to contain [an unknown] parameter," the endpoints of which range reflect the confidence limits–which are defined by a stated probability that the unknown parameter is contained within the estimated range. See Dorland's at 944.

mcg/L[154]), a blood mercury level that is slightly higher than the blood mercury level (under five micrograms per liter) that is considered normal. Cedillo Ex 55NN at 1740 (2002 Pichichero article).

Respondent's expert Dr. Brent criticized Dr. Aposhian's suggestion that the results of the study would have been different if autistic children were among the subjects in the 2002 Pichichero study. Dr. Brent asserted that there is no scientific evidence that the kinetics of ethylmercury in autistics differs from the kinetics of ethylmercury in others. Cedillo Tr. at 2362A (Dr. Brent).

As acknowledged by the experts for both parties, the 2002 Pichichero study is of very limited assistance in evaluating petitioners' claim of a mercury efflux disorder because the study did not involve autistic children. Because the article contains no information about the mercury blood levels in autistic children, petitioners' reliance on the article for support is poorly placed.

To put measured mercury blood levels into perspective, Dr. Aposhian noted that the Dartmouth professor who died after her laboratory exposure to dimethylmercury had "horrendously elevated" blood mercury levels of more than 2000 micrograms per liter. See Cedillo Ex. 55 at 4 (Dr. Aposhian's report); Cedillo Tr. at 132 (Dr. Aposhian) (unable to remember, without looking at the article, whether the measured blood level was 2,000 or 20,000 micrograms/liter); Cedillo Ex. 55LL at 1672 (1998 Nierenberg article[155])(after chelation therapy, a whole blood mercury level of 4000 micrograms/liter reported and after a transfusion exchange, a mercury blood level greater than 2,000 micrograms/liter reported). The dose of dimethylmercury to which the professor had been exposed was estimated to have been about 1,344,000 micrograms/liter. Cedillo Ex. 55LL at 1675 (1998 Nierenberg article) ("about 1344 m[illigrams]"); Cedillo Tr. at 143 (Dr. Aposhian).

Petitioners drew attention to the 2000 Stajich article,[156] filed as Cedillo Ex. 55QQ, to support their position that the administration of thimerosal-containing vaccines to pre-term and term infants can cause a significant elevation in the infants' blood levels. See Cedillo Brief at 209; Cedillo Ex. 55 at 9 (Dr. Aposhian's report). Reported in the 2000 Stajich article were the measured mercury blood levels in infants following administration of hepatitis B vaccines containing thimerosal. Cedillo Tr. at 138A-139 (Dr. Aposhian); Cedillo Ex 55 at 9 (Dr. Aposhian's report); Cedillo Ex. 55QQ at 679-680 (2000 Stajich article). The measured mercury blood levels in the children in the 2000 Stajich article

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[154] The conversion from nmol/L to mcg/L is performed as follows:

29 nmol/L x 200.59 g/mol = 5817.11 ng/L or 5.817 mcg/L

[155] D. W. Nierenberg et al., Delayed cerebellar disease and death after accidental exposure to dimethylmercury, New England J. of Med. 338(23): 1672-1676 (1998).

[156] T. Stajich, et al., Iatrogenic exposure to mercury after hepatitis B vaccination in preterm infants, Clin. Lab. Observations 136: 679-681 (2000).

ranged from 2.24 micrograms per liter to 7.36 micrograms per liter. See Cedillo Tr. at 138A-139A (Dr. Aposhian); Cedillo Ex. 55QQ at 680 (2000 Stajich article). Dr. Aposhian testified that an exposure to 12.5 or 25 micrograms of mercury results from an administered hepatitis B vaccine (a thimerosal-containing vaccine) and an exposure to "about 180 or 200 micrograms of mercury" results from the administration of the prescribed schedule of childhood vaccines. See Cedillo Tr. at 143-144 (Dr. Aposhian).

Putting this exposure level into perspective, respondent's expert Dr. Brent testified that the mercury exposure doses referenced in the 2000 Stajich article "are certainly not anything close to what you would expect to be associated with any toxic effects." Cedillo Tr. at 2421 (Dr. Brent). And petitioners' expert Dr. Aposhian acknowledged during the Cedillo hearing, that the mercury blood level measurements in the vaccinated infants in the 2000 Stajich article are 600 times less than the mercury blood levels measured on autopsy in children that were reported in the 1977 Fagan article filed and cited by petitioners. See Cedillo Ex. 55 at 3-4 (Dr. Aposhian's report); Cedillo Tr. at 137- 140 (referencing Cedillo Ex. 55P at 962-963 (1977 Fagan article[157])). The children in the 1977 Fagan article were exposed to thimerosal tincture (which was applied topically to their umbilical protrusions over a period of time), and the children subsequently died. See Cedillo Ex. 55P at 962-963 (1977 Fagan article).

In further support of the theory advanced by petitioners that autistic children have a mercury efflux disorder, Dr. Aposhian testified that "[v]ery important studies now show that changes in the human gene . . . modif[y] the effect of mercury on a biological process." Cedillo Tr. at 70 (Dr. Aposhian). But respondent's expert Dr. Cook pointed out in his testimony that although investigators in the 2006 Heyer article to which Dr. Aposhian referred in his testimony did evaluate the effect of mercury on metabolism and a possible relationship to a particular gene, the investigators did not report a positive association between the gene and mercury toxicity.[158] See Cedillo Tr. at 1502A-1503 (Dr. Cook); see also Snyder Ex. T5 at 165 (investigators stating that studies are underway to evaluate the effect of CPOX4, a recently discovered genetic polymorphism (or variation), on "mercury toxicity in human subjects").

Respondent's experts took a dim view of petitioner's mercury efflux disorder theory. Dr. Brent pointed out that there is no classification for the concept of a "mercury efflux disorder" included in the World Health Organization's International Classification of Diseases (ICD). Cedillo R's Trial Ex. 17 at 40 (Dr. Brent's trial slides); see Dorland's at 903 (defining ICD). Nor is the concept described in any standard medical textbook. Cedillo R's Trial Ex. 17 at 40 (Dr. Brent's trial slides). Dr. Cook stated that the theory of

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[157] D. G. Fagan et al., Organ mercury levels in infants with omphaloceles treated with organic mercurial antiseptic, Arch Dis. Childhood 52: 962-965 (1977).

[158] Dr. Aposhian referred to the 2006 Heyer article in his testimony during the Cedillo hearing. The article was not filed, however, into the Cedillo record. The article was filed subsequently into the Snyder record as Snyder Ex. T5 (2006 Heyer article). The article was filed with the scientific literature attached to the expert report of respondent's expert, Dr. McCabe.

petitioners' experts that certain children are genetically predisposed to be unable to clear thimerosal from their bodies is "speculation." Cedillo Tr. at 1505 (Dr. Cook).

The difficulty with petitioners' mercury efflux disorder theory is that the presented support for the theory is derived either from scientifically questionable studies or from studies that do not support petitioners' proposition when the measured levels of mercury in the body are considered in the context of the levels of mercury exposure resulting from vaccinations. Although the existence of an efflux disorder for the heavy metal copper (known as Wilson's disease) is recognized and undisputed, there is no similar recognition–either medically or toxicologically–of an efflux disorder for mercury. While a medical theory does not have to be "recognized" or "undisputed" under Althen, it must be supported by a "reputable medical or scientific explanation" or a medical opinion. See Althen, 418 F.3d at 1278; Grant, 956 F.2d at 1148. This aspect of petitioners' theory lacks the requisite support.

6. Petitioners' Claim that Mercury Exposure can Cause Immunosuppression in Genetically Susceptible Persons

Petitioners' expert Dr. Aposhian testified that the human immune system is affected by exposures to mercury vapor, methylmercury, thimerosal, and mercuric mercury. Cedillo Tr. at 74A (Dr. Aposhian); Cedillo Ex. 55 at 10 (Dr. Aposhian's report). He posited that in a genetically susceptible person, mercury exposure would first trigger immune dysfunction which, in turn, would lead to immunosuppression. Cedillo Tr. at 207A.

Before considering petitioners' claim regarding mercury-induced immunosuppression, the undersigned turns her attention to the workings of the immune system.

a. The Immune System

The immune system is comprised of two components, the innate immune system and the adaptive immune system. Cedillo Tr. at 689 (Dr. Kennedy); Cedillo Petitioners' Trial Ex. 8 at 2-3 (Dr. Kennedy's trial slides). The first component, the innate immune system, functions as the "first responder" to the presence of a foreign entity (such as an infection) within a host. Cedillo Tr. at 690A (Dr. Kennedy). The innate immune system is fast, utilizes natural barriers such as skin, gastrointestinal lining, and mucous, and mounts a nonspecific response to foreign agents that are present within a host and have not moved into the cells of the host. Cedillo Tr. at 691A (Dr. Kennedy); see also L. Sompayrac, How the Immune System Works at 24 (2d ed., Blackwell Publishing 2003).[159] The innate immune system contains pattern recognition molecules that contain specific receptors, called toll-like receptors. Cedillo Tr. at 691A, 693 (Dr. Kennedy). Upon recognition of

[159] The undersigned has referred to How the Immune System Works to aid the undersigned in understanding the basic underpinnings of the immunological concepts addressed by the experts in this litigation.

particular patterns, such as protein sequences (including viral RNA or viral DNA), the toll-like receptors become activated and cause inflammation. Cedillo Tr. at 693, 697A (Dr. Kennedy). It is the innate immune system that is "predominantly responsible" for the inflammation that results when a foreign entity breaches the innate immune system. Cedillo Tr. at 691A (Dr. Kennedy).

The pertinent cells in the innate immune system are phagocytes, which are cells that can ingest and kill bacteria, foreign particles, and other cells. Cedillo Tr. at 697A (Dr. Kennedy); Stedman's at 1470. These phagocytic cells include white blood cells, macrophages and dendritic cells. Cedillo Tr. at 697A (Dr. Kennedy). White blood cells "are the precursors of macrophages and dendritic cells." L. Sompayrac, How the Immune System Works at 118. A macrophage is a type of blood cell that is produced in the bone marrow. See Stedman's at 1141; L. Sompayrac, How the Immune System Works at 4. Programmed to recognize many of the most common invaders of the human body, macrophages produce proinflammatory cytokines, the proteins that cause swelling at the site of a wound or infection. See L. Sompayrac, How the Immune System Works at 5. When alerted by a direct signal from an invading agent (an antigen) in the body, macrophages become "hyperactivated" and ingest the antigens at an increased rate. See id. at 19. Dendritic cells are "starfish-shaped" cells that are positioned just below the body's natural barriers.[160] Id. at 48; see also Cedillo Tr. at 906A (Dr. Byers) (describing the places where dendritic cells live as the points of invasion by pathogens and identifying the principal points of invasion as the skin, the lining of the lungs, and the lining of the "gut"). When alerted that an invasion has occurred, the dendritic cells perform some phagocytosis and also carry some antigen from the body's tissues to the lymph nodes for presentation to T cells in the lymph nodes, an act that provokes the adaptive immune system, which is the second component of the immune system, to respond. See L. Sompayrac, How the Immune System Works at 48; Cedillo Tr. at 907A-908A (Dr. Byers); Cedillo Ps' Trial Ex. 9 at 19-20 (Dr. Byers' slides).

The adaptive immune system is activated if the innate immune system cannot clear the inflammation. Cedillo Tr. at 691A-693, 698A (Dr. Kennedy). As part of the adaptive immune system, the T cells respond (according to the kind of T cell) either by killing infected cells, secreting message proteins (cytokines) that communicate with other parts of the immune system, or regulating the responses of other T-cells. See L. Sompayrac, How the Immune System Works at 9; see also Cedillo Ex. R at 2-3 (Dr. Fujinami's report).

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[160] Acting as antigen presenting cells (APCs or cells that present substances that can induce an immune response), dendritic cells travel to the lymph nodes. See Dorland's at 103; see also L. Sompayrac, How the Immune System Works at 48-50 (2d ed. 2003); Cedillo Ex. 55A at 475 (2007 Agrawal article). In the lymph nodes, the dendritic cells provoke T-cells (cells that mature in the thymus) that are specific for the presented protein substance (or protein antigen), and thereby initiate an immune response by the adaptive immune system. See Dorland's at 103; see also L. Sompayrac, How the Immune System Works at 9, 48-50 (2d ed. 2003); Cedillo Ex. 55A at 475 (2007 Agrawal article). The adaptive immune system adapts to defend against specific antigens. See L. Sompayrac, How the Immune System Works at 5-6 (2d ed. 2003).

Unlike the innate immune system, the adaptive immune system is slow; "it takes days to evolve." Cedillo Tr. at 692 (Dr. Kennedy). The adaptive immune system also has memory–unlike the innate immune system–which permits a broader and faster immune response to a second exposure to the foreign agent. Cedillo Tr. at 692 (Dr. Kennedy). The adaptive immune system is comprised of two parts, namely, the humoral arm and the cell-mediated arm. Cedillo Tr. at 698A, 701 (Dr. Kennedy).

The first part of the adaptive immune system, which is referred to as the humoral arm, contains lymphocytes and CD4+T cells. Cedillo Tr. at 698A, 701 (Dr. Kennedy). The B- lymphocytes (or B-cells) are the cells that generate antibodies, which are serum proteins that may generally be referred to as immunoglobulins. Cedillo Tr. at 699 (Dr. Kennedy); accord id. at 883A (Dr. Byers). These cells are effective in attacking pathogens that have not penetrated to the interior of a cell. See Cedillo Tr. at 700, 703 (Dr. Kennedy). The T cells that are invoked during a B cell-type response are called TH2 type cells. Cedillo Tr. at 700 (Dr. Kennedy).

The second part of the adaptive immune system, which is referred to as the cell-mediated arm, contains T lymphocytes (or T-cells) and CD8+ T cells. Cedillo Tr. at 698A, 701 (Dr. Kennedy). The T-cells are also referred to as helper inducer cells because they help induce the B-cells to produce antibodies. Id. at 1002A (Dr. Byers). The components of this arm of the adaptive immune system attack the pathogens that are inside of a cell. Cedillo Tr. at 701 (Dr. Kennedy). These cells attack infected cells. See Cedillo Tr. at 703 (Dr. Kennedy); see also id. at 883A (Dr. Byers). The cells that are invoked in a T cell-type response are called TH1 type cells. Cedillo Tr. at 701-702 (Dr. Kennedy).

In a normally functioning immune system, the two arms of the adaptive immune system regulate one another. Cedillo Tr. at 703 (Dr. Kennedy). The magnitude of the immune response is determined by the severity of the infection. L. Sompayrac, How the Immune System Works at 49. The normal CD4:CD8 ratio is 1.2, and typically, there should be as many CD4 cells as CD8 cells. Id. at 880A (Dr. Byers). These cells are signaling cells. See L. Sompayrac, How the Immune System Works at 58; see also Cedillo R's Trial Ex. 23 at 5 (Dr. Griffin's trial slides showing the timing of the CD4 and CD8 immune responses following a measles infection). The CD4 T-cells help generate a mature antibody response against invading agents and are involved in what is described as TH2 type immune responses. Id. at 2803 (Dr. Griffin). The CD8 T-cells are the cells that "are probably most responsible for clearing the virus" by killing the cells that have a virus infection. Id. at 2802 (Dr. Griffin). The CD8 T-cells are involved in what is described as a TH1 type immune response. See id. at 2813A (Dr. Griffin).

Helper T cells assist in directing the immune system's response to a bacterial or viral attack by secreting cytokine subsets that are referred to as either TH1 type responses or TH2 type responses. See L. Sompayrac, How the Immune System Works at 9, 61 (2d ed. 2003). TH1 cytokines "instruct the innate and adaptive systems to produce cells and antibodies that are especially effective against these invaders." Id. The profile of TH2 cytokines is necessary to generate "antibodies to defend against a parasitic (IgE) or [a] mucosal (IgA) infection." Id.

Both TH1 cells and TH2 cells secrete cytokines, which are proteins. L. Sompayrac,

How the Immune System Works at 60-61; see also Cedillo Tr. at 916 (Dr. Byers). Cytokines "are essentially messages sent from one cell to another so that individual cells can communicate with each other and tissues can communicate across large distances in the body." Cedillo Tr. at 1812A-1813A (Dr. Ward). Some cytokines act locally in the body, and others act over great distances. Id. at 1813A; see also id. at 2236-2237 (Dr. McCusker). Cytokines can be either pro- or anti-inflammatory. See id. at 998-999 (Dr. Byers); accord id. at 2236 (Dr. McCusker). The unnumbered cytokines and the earliest numbered ones such as interleukin-1 (IL-1) and interleukin-2 (IL-2) are produced in large quantities in the body, are not well-regulated, and often elicit proinflammatory responses. Id. at 1813 (Dr. Ward). In particular, interleukin-1 (IL-1) and interleukin-6 (IL-6) act to induce fever. Id. at 2238A (Dr. McCusker). In a feverish environment, bacteria and viruses do not replicate as well, and the slowed replication process allows other aspects of the immune system to respond. See id. at 2238A-2239 (Dr. McCusker). Proinflammatory cytokines can circulate in measurable amounts for weeks or months before they are detected medically. See id. at 1813A-1814 (Dr. Ward). The later-numbered cytokines bearing higher numbers generally are produced in much smaller quantities and their effects on the body are much more tightly regulated. Id. at 1813A.

The subset of TH1 cytokines "instruct the innate and adaptive immune systems to produce cells and antibodies" to "defend against a viral or bacterial attack in the blood and tissues." L. Sompayrac, How the Immune System Works at 61; see also Cedillo Tr. at 916 (Dr. Byers) (stating that cytokines "are produced both by the innate and by the adaptive immune system[s]"). The subset of TH2 cytokines promotes the production of antibodies to defend against a parasitic or mucosal infection." L. Sompayrac, How the Immune System Works at 61.

b. An Improperly Functioning Immune System

The condition of an improperly functioning immune system is described alternatively as immunodeficiency, immune dysfunction, or immune dysregulation. Cedillo Tr. at 706-707A (Dr. Kennedy). There are two types of immunodeficiencies, primary and secondary. Cedillo Tr. at 707A (Dr. Kennedy). A primary immunodeficiency is genetic and congenital. Cedillo Tr. at 707A (Dr. Kennedy). A secondary immunodeficiency is acquired. Cedillo Tr. at 707A (Dr. Kennedy). Even within the different types of dsyregulated immune systems, there are "variations." See id. at 943 (Dr. Byers).

Primary congenital immunodeficiencies occur "in quite a few individuals" and typically involve a malfunction in an otherwise properly functioning immune system. See Tr. at 708A (Dr. Kennedy). A secondary or acquired immunodeficiency "can result" from certain environmental triggers or factors. Id. at 709 (Dr. Kennedy). Among the known environmental factors that can cause either immune dysfunction or immunosuppression are malnutrition, heavy metal exposure, chronic malarial infection, cancer treatment, severe burns, and the measles virus. Id. at 709-710.

Immune dysregulation is distinguishable, however, from immunosuppression. See Cedillo Tr. at 1801A (Dr. Ward); id. at 2820-2821A (Dr. Griffin). See also id. at 966-968,

970A (Dr. Byers addressing the "umbrella of immune dysregulation" which includes a range of abnormality from mild to severe). The term "immune dysfunction" may be used to describe a circumstance in which a child's measured immune system parameters are normal, but the child's presentation with multiple infections suggests that something may be immunologically awry. See id. at 2262 (Dr. McCusker). The term "immune abnormality" is used to describe an abnormality detected by objective laboratory testing. See id. at 2263 (Dr. McCusker). The term "immune deficient" is used in the circumstance where both a clinical abnormality is present and laboratory testing has revealed an objective abnormality. Id. These states can be genetically influenced. See id. at 1809 (Dr. Ward stating that genetic influences can cause immune dysregulation or an immune imbalance). When a person has a genetically influenced immune imbalance that produces a state of either TH1 or TH2 predominance, that person has a tendency to respond to every pathogen "in either a TH1 or TH2 way." Id. at 1808 (Dr. Ward). The phenomenon of TH1/TH2 skewing is a characteristic of immune dysregulation. Id. at 879A (Dr. Byers). Even with an immune imbalance, both a cellular response and an antibody response are generated, but the generated response leans toward one response. See id. at 1810A-1811A (Dr. Ward). Petitioners in the OAP litigation have argued that the immunological profiles of autistic children suggest that there is a TH2 skewing in the children, which permits the generation of antibodies but not the clearance of infectious agents such as the measles component of the MMR vaccine. See, e.g., Cedillo Ex. 57 at 3-5 (Dr. Byers' report); Cedillo Ex. 61 at 8 (Dr. Kinsbourne's report). The classic, clinical example of an individual with TH2 skewing, however, is someone with allergies, and the only easily accessible biomarker that is available in patients with a TH2 skewing is an elevated level of the immunoglobulin IgE. Cedillo Tr. at 2240 (Dr. McCusker).

An immune imbalance or an abnormality of the immune system is not, however, equivalent to immunosuppression. See id. at 1817 (Dr. Ward); see also id. at 2239-2240 (Dr. McCusker). From a clinical standpoint, immunosuppression is an induced state in which the immune system does not function properly as a result of an administered treatment or medication. Id. at 2240; see also id. at 2790-2792 (Dr. Griffin).

c. Clinical Evidence of an Immune System Abnormality

Because the immune system is not static but changes as an individual develops and ages, a single evaluation may not be sufficient to permit a clinician to draw conclusions about the function of an individual's immune system. See Cedillo Tr. at 2208A (Dr. McCusker). A patient undergoing evaluation for an immunodeficiency generally receives an initial screen of the immune system, and if any abnormalities are detected, the patient undergoes repeated testing to determine if the detected abnormalities are consistent over time. Id. If an abnormality is found in a patient's immune system, the clinician may authorize more sensitive testing, including genetic testing, to be conducted. See id. at 2210A.

Petitioners' expert Dr. Byers described how a patient might be evaluated for an immune system abnormality. She stated that a clinician may evaluate a child for immune dysregulation by taking first a family history of the patient. Id. at 873A (Dr. Byers). A family history of immune disorders is of interest. Id. A clinician next takes a personal

history of the patient. Id. A personal history of frequent or unusual infections for which the child sees the doctor or for which the child is treated with antibiotics is of particular interest. Id. A history of frequent infections may be indicative of an immunodeficiency. Id. at 887-888A. Also of interest are chronic inflammatory conditions and any "aberrant reactions to vaccines." Id. at 874A; see also Cedillo Ps' Trial Ex. 9 at 9 (Dr. Byers' slides). The chronic inflammatory conditions in particular may signal the presence of an autoimmune disorder. See Cedillo Tr. at 888; Cedillo Ps' Trial Ex. 9 at 9 (Dr. Byers' slides). If, after taking the patient's family and personal history, the clinician determines that further evaluation is merited, the clinician orders laboratory tests. Id. at 874A; see also Cedillo Ps' Trial Ex. 9 at 2 (Dr. Byers' slides).

The standard panel of tests ordered to evaluate the immune system includes: (1) a complete blood count; (2) a differential count, which is a measurement of the B cells and the T cells in the lymphocyte population;[161] (3) a chemistry panel that includes tests of liver and renal function; (4) and a urinalysis. Cedillo Tr. at 874A-875A (Dr. Byers); Cedillo Ps' Trial Ex. 9 at 3 (Dr. Byers' slides). Additional standard tests include: (1) an analysis of the B cells and the T cells with a subset analysis; (2) an analysis of the child's serum immunoglobulin levels with a subclass analysis; (3) an analysis of the child's response to antigens (which substances are capable of inducing an immune response[162]) that are commonly found in the environment; and (4) analysis of the child's response to nonspecific mitogens which are substances that indirectly induce cell division or transformation and are "nonspecific stimulants of the B cells or the T cells."[163] Cedillo Tr. at 875A-876A (Dr. Byers); Cedillo Ps' Trial Ex. 9 at 3 (Dr. Byers' slides); accord id. at 2214A-2225A (Dr. McCusker describing the laboratory tests used to evaluate an immune system's functioning). The clinician is not only interested in the number of immune system components that are present in the child, but also whether the components are functioning properly. See id. at 876A, 881A; accord id. at 2209A-2210A (Dr. McCusker stating that an immunologist is interested in the respective numbers of B cells and T cells in a patient as well as whether the cells activate properly in the presence of administered stimuli). The conducted laboratory tests yield information about the number of component cells in the immune system, the type of components detected, and the state of the components' function. See id. at 2215-2221A (Dr. McCusker describing how a flow cytometer machine works to differentiate between types of cells and describing how proliferation assays conducted in a petri dish yield information about the health of cells when the cells are exposed to stimulating agents).

Petitioners' immunologist, Dr. Byers, cautioned that when evaluating the obtained test results, no comparisons should be made between the normal range for test results obtained from one laboratory and the normal range for test results obtained later from a different laboratory. Cedillo Tr. at 885A. Dr. Byers explained that different laboratories

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[161] See Mosby's Manual of Diagnostic and Laboratory Tests at 88-89 (3d ed. 2006).

[162] See Dorland's at 103.

[163] See Dorland's at 1162.

use different reagents and different instruments which lead to different results for the normal range. See id. Respondent's immunologist Dr. McCusker agreed that maintaining consistency in the test results is important. See id. at 2214A. She stated that consistent test results are best achieved by conducting initial testing and follow-up testing in the same accredited laboratory that performs regular quality assurance and by using the laboratory's age-specific range for normal test results (that is, adult ranges for adult testing and pediatric ranges for pediatric testing) to evaluate the obtained test results. See id. at 2211, 2214A, 2261A, 2267. She explained that while there are variances between laboratories, all laboratories use the published ranges for test results and not just the laboratory-specific ranges. See id. at 2270. She added that the use of age-specific ranges for test results is not simply a widely accepted practice but is "considered standard of care." See id. at 2210A-2211.

d. Evidence of the Impact of Mercury Exposure on the Immune System

Conceding that the offered hypothesis of mercury-induced immunosuppression was a late development in petitioners' case, Dr. Aposhian asserted that evidence of the effects of mercury on the immune system is supplied by various studies. See Cedillo Tr. at 207A (Dr. Aposhian stating that the hypothesis was "made less than three or four weeks" before the hearing in the Cedillo case). Dr. Aposhian pointed to two studies, the 1975 Koller article[164] and the 1981 Koller article,[165] that demonstrate that chronic exposure to mercury compounds leads to the development of autoimmunity in mice and reduces the resistance of the mice to viral infection. Cedillo Ex. 55 at 10 (Dr. Aposhian's report); Cedillo Ex. 55BBB at 1501 (1975 Koller article).

Review of the 1975 Koller article indicates that the study involved chronic exposure to methylmercury exposure. Methylmercury is different, however, from ethylmercury, the form of mercury present in vaccines when thimerosal dissociates in the body. Moreover, mercury exposure that results from vaccinations is not chronic; it does not persist over a long period of time. See Dorland's at 363. Rather the exposure to ethylmercury is episodic, and based on its known half-life (less than ten days in the blood serum, see Section III.B.2.b), that form of mercury does not remain in the body a long time. The 1975 Koller article provides little guidance to the undersigned about the effect of thimerosal-containing vaccines on the immune system because the form of mercury studied and the duration of the mercury exposure are distinguishable.

Dr. Aposhian also pointed to the 1990 Petruccioli article in which investigators found that the immunoglobulin levels of monkeys who received daily oral administrations over a 120-day period in varying dosages of methylmercury chloride were affected.

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[164] L. D. Koller, Methylmercury: effect on oncogenic and nononcogenic viruses in mice, Am. J. Vet. Res. 36(10): 1501-1504 (1975).

[165] This article, however, did not appear in Dr. Aposhian's bibliography. Nor did he file a copy of this article into the record.

Cedillo Ex. 55 at 10 (Dr. Aposhian's report); Cedillo Ex. 55CCC at 299-300 (1990 Petruccioli article[166]). Prior to the start of the administrations, the investigators measured the levels of immunoglobulins A, G, and M (IgA, IgG, and IgM) in the monkeys.[167] Cedillo Ex. 55CCC at 300-301 (1990 Petruccioli article). The investigators charted the dose-response effects on the monkeys' immmunoglobulin levels. See id. at 302-304 (1990 Petrucioli article). The investigators found a dose-related reduction in the each of the immunoglobulin levels, but after 45 days of administration, there was an increase in the immunoglobulin levels of IgA. See id. at 301-303. While the investigators measured changes in the animals' immunoglobulin levels, the investigators saw no clinical or behavioral signs of mercury toxicity. Id. at 301. A slight initial weight loss, however, was observed during the period of acclimatization. Id. Although noted, the slight weight loss was not attributed to toxicity. Id.

Dr. Aposhian opined that two recent studies, specifically the 2006 Goth study of murine (taken from mice) dendritic cells and the 2007 Agrawal study of human dendritic cells, provide evidence "that [t]himerosal is an immunosuppressant, even in nanomolar amounts."[168] Cedillo Ex. 55 at 10 (Dr. Aposhian's report) (citing Cedillo Ex. 55Q (2006 Goth article[169]) and Cedillo Ex. 55A (2007 Agrawal article[170])); see also Cedillo Tr. at 902A-905A (Dr. Byers) (citing the 2006 Goth study and the 2007 Agrawal study for the proposition that exposure of dendritic cells to an amount of thimerosal that is roughly one-seventh of the amount of thimerosal contained in the prescribed childhood vaccination schedule resulted in abnormal secretions from the dendritic cells); Cedillo Ps' Trial Ex. 9

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[166] L. Petruccioli and P. Turillazzi, Serum immunoglobulin levels in monkeys treated with methylmercury, Drug Chem. Toxicol. 13(4): 297-307 (Jan. 1990).

[167] 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. These antibodies are produced by B cells, which are white blood cells that are "born in" and mature in the bone marrow. L. Sompayrac, How the Immune System Works at 6, 9 (2d ed. 2003). B cells make antibodies that can recognize any organic molecule. Id. at 9.

[168] Dendritic cells are the "most potent" of the antigen presenting cells (cells that present substances that can induce an immune response) of the immune system. Cedillo Ex. 55A at 475 (2007 Agrawal article). Functioning as "sentinels of the immune system," they patrol the body, discriminate between self and nonself, and relay information to the adaptive immune system. Id. Dendritic cells respond to a threat by transporting the discovered antigens to local lymphoid organs, where T cells specific for the antigen are activated. Id.

[169] S. R. Goth et al., Uncoupling of ATP-mediated calcium signaling and dysregulated interleukin-6 secretion in dendritic cells by nanomolar thimerosal, Environ. Health Perspect. 114: 1083-1091 (2006).

[170] A. Agrawal et al., Thimerosal induces TH2 responses via influencing cytokine secretion by human dendritic cells, J. Leukocyte Bio. 81: 474-482 (2007).

at 16 (Dr. Byers' slides) (same). In the 2006 Goth article, the investigators examined the effects of low level thimerosal exposures (in nanomolar amounts) on the dendritic cells of mice. See Cedillo Ex. 55Q at 1083 (2006 Goth article). The study was in vitro (which means the experiments were conducted in vials of tissue culture or in petri dishes, rather than on living subjects of either animals or humans).[171] See id. at 1084, 1088; see also Cedillo Ex. L at 6-7 (Dr. Brent's report describing how in vitro studies are conducted). As explained by Dr. Aposhian during the Cedillo hearing, an in vitro study involves the study of cells of an organism or isolated enzymes of that organism, but not a study of the whole animal. Cedillo Tr. at 172 (Dr. Aposhian). The investigators found that the immunoregulatory function of the dendritic cells was altered by low level exposure to thimerosal and ethylmercury over a period of 20 hours. Cedillo Ex. 55Q at 1090.

In the 2007 Agrawal study, the investigators examined the immunological effects of exposing dendritic cells in human blood samples to thimerosal exposure. Cedillo Ex. 55A at 475 (2007 Agrawal article). Based on the central role of dendritic cells in the coordination of immunologic defenses, the investigators sought to understand the "cellular basis of [any] immunological abnormalities associated with mercury exposure." Id. at 475. The investigators explained that "[t]he nature of [the] . . . cytokines [either proinflammatory or anti-inflammatory] secreted by the [dendritic cells] in response to [a threat (like mercury exposure)] dictates the type of the T cell responses," which could include immunologically abnormal responses such as allergy and autoimmunity.[172] Id. The investigators found that "in a concentration-dependent manner," thimerosal suppressed the secretion of proinflammatory cytokines without significantly affecting the secretion of anti-inflammatory cytokines, leading to a TH2 skewed response. Id. at 476, 480 (emphasis added). The investigators further found that the addition of exogenous glutathione (GSH) to dendritic cells exposed to thimerosal "restores" the secretion of proinflammatory cytokines by dendritic cells to "normal levels."[173] Cedillo Ex. 55A at 480 (2007 Agrawal article).

On questioning during the Cedillo hearing, Dr. Aposhian acknowledged that in the Goth and Agrawal articles, the entire amount of the administered thimerosal in the in vitro studies would bind to the dendritic cells in the absence of anything else to which the thimerosal could bind. Cedillo Tr. at 185A. Dr. Aposhian did not dispute that, in contrast to the behavior of thimerosal observed during in vitro studies, 90 percent of administered

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[171] In contrast, an in vivo study is conducted within a living body. See Dorland's at 948.

[172] Cytokines are non-antibody proteins released by a cell population (specifically primed T lymphocytes) on contact with a specific antigen. See Dorland's at 469. The release of cytokines is part of a generated immune response. Id.

[173] Glutathione (GSH) "is a small molecule, which is present at high concentrations (mM range) inside . . . cells and plays key roles in basic metabolic and cell-cycle-related processes." Cedillo Ex. 55A at 480 (2007 Agrawal article). The peptide is comprised of three amino acids. See Dorland's at 784, 1396.

ethylmercury by vaccination does not come into contact with dendritic cells, but rather binds to red blood cells, proteins, and other molecules in human beings. See id.; accord id. at 2329A (Dr. Brent explaining that because 90 percent of the mercury found in blood binds to red blood cells and the remaining 10 percent circulates in the blood plasma or serum, it takes 200 micrograms per liter of mercury in the blood (a very high level of mercury) to effect a 20-microgram per liter level of mercury exposure in plasma (the level of mercury concentration involved in the Goth study)). Due to important differences between the in vitro and in vivo environments, observations of how thimerosal reacts in the in vitro environment do not translate well in the in vivo environment, and are of limited assistance in evaluating the alleged immunosuppressive effects of mercury in the body.

Dr. Aposhian also pointed to three articles (1992a Shenker article, the 1992b Shenker article, and the 1998 Shenker article) as evidence of the immunotoxic effects of mercuric compounds on human lymphoid cells. Cedillo Ex. 55 at 10 (Dr. Aposhian's report); Cedillo Ex. 55DDD at 539 (1992a Shenker article[174]); Cedillo Ex. 55EEE (1992b Shenker article[175]); Cedillo Ex. 55FFF (1998 Shenker article[176]). In the 1992a Shenker article, the investigators reported that the results of their in vitro study "indicate[d] that low doses of mercury have a profound inhibitory effect on human T-lymphocyte activation." Cedillo Ex. 55DDD at 541 (1992a Shenker article). In the 1992b Shenker article, the investigators again examined, through in vitro study, the immunotoxic effects of mercuric compounds on human lymphoid cells and concluded:

> [D]ata from this study confirms that human defense mechanisms represent a vulnerable target for both organic and inorganic compounds of mercury. The toxic response is complex in that effects of mercury on the host will be in part dependent upon the level of exposure. High level exposure may lead to [T-]cell death while chronic low levels of mercury may result in insidious effects associated with depressed immune function.

Cedillo Ex. 55EEE at 575 (1992b Shenker article); see also Cedillo Tr. at 1003A (Dr. Byers noting that the presence of mercury can induce cell death (known as apoptosis) in T-cells). Subsequently, in the 1998 Shenker article, the investigators concluded, after further in vitro study, that exposing human T cells to chronic low levels of methylmercury "may

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[174] B. J. Shenker et al., Immunotoxic effects of mercuric compounds on human lymphocytes and monocytes: I. Suppression of T-cell activation, Immunopharmacol. Immunotoxicol. 14(3): 539-553 (1992a).

[175] B. J. Shenker et al., Immunotoxic effects of mercuric compounds on human lymphocytes and monocytes: II. Alterations in cell viability, Immunopharmacol. Immunotoxicol. 14(3): 555-577 (1992b).

[176] B. J. Shenker et al., Low-level methylmercury exposure causes human T-cells to undergo apoptosis: evidence of mitochondrial dysfunction, Environ. Res. 77: 149-59 (May 1998).

induce" the death (or apoptosis) of the T cells. Cedillo Ex. 55FFF at 157 (1998 Shenker article).

Dr. Aposhian testified that methylmercury exposure can lead to human cell death by depleting the cells of glutathione, which results in an increased sensitivity in the cells to oxidative stress. Cedillo Ex. 55 at 10 (Dr. Aposhian's report) (citing the 1998 Shenker article). The increased sensitivity to oxidative stress, in turn, triggers the cell death process. Id.

The Shenker articles, however, have limited relevance to the analysis required here. The form of mercury to which vaccinees are exposed is not methylmercury but ethylmercury (upon the dissociation of thimerosal). Moreover, the exposure to ethylmercury in vaccinations is not chronic (continues over time). See Dorland's at 363. Rather the childhood vaccination schedule allows a series of discrete exposures, and based on the known half-life of ethylmercury (less than ten days in the blood serum, see Section III.B.3.b), ethylmercury does not remain in the body a long time.

Dr. Aposhian also cites to two review articles, specifically, the 2002 Krause article and the 2006 Ashwood article for the proposition that defects in the immune system may be linked to the symptoms of autism. See Cedillo Ex. 55 at 10 (Dr. Aposhian's report) (citing Cedillo Ex. 59G (2002 Krause article[177]) and Cedillo Ex. 55C at 1 (2006 Ashwood article[178])); see also Cedillo Tr. at 889A, 893A (Dr. Byers pointing to the 2006 Ashwood article as a summary of "what is known about the immune status of autistic children in general"). In the 2002 Krause article, the authors noted that "various immune system abnormalities . . . have been reported in children with autistic disorder" in studies that have been "largely association based." Cedillo Ex. 59G at 342 (2002 Krause article). The authors acknowledged that "draw[ing] conclusions regarding the role of immune factors in the etiopathogenesis of th[e] neurodevelopmental disease [of autism]" "remain[ed] difficult." Id. (emphasis added). In the 2006 Ashwood article, the authors conducted a review of various studies presenting hypotheses about the immune systems of autistic subjects and acknowledged the "apparently conflicting results, and thus far, [lack of] consensus about the described immune findings" in numerous studies of immune dysfunction in autistic patients. Cedillo Ex. 55C at 11 (2006 Ashwood article) (emphasis added). While admitting that further study is required on the subject, the authors concluded that the role of immune dysfunction in autism cannot be discounted. Id. Although the articles do address the possibility that immune system defects may be associated with the symptoms of autism, the articles do not support a finding that the suggested association is more likely than not.

Petitioners' expert Dr. Byers attempted to link mercury's alleged toxic effect on the

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[177] I. Krause et al., Immune factors in autism: A critical review, J. Autism Dev. Disord. 32(4): 337-45 (Aug. 2002).

[178] P. Ashwood et al., The immune response in autism: the new frontier in autism research, J. Leukocyte Biol. 80: 1-15 (July 2006).

immune system to the development of autism. She observed, as a threshold matter, that there is a genetic susceptibility to immune dysregulation and there is evidence of an abnormal immune system in many of the children who have received thimerosal-containing vaccines and have suffered immune system dysregulation as a result of the mercury exposure from the vaccines. Id. at 937-938A. Deferring to Dr. Aposhian to address the toxicity of mercury, Dr. Byers testified that there is evidence in the medical literature that mercury has "had multiple roles in disturbing the immune system." Cedillo Tr. at 896A. She further testified that different species of mercury affect the body differently and remain in the body for different lengths of time. See id. at 984A, 987A. She stated that one of the difficulties that she encountered in her review of the medical literature was determining the exposure dose of mercury involved in the various studies describing an effect on the immune system. Id. at 897A. In some of the reviewed studies, there was no information about exposure dosage, and in other studies, such as the in vitro studies, the mercury doses were "pretty high." Id. Ultimately relying on the 2006 Goth article and the 2007 Agrawal article to support petitioners' proposition that small amounts of thimerosal exposure are sufficient to disrupt the functioning of the dendritic cells within the immune system, Dr. Byers opined that mercury causes immune dysfunction by impairing "the ability of dendritic cells to behave in a normal fashion so that they can clear viruses." Id. at 913-914; Cedillo Ps' Trial Ex. 9 at 24. Dr. Byers further opined that such an impairment affects the immune system's ability to clear viruses and bacteria in a normal manner from the body and causes the continued release of cytokines in the body that could lead to a chronic low-grade inflammatory response that ultimately produces an autoimmune disease. Cedillo Tr. at 914-915, 918 (Dr. Byers seeming to suggest that mercury exposure could cause immune dysfunction that could trigger an autoimmune process that could lead to a nervous system injury and the development of autism).

Dr. Byers testified that receipt of thimerosal-containing vaccines could contribute to the dysregulation of a child's immune system that, in turn, could permit the measles component of the MMR vaccine to persist and to cause inflammation, which inflammation could produce a neural injury that presents as autism. Id. at 915-920A; 928-930B. But, she stated later in her testimony that receipt of thimerosal-containing vaccines was "not" critical to her theory of causation when there is evidence that the affected child already had a dysregulated immune system. See id. at 941-943. Dr. Byers also clarified later in her testimony that she lacks the qualifications to offer an opinion about whether the MMR vaccine causes autism spectrum disorder, and for that portion of the theory advanced by petitioners, she must rely on the testimony of a qualified pediatric neurologist. Id. at 946-947.

Dr. Byers' testimony that mercury exposure impairs the ability of dendritic cells "to clear viruses" must be put into proper perspective immunologically. Although dendritic cells have some phagocytic capability (ability to kill invading organisms), the primary function of dendritic cells is not to clear viruses, but rather to present the foreign substances (known as antigens) to the B cells and to the T cells. See Cedillo Tr. at 2231A-2233A (Dr. McCusker); Snyder Tr. at 575A (Dr. Zweiman); Snyder Tr. at 756 (Dr. McCabe). The B cells and the T cells comprise the adaptive immune system and, once presented with antigen, these cells are activated to attack viruses. See id.; accord Cedillo Tr. at 692-703 (Dr. Kennedy). The B cells attack the viral material in circulation; the T cells attack infected cells. See id. at 2231A-2233A (Dr. McCusker); accord Cedillo Tr. at

692-703 (Dr. Kennedy).

Moreover, Dr. Byers' testimony that mercury exposure could influence the development of autoimmunity was described by respondent's expert immunotoxicologist Dr. McCabe as "highly provocative." See Snyder Tr. at 748-749A (Dr. McCabe); see also. Cedillo Tr. at 897A-898 (Dr. Byers' explaining that mercury "induces the differentiation of autoreactive T cells," that would permit the development of autoimmune conditions). Dr. McCabe explained that the suggestion by Dr. Byers that mercury exposure causes T-regulatory cells to become self-reactive and thereby to set in motion the development of an autoimmune condition is "provocative because it turns out that these T-regulatory cells are very important in or appear to be very important in . . . at least one mechanism that controls autoimmune diseases," rather than a mechanism that induces autoimmune diseases. Snyder Tr. at 748-749A.

Respondent's immunologist Dr. Zweiman observed that although certain antibodies[179] that attack myelin basic protein (MBP), a protein component of the myelin sheath that protects the electrical communication signals between neurons in the central nervous system, have been reported in patients with autism spectrum disorders, these detected antibodies are not specific for autism. Snyder Tr. at 581A. The same antibodies have been detected in patients with neurodegenerative diseases, autoimmune conditions, epilepsy, as well as in patients with no ostensible clinical disease. Id. Moreover, the myelin damage that can be observed by imaging of the brains of patients with autoimmune conditions does not appear in the brains of autistic patients. Snyder Tr. at 572, 577A-578.

Additionally, Dr. McCabe observed, as a scientist actively working in the emerging discipline of immunotoxicology, that Dr. Byers' discussion about the volume of literature that "reports on mercury modulating the immune response in animal models," appeared to lack the understanding that researchers working in this area "are well aware that they are using very high doses of mercury to elicit [particular immunological] changes" because the researchers desire to study the attributes of the induced immune disease, and not the risks associated with the particular exposure. Snyder Tr. at 750-751A. Because the exposure doses involved in the mouse studies are "1,000-fold" compared to the mercury exposure resulting from the administration of thimerosal-containing vaccines, the research conducted by those working with mouse models of mercury modulation "cannot readily be applied to risk assessments." Id. at 751A, 753. Dr. McCabe added that even at lower doses, the features of the diseases that have been induced in mouse models following mercury exposure have not been shown in humans. Id. at 753.

The undersigned found the testimony of respondent's witnesses to be consistent with and supported by peer-reviewed literature and much more persuasive than the testimony of petitioners' witnesses on the issue of whether mercury exposure through thimerosal-containing vaccines can cause clinically significant immunosuppression. In support of their claims, petitioners have relied on evidence involving substantially greater exposure doses of mercury than are involved in childhood vaccines, and petitioners relied

[179] Such antibodies are known as anti-MBP antibodies. See Snyder Tr. at 572, 574A, 576A, 579A (Dr. Zweiman).

on evidence of mercury exposure under isolated laboratory conditions that do not reflect the balance of immunological workings that occur within the body. Moreover, petitioners have asserted that mercury exposure leads to an immunological skewing that would permit the measles virus to persist. But the immunological skewing that petitioners have discussed does not cause the type of immune system dysregulation that petitioners posit. Rather, it produces allergy-like symptoms in the affected individual. Additionally, petitioners' claim that mercury exposure could influence the development of an autoimmune process that leads to the development of autism is scientifically unsupported. Petitioners' contentions regarding the immunosuppressive effects of mercury exposure through thimerosal-containing vaccines lack reliable, scientific support.

7. Legal Evaluation of Petitioners' Claim regarding the Role of Thimerosal-Containing Vaccines in the Development of Autism Spectrum Disorders

The undersigned now evaluates the aspect of petitioners' claim that receipt of thimerosal-containing vaccines contributes to the development of autism spectrum disorder. The undersigned evaluates this aspect of petitioners' claim in accordance with 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.

a. The Proposed Medical Theory

With respect to the aspects of petitioners' arguments in the litigation of the OAP's first theory of general causation that pertains to the impact of thimerosal exposure on the development of autism, petitioners assert that mercury exposure is an environmental exposure that could have immunosuppressive effects and could cause neurological impairments. The filed scientific literature informs, and the parties' experts agreed, that 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. See Section III.B.2, above. Nonetheless, in support of petitioners' assertions regarding the effects of mercury exposure in this first theory of general causation, petitioners relied heavily on evidence of the effects of exposure to forms of mercury other than ethylmercury (the organic form of mercury contained in thimerosal-containing vaccines), the effects of exposure to doses of mercury that greatly exceed the amount of mercury contained in the prescribed childhood immunization series, and the effects of exposure to mercury under conditions that varied considerably from vaccines intravenously injected three or four different times over a period of six months. Therefore, petitioners' arguments are not persuasive.

Petitioners advanced the theory that certain children are genetically hypersusceptible to mercury and are predisposed to have difficulty excreting mercury based primarily on petitioners' interpretation of mercury-related injuries for which there is evidence of a dose-related response to mercury exposure. Without more than petitioners' interpretation of evidence as support for petitioners' theory, the theory regarding the

existence of a genetic hypersusceptibility to mercury and a mercury efflux disorder is unpersuasive. See Section III.B.5, above.

Moreover, petitioners' theory that the mercury retained in the body from thimerosal-containing vaccines causes dysregulation of the children's immune systems is unsupported by the evidence. The Goth and the Agrawal studies on which petitioners so heavily relied involve exposure to thimerosal in an isolated laboratory environment (in vitro studies) that has not been replicated in the human body. The effects of thimerosal on particular cells observed in an isolated laboratory environment are not comparable to the effects of ethylmercury in the complex environment of the human body. Contrary to what petitioners have urged, evidence that mercury exposure causes dysregulation of the human immune system is lacking. See Section III.B.6.e, above.

Petitioners' arguments concerning the biological effects of thimerosal exposure from administered vaccines (which is no longer thimerosal once injected into the body, but becomes ethylmercury) must be considered in connection with the period of time that ethylmercury remains in the body. The half-life of ethylmercury in blood is less than two weeks. It is much shorter than the half-life of methylmercury, and because ethylmercury has a shorter half-life, less ethylmercury is available in the blood to reach the brain and to penetrate the blood-brain barrier (not in the organic form of mercury of ethylmercury, but rather as the inorganic form of mercury). As is amply demonstrated in the literature, it is the methylmercury form of mercury–not the ethylmercury form–that can cause, at higher doses than are implicated by vaccinations, the reported injuries.

Notably, none of the injuries described by the parties' experts and in the filed literature that resulted from the various mercury exposures resembled the deficits in communication, social interaction, and range of interests that characterize an autism spectrum disorder. Rather, the constellation of symptoms associated with the variously described mercury toxicities were impaired coordination, gait, vision, hearing, strength, and speech. Additionally, the particular symptoms associated with pink disease (the condition resulting from the use of mercury-containing teething powders) were red, swollen and peeling hands and feet, and feverish sweating. Although some of the symptoms of mercury toxicity may bear similarity to symptoms that appear in children with autism, such as the symptom of impaired speech, the two conditions are otherwise distinguishable.

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. First, scientifically reliable evidence is lacking that there is a genetically hypersusceptible population to mercury exposures. Second, scientifically reliable evidence is lacking that a mercury efflux disorder exists. Third, petitioners have failed to present scientifically reliable evidence that the thimerosal content of the vaccines leads to immune dysregulation in the vaccinee that is clinically significant or would allow vaccine-strain measles virus to persist. 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 in the manner that petitioners have proposed under the first theory of general causation in the OAP litigation. 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

Because petitioners have failed to present scientifically reliable evidence on the different aspects of their first general causation theory concerning the role of thimerosal-containing vaccines in the development of autism, their proposed sequence of cause and effect 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. 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 10 days in the blood. Based on the prescribed schedule under which children formerly received thimerosal-containing vaccines (which was approximately every eight weeks for the first six months of life), it is more likely than not that the amount of ethylmercury remaining in a child's body at the time of receipt of the MMR vaccine (approximately six months after the last administration of thimerosal-containing vaccines) would be considerably diminished. Moreover, because of the short half-life of ethylmercury in the blood, less ethylmercury is available to reach the brain to penetrate the blood-brain barrier and produce the neurological effects that petitioners have asserted. See Section III.B.3, above.

The filed scientific literature addresses the observed adverse effects that are associated with mercury exposures that have occurred under conditions that effectively involve exposure doses that are much higher than the level of mercury exposure from childhood vaccines. Because the exposure doses of mercury associated with observed adverse effects are higher than the level of exposure attributable to thimerosal-containing vaccines and because the half-life of ethylmercury in blood is less than two weeks, the undersigned finds that the temporal association is too attenuated between the administration of the thimerosal-containing vaccines, the administration of the MMR vaccine, and the onset of the immunosuppressive effects that petitioners contend the administered vaccines produce. The undersigned finds that petitioners have failed to meet their burden under the third prong of the Althen standard.

Petitioners have failed to prove by a preponderance of the evidence the first aspect of their general causation theory, specifically that the mercury component of the thimerosal-containing vaccinations causes immune dysfunction that leads to the development of autism. The undersigned turns now to address the second aspect of petitioners' general causation theory pertaining to the MMR vaccine.

C. Examining Petitioners' Claim that the MMR Vaccine Causes Immune Dysfunction that Allows an Attenuated Strain of the Measles Virus to Persist and Leads to Chronic Inflammation that Results in a Neurological Injury that Manifests as Autism

As the second aspect of their general causation theory, petitioners assert that the measles component of the MMR vaccine also leads to the development of autism. Specifically, petitioners assert that the measles component of the MMR vaccine causes an immune dysfunction that impairs the vaccinee's ability to clear the measles virus. Unable to clear properly clear the measles virus from the body, the vaccinee experiences measles virus persistence which leads to chronic inflammation in the gastrointestinal system and, in turn, chronic inflammation in the brain. Petitioners argue that the inflammation in the brain causes neurological damage that manifests as autism. It is also the position of petitioners that the viral persistence is facilitated by the vaccinee's receipt of thimerosal-containing vaccines that suppress the immune system of the vaccinee and impair the immune system's ability to respond properly to the viral presence.[180]

1. Earlier Litigation in the United Kingdom Examining the Causal Relationship, if any, between the MMR Vaccine, Gastrointestinal Symptoms, and Autism

Before examining the aspect of petitioners' causation theory involving the MMR vaccine, the undersigned addresses, by way of background, the earlier litigation in the United Kingdom examining the causal relationship, if any, between the MMR vaccine and autism. Because several of petitioners' witnesses and several of respondent's witnesses were expert witnesses in that litigation and have relied on aspects of their prepared opinions in that litigation to inform their opinions in the OAP litigation, a brief discussion of the litigation in the United Kingdom is merited here.

a. Dr. Wakefield's Work

The litigation in the United Kingdom was precipitated by the work of Dr. Andrew Wakefield and his colleagues. 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 Cedillo Ex. BB at 10 (Dr. Ward's report). As first proposed in the mid-1990s, Dr. Wakefield's hypothesis implicated the vaccine-strain measles virus in the development of inflammatory bowel disease. Id. (citing, among others, Cedillo Ex. BB98

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[180] The aspect of the theory concerning the effect of the thimerosal-containing vaccines on a vaccinee was not advanced by petitioners' expert neurologist Dr. Kinsbourne, who testified during both the Cedillo and Snyder hearings, but rather by petitioners' expert neurologist Dr. Corbier, who testified during the Hazlehurst hearing. Compare Cedillo Tr. at 1125A, 1172 (Dr. Kinsbourne) with Hazlehurst Tr. at 284A-286A (Dr. Corbier).

(1993 Wakefield article[181]), Cedillo Ex. BB89 (1993 Smith article[182]), Cedillo Ex. BB33 (1994 Ekbom article[183]), Cedillo Ex. BB72 (1995 Miyamoto article[184]), Cedillo Ex. BB78 (2000 Pardi article[185])). The techniques used by Dr. Wakefield and his colleagues to implicate the measles vaccine in the development of inflammatory bowel disease were criticized. See Cedillo Ex. BB at 10 (Dr. Ward's report); see also Hazlehurst Tr. at 630A-631A (Dr. MacDonald, respondent's expert in gastrointestinal immunology, testifying that when Dr. Wakefield published the 1993 Wakefield article attributing observed infarctions in the gastrointestinal walls of Crohn's disease patients to measles virus, the paper received widespread media attention and provoked a close look from scientists in the field who found that Dr. Wakefield's study lacked appropriate scientific rigor).

The public "furor" created by the 1993 Wakefield article prompted a review of Dr. Wakefield's work by the Medical Research Council (MRC) of the United Kingdom.[186] Hazlehurst Tr. at 631A (Dr. MacDonald). The MRC determined that Dr. Wakefield had performed his experiments (or tests) with reagents that were not specific for measles virus and without the important controls for the experiments that the manufacturer of the equipment recommended for use when conducting the experiments. Id. The provost of the Royal Free Hospital where Dr. Wakefield had been employed asked Dr. Wakefield to repeat the studies and although Dr. Wakefield agreed to repeat the studies, he never did. Id.

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. Cedillo Ex. BB at 10-11 (citing, among others, Cedillo Ex. BB99 (1997 Ward

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[181] A. J. Wakefield et al., Evidence of persistent measles infection in Crohn's disease, J. Med. Virol. 39(4): 345-353 (Apr. 1993).

[182] M. S. Smith and A. J. Wakefield, Viral Association with Crohn's disease, Ann. Med. 25(6): 557-561 (Dec. 1993).

[183] A. Ekbom et al., Perinatal measles infection and subsequent Crohn's disease, Lancet 344(8921): 508-510 (Aug. 20, 1994).

[184] H. Miyamoto et al., Detection of immunoreactive antigen, with a monoclonal antibody to measles virus, in tissue from a patient with Crohn's disease, J. Gastroenterol. 30(1): 28-33 (Feb. 1995).

[185] D. S. Pardi et al., Early measles virus infection is associated with the development of inflammatory bowel disease, Am. J. Gastroenterol. 95(6): 1480-1485 (Jun. 2000).

[186] The Medical Research Council (MRC), a body correlative in function to the IOM, "is a publicly-funded organisation dedicated to improving human health" through research efforts "across the entire spectrum of medical sciences." See www.mrc.ac.uk/About/index.htm (last visited on 2/1/09).

article[187]), Cedillo Ex. BB43 (1995 Hermon-Taylor article[188]), Cedillo Ex. BB41 (1996 Haga article[189]), Cedillo Ex. BB50 (1997 Jones article[190]), Cedillo Ex. BB76 (1998 Nielsen article[191]), Cedillo Ex. BB2 (1999 Afzal article[192]), Cedillo Ex. BB21 (2001 Davis article[193]), and Cedillo Ex. BB47 (2001 Iizuka article[194])). These efforts to replicate Dr. Wakefield's findings were unsuccessful. See Hazlehurst Tr. at 632A-633A (Dr. MacDonald). "Particularly damaging to the hypothesized [MMR and inflammatory bowel disease] link was the discovery that a critical monoclonal antibody cross-reacted with a normal human protein" and not the MMR vaccine. Cedillo Ex. BB at 11 (Dr. Ward's report) (citing the 2000 Iizuka article[195]). In the view of the scientific community, either Dr. Wakefield was "too enthusiastic over his interpretation of the flawed data or . . . there was some degree of scientific fraud" behind Dr. Wakefield's efforts. See Hazlehurst Tr. at 633A (Dr. MacDonald).

In 1998, Dr. Wakefield and his colleagues advanced the hypothesis that the MMR vaccine led to the development of ASDs with gastrointestinal manifestations based on a small case series purporting to link the MMR vaccine to autistic disorders with

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[187] B. Ward and P. DeWals, Association between measles infection and the occurrence of chronic inflammatory bowel disease, Can. Commun. Dis. Rep. 23(1): 1-6 (Jan. 1, 1997).

[188] J. Hermon-Taylor et al., Measles virus and Crohn's disease, Lancet 345(8954): 922-923 (Apr. 8, 1995).

[189] Y. Haga et al., Absence of measles viral genome sequence in intestinal tissues from Crohn's disease by nested polymerase chain reaction, Gut 38(2): 211-215 (Feb. 1996).

[190] P. Jones et al., Crohn's disease and measles, Lancet 349(9050): 473 (Feb. 15, 1997).

[191] L. L. Nielsen et al., Exposure to measles in utero and Crohn's disease: Danish register study, BMJ 316(7126): 196-197 (Jan. 17, 1998).

[192] M.A. Afzal et al., Measles virus and Crohn's disease, Gut 44(6): 896-897 (Jun. 1999).

[193] R. L. Davis and K. Bohlke, Measles vaccination and inflammatory bowel disease: controversy laid to rest? Drug Sat. 24(13): 939-946 (2001).

[194] M. Iizuka et al., No evidence of persistent mumps virus infection in inflammatory bowel disease, Gut 48(5): 637-641 (May 2001).

[195] M. Iizuka et al., Immunohistochemical analysis of the distribution of measles related antigen in the intestinal mucosa in inflammatory bowel disease, Gut 46(2): 163-169 (Feb. 2000).

gastrointestinal manifestations. Cedillo Ex. BB at 11 (Dr. Ward's report) (citing Cedillo Ex. BB97 (1998 Wakefield article[196])). The 1998 Wakefield article described findings of lymphoid hyperplasia and mild non-specific colitis (inflammation of the colon) in the small intestines of 12 autistic children who "were colonoscopied" for complaints of abdominal pain, food intolerance, and constipation. Hazlehurst Tr. at 633A-634A, 637A-638 (Dr. MacDonald); see also Cedillo Ex. BB97 at 637-639 (1998 Wakefield article). The mild colitis was reported to have occurred shortly after the children received the MMR vaccine. Hazlehurst Tr. at 636A; see also Cedillo Ex. BB97 at 638 (1998 Wakefield article). No control subjects were involved in the study. Hazlehurst Tr. at 637A; see also Cedillo Ex. BB97 at 637 (1998 Wakefield article). The articulated theory in the 1998 Wakefield article regarding how the MMR vaccine causes autism was as follows: (1) due to the vaccine combination, the measles component of an administered MMR vaccine interferes with the immune response of the vaccinee to the measles virus; (2) the measles virus persists in the vaccinee; (3) the persisting measles virus infects the gut; (4) the persistent measles infection in the gut causes inflammation that is evidenced by the lymphoid hyperplasia; (4) the inflamed gut becomes "leaky" and permits digestion products (specifically, opioid peptides) to seep through the "walls" or lining of the gut; and (5) the peptides enter the blood stream, travel to the developing brain, and cause autism. See Hazlehurst Tr. at 641A (Dr. MacDonald); see also Hazlehurst R's Trial Ex. 2 at 4 (Dr. MacDonald's slides) (a schematic showing the mechanism of the vaccine-related harm that formed the basis of the litigation in the United Kingdom); see Cedillo Ex. BB97 at 639-641 (1998 Wakefield article). Dr. MacDonald testified that the Dr. Wakefield's hypothesis required "a number of . . . highly improbable events to occur" and "was not based on any data." Hazlehurst Tr. at 642A-643A. Dr. MacDonald observed that a finding of persistent measles virus in the gut of autistic children was critical to the hypothesis. See id. at 642A.

Dr. Wakefield published another article in 2000. See Hazlehurst Ex. 37D (2000 Wakefield article[197]). The study discussed in the 2000 Wakefield article involved 60 autistic subjects, including the 12 autistic children that were referenced in the 1998 Wakefield article. See Hazlehurst Ex. 37D at 2286 (2000 Wakefield article); Hazlehurst Tr. at 643A (Dr. MacDonald). The study also included 37 controls. See Hazlehurst Ex. 37D at 2286 (2000 Wakefield article); Hazlehurst Tr. at 643A (Dr. MacDonald). Each of the children had an ileocolonoscopy and a mucosal biopsy. Hazlehurst Ex. 37D at 2286 (2000 Wakefield article). The study reported finding enterocolitis (inflammation in both the end of the small intestine (the ileum) and the colon) in the children with the developmental disorders. See Hazlehurst Ex. 37D at 2290 (2000 Wakefield article); Hazlehurst Tr. at 644 (Dr. MacDonald). Dr. MacDonald explained that a closer examination of the 2000 Wakefield article reveals that there was no difference between the

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[196] A. J. Wakefield et al., Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children, Lancet 351(9103): 637-641 (Feb. 28, 1998).

[197] A. J. Wakefield et al., Enterocolitis in children with developmental disorders, Am. J. Gastroenterology 95(9): 2285-2295 (2000).

autistic children and the control children in "what pathologists considered to be inflammation." See Hazlehurst Ex. 37D at 2290 (2000 Wakefield article); Hazlehurst Tr. at 644-645A (Dr. MacDonald). Dr. MacDonald further explained:

> [I]t was very important for . . . [the Wakefield] theory . . . that there [was] a small bowel inflammation so that the peptides [could] cross because the small intestine is the organ of digestion, not the colon, so these children had to have inflammation of the ileum.
> . . .
> What Wakefield did is he called ILH [ileal lymphoid hyperplasia] pathology so that he could say that they had small bowel pathology so that he could substantiate[] his argument.

Hazlehurst Tr. at 644-645A.

Dr. MacDonald asserted that Dr. Wakefield "invented new pathological abnormalities which were not recognized by anyone in the world." Hazlehurst Tr. at 645A. Having "seen hundreds and thousands of colonsocopies," Dr. MacDonald testified that "[l]ymphoid nodular hyperplasia is actually an enlargement of the lymph nodes in the small intestine and the colon." Id. at 616A. It is well-documented "as part of the normal situation," that there are more lymph nodes and larger lymph nodes in the intestines of children than in the intestines of adults. Id. An endoscopist may determine that the observed nodules during an examination "are larger or more prominent than would normally be seen," but such a determination is "a very subjective assessment." Id. at 617A.

Dr. MacDonald stated that a finding of lymphoid nodular hyperplasia is not diagnostic of a disease. See id. (presence of lymphoid nodular hyperplasia offers "[n]o" pathological diagnosis). Nor is a finding of lymphoid nodular hyperplasia an indication that one has inflammatory bowel disease. Id. at 618. Dr. MacDonald testified that lymphoglandular complexes, which include lymphoid nodular hyperplasia, that appear in autistic subjects are "identical to" the lymphoglandular complexes that appear in "healthy individuals" and are considered a normal component of the gastrointestinal tract. Id. at 617A-618 (citing Hazlehurst Ex. H at 978-979 (the Levine article[198])).

Dr. MacDonald continued his testimony stating that "the deception" in the 2000 Wakefield article "goes further" than the discussed misrepresentation of normal lymphoid follicles as pathological abnormalities. Hazlehurst Tr. at 645A-646A. He pointed to images included in the 2000 Wakefield article purporting to compare images taken during a colonoscopy of a normal ileum and of the ileum of an autistic child that contains lymphoid hyperplasia. Id. at 646A-648A; Hazlehurst R's Trial Ex. 2 at 5-6 (Dr. MacDonald's trial slides). Dr. MacDonald testified that the four different images purporting to show the ileal comparison were, in fact, images taken within a 20 minute

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[198] D. Levine and R. Haggitt, Normal histology of the colon, Am. J. Surg. Pathology 13(11): 966-984 (Nov. 1989).

period (according to the time and date stamps on the images) but the images were not in chronological order. Hazlehurst Tr. at 647A-648A; Hazlehurst R's Trial Ex. 2 at 5-6 (Dr. MacDonald's trial slides). Dr. MacDonald testified that although a "really fast" colonoscopy could take 20 minutes, it was more likely that the images were from the same patient and did not reflect an ileal comparison. Hazlehurst Tr. at 646A-648A. Dr. MacDonald opined that it was "highly unlikely" that the disordered series of images was a "mistake." Id. at 648A.

Dr. Wakefield's hypothesis continued to receive scientific scrutiny. The hypothesis prompted review by the Institute of Medicine and other research groups, and all concluded that the hypothesis had little scientific merit.[199] See Cedillo Ex. BB at 11 (Dr. Ward's report) (citing Cedillo Ex. HH (2001 IOM report[200]), Cedillo Ex. JJ (2004 IOM report), Cedillo Ex. P37 (2005 Demicheli article), and Cedillo Ex. BB70 (2001 MRC report[201])).

Respondent's expert Dr. MacDonald observed that "[s]cience is about being conservative and safe and careful and making sure that before you go out into the world that you've . . . covered all your bases." Hazlehurst Tr. at 649A. Succinctly summarizing the many criticisms of Dr. Wakefield's hypothesis and the study methods he employed, Dr. MacDonald stated that science "was not done in this case." Id.

The weight of the evidence compels a finding by the undersigned that the Wakefield series of studies are scientifically unreliable.

b. The Litigation in the United Kingdom

Stirred by the hypothesis proposed by Dr. Wakefield, British claimants who alleged

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[199] 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 2/1/09); see also Cedillo Ex. JJ at iv (Institute of Medicine, Immunization Safety Review: Vaccines and Autism (National Academies Press 2004)). 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 Cedillo Ex. JJ at ix (Institute of Medicine, Immunization Safety Review: Vaccines and Autism (National Academy Press 2004)).

[200] Institute of Medicine, Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism (National Academy Press 2001).

[201] See Cedillo Ex. BB70 at 28-32 (2001 MRC report discussing the dearth of evidence linking autism to either MMR vaccines or thimerosal-containing vaccines); see also www.mrc.ac.uk/pdf-autism-report.pdf.

that their children developed autism as a result of administered MMR vaccines brought suit against Merck & Co., Inc., Aventis Pasteur MSD Ltd., and SmithKline Beecham Plc, three of the pharmaceutical companies that manufacture the MMR vaccine commonly administered to children. See Sayers v. SmithKline Beecham, 2004 WL 1640222, at ¶ 4 (Queens Bench 2004); see also Cedillo Tr. at 2053A (Dr. Bustin). As Dr. Kinsbourne explained during the Cedillo hearing, "[t]he British [g]overnment pays for [the] people to sue the British [g]overnment . . . [a]nd to sue its own public health service and to sue the [drug] manufacturer[s]." Cedillo Tr. at 1116A-1117 (Dr. Kinsbourne); see also Sayers v. SmithKline Beecham, 2004 WL 1640222, at ¶ 4. To pursue litigation on issues of major importance that might not proceed due to lack of funds, plaintiffs may receive grants of funding from the Legal Services Commission. Cedillo Tr. at 1117 (Dr. Kinsbourne); see also Sayers v. SmithKline Beecham, 2004 WL 1640222, at ¶ 11. It was Dr. Kinsbourne's understanding that the Legal Services Commission will grant funds if there is a belief that the action has a probability of success that exceeds fifty percent. Cedillo Tr. at 1117; see also Sayers v. SmithKline Beecham, 2004 WL 1640222, at ¶¶ 1, 8, 11 (referencing the process under the British legal system for providing claimants with public funding to gather evidence in support of their claims). Claimants who brought action in the United Kingdom received legal aid certificates entitling them to public funding to pursue the autism litigation against three vaccine manufacturers. See Sayers v. SmithKline Beecham, 2004 WL 1640222, at ¶ 7.

The experts retained by the claimants in the United Kingdom litigation produced a series of intermediate reports addressing the possible mechanisms of inducing an autism spectrum disorder and then produced final written expert reports. See Cedillo Tr. at 1117 (Dr. Kinsbourne); see Sayers v. SmithKline Beecham, 2004 WL 1640222, at ¶ 23. Additionally, the experts retained by the drug manufacturers in the United Kingdom litigation produced written expert reports. See Sayers v. SmithKline Beecham, 2004 WL 1640222, at ¶ 23. After reviewing the filed reports, the Legal Services Commission determined that the claims for autism spectrum disorders were unlikely to succeed. See Cedillo Tr. at 1118 (Dr. Kinsbourne); see also Sayers v. SmithKline Beecham, 2004 WL 1640222, at ¶ 9 (noting that some claimants alleged injuries other than autism and inflammatory bowel disease–including but not limited to deafness, arthritis, and epilepsy–and noting that public funding for all claims was withdrawn). The Legal Services Commission suspended funding for the litigation in September 2003. See Cedillo Tr. at 1118A; see also Sayers v. SmithKline Beecham, 2004 WL 1640222, at ¶ 7 (discussing the withdrawal of funding by the Legal Services Commission). A number of claimants withdrew their claims, and the claimants' action against the pharmaceutical companies was discontinued. See Cedillo Tr. at 1108, 1119A.

After the discontinuation of the claimants' action, 10 of Dr. Wakefield's 12 co-authors on the 1998 Wakefield article retracted the earlier offered interpretation of the conducted study–retracting, in particular, the conclusion that a potential causal link existed

between the MMR vaccine and autism. See Cedillo Ex. P114 at 750 (2004 Lancet commentary[202]). At the time that Dr. Wakefield authored the 1998 Wakefield article, he did not disclose in the article that he had been contacted by lawyers for the Legal Services Commission to participate in the United Kingdom autism litigation against three MMR vaccine manufacturers.[203] See Cedillo Tr. at 1198A-1200 (Dr. Kinsbourne). Dr. Wakefield was one of the three top recipients of payment in the claimants' action in the United Kingdom.[204] See Cedillo R's Trial Ex. 6. After the discontinuation of the claimants' action in the United Kingdom, disciplinary proceedings were instituted against Dr. Wakefield in the United Kingdom by the General Medical Council.[205] The proceedings are still ongoing. See S. Boseley, Autism study: MMR: GMC resumes case against Wakefield, The Guardian (London) (Jan. 12, 2009) at 7 (stating that "[t]he case has been running since July 2007 and the end is not yet in sight"). At the time of the hearings in the OAP litigation, Dr. Wakefield was affiliated with the Thoughtful House Center for Children in Austin, Texas, a resource center for autistic children. See Cedillo R's Trial Ex. 1 at 1-2 (two pages from the Thoughtful House Center for Children's website available at http://www.thoughtfulhouse.org/thcfc_treatment.htm) (last visited on 1/24/09).

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[202] S. H. Murch et al., Retraction of interpretation, Lancet, 363: 750 (Mar. 6, 2004).

[203] Also at the time that Dr. Wakefield published the 1998 Wakefield article, he may have had on file a patent for a monovalent measles vaccine (a measles vaccine without the mumps and rubella components), that would have positioned him to benefit financially from a dispute involving the use of the MMR vaccine. See Cedillo R's Trial Ex. 7. The evidence proffered as Cedillo R's Trial Ex. 7 was a copy of a patent application filed by the Royal Free Hospital School of Medicine, Dr. Wakefield's former employer. Attached to the patent application is documentation pertaining to a clinical trial conducted by Dr. Wakefield studying "the effect "oral measles virus-specific dialysable lymphocyte extract transfer factor." Id. at 2. Also attached to the patent application are findings pertaining to the 12 children featured in Dr. Wakefield's research. It is not apparent from the face of the patent application, however, what the application covered. Accordingly, the undersigned declines to accord the document any weight in this decision.

[204] The other two top recipients of payment in the United Kingdom litigation were the Unigenetics laboratory and Dr. Kinsbourne, petitioners' expert neurologist in the instant OAP litigation. See Cedillo R's Trial Ex. 6.

[205] The General Medical Council (GMC) registers doctors to practice medicine in the United Kingdom. See http://www.gmc-uk.org (last visited on 2/1/09). The purpose of the GMC is "to protect, promote and maintain the health and safety of the public by ensuring proper standards in the practice of medicine." Id. at http://www.gmc-uk.org/about/role/index.asp. The four main functions of the GMC, as set forth in the Medical Act of 1983, are: (1) to keep current registers of qualified doctors; (2) to foster good medical practice; (3) to promote high standards of medical education; and (4) to deal "firmly and fairly with doctors whose fitness to practise is in doubt." Id.

c. Opinions of Experts Informed by the Proceedings in the United Kingdom

Four participants in the United Kingdom litigation who served as expert witnesses for the claimants also appeared as expert witnesses for petitioners in this litigation. See Cedillo R's Trial Ex. 6. The witnesses Dr. Byers, Dr. Kennedy, Dr. Kinsbourne, and Dr. Krigsman offered testimony in both proceedings that would support a finding of a causal link between the vaccines of interest and the development of autism.

After submitting an expert opinion in the United Kingdom litigation, Dr. Kennedy wrote an article in 2004, filed in this litigation as Cedillo R's Trial Ex. 3, addressing the limitations of the hypothesized relationship between the MMR vaccine and autism. See Tr. at 804-805. He stated in that paper that "the biological model linking MMR and autism spectrum disorder remains incomplete." Cedillo Tr. at 806-807A (quoting Cedillo R's Trial Ex. 3 at 133). In that same paper, he also stated that "there is little evidence to support persistent infection by vaccine strain of measles virus except for individuals with a compromised immune system who are immune dysfunctional." Cedillo Tr. at 806 (quoting Cedillo R's Trial Ex. 3 at 132).

Three participants in the United Kingdom litigation who served as expert witnesses for the pharmaceutical companies also appeared as expert witnesses for respondent in this litigation. The witnesses Dr. Bustin, Dr. MacDonald, and Dr. Rima offered expert opinions in both proceedings challenging the reliability of the reported findings of persistent measles virus in the tissues of autistic children based on the irregularities in both the testing practices and reporting practices of the Unigenetics lab.

Additionally, Dr. Chadwick offered testimony in this proceeding challenging the reliability of the reported findings of persistent measles virus in the tissues of autistic children. Dr. Chadwick was a graduate student in Dr. Wakefield's laboratory when the testing was conducted that underlay Dr. Wakefield's published articles reporting findings of persistent measles virus. He testified about matters known to him based on his personal experience working in the Dr. Wakefield's laboratory.

Dr. Rima also described his personal experience with Dr. Wakefield before the commencement of the litigation in the United Kingdom. He explained that prior to agreeing to serve as an expert witness for the pharmaceutical companies in the United Kingdom litigation, he had attended, at Dr. Wakefield's invitation in 1992, a couple of pre-litigation scientific meetings with other measles virologists "to look at the material that [Dr. Wakefield] had produced." Snyder Tr. at 843A. From these meetings, Dr. Rima concluded "that whatever material was put in front of [him] was highly selective[, and] [w]hen criticisms were made, they were not followed up." Id. Dr. Rima's criticisms were twofold. First, during a meeting that Dr. Rima attended, investigators from Dr. Wakefield's lab presented data purporting to be measles virus in cells; but the detected material was not measles virus because the "size wasn't right." See id. at 843-844A. Second, on a separate occasion, investigators from Dr. Wakefield's lab presented data to Dr. Rima from a sequence analysis of measles virus that indicated contamination. See id.

at 844A. Dr. Rima "formally withdrew [his] collaboration with Andy Wakefield" when Dr. Wakefield's colleagues refused to "retract[]" the problematic data. Id.

Similarly, Dr. Griffin, who also appeared as an expert for respondent in this litigation, was invited to participate in pre-litigation scientific discussions in 1998 with Dr. Wakefield and others who were trying to implicate the MMR vaccine as a cause of autism. See Cedillo Tr. at 2832A-2833, 2862. During that meeting, she learned of the difficulty that Dr. Wakefield's laboratory was having in "trying to make the[] PCR work," gained insight into the investigators' thinking, and ultimately declined an extended invitation to serve as a consultant for Dr. Wakefield's efforts that culminated in the MMR/autism litigation in the United Kingdom. See id. at 2832A-2833, 2862.

The testimony of the witnesses in this litigation who either participated in the meetings that preceded the United Kingdom litigation or participated in the United Kingdom litigation is relevant and important because both the claimants in the United Kingdom litigation and the petitioners in the OAP litigation have relied heavily on the reported findings by Dr. Wakefield and subsequently by his colleagues at the Unigenetics laboratory (Drs. O'Leary and Shiels) to support the claim that the MMR vaccine contributed to the development of autism and inflammatory bowel disease in certain children. The experts who participated in the United Kingdom litigation testified in this litigation about matters known to them based on their participation in the United Kingdom litigation, and where required, in conformance with the releases obtained from the court in the United Kingdom that limited the scope of their testimony.

d. Petitioners' Motion to Strike[206]

Prior to the conduct of the hearings in this litigation, petitioners moved to strike the testimony of Dr. Bustin pertaining to information that he acquired during the course of the United Kingdom litigation.[207] Petitioners alleged in the motion to strike that consideration of Dr. Bustin's reports in the absence of the other expert reports prepared for the United Kingdom litigation would be prejudicial. By Order dated June 11, 2007, filed into the OAP master file, the undersigned and the special masters hearing the other two test cases advised that we would "favorably consider joining in a request for release of relevant reports" if the OAP's Petitioners' Steering Committee[208] filed a formal application in the United Kingdom court for the release of additional expert reports from the proceeding

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[206] In a separate Order issued on the same date as the issuance of this decision, the undersigned addresses the motion to strike in greater detail. A summary discussion is included here for ease of reference.

[207] Petitioners in the Cedillo case, one of the three test cases, filed the initial motion to strike. After the Cedillo hearing, the Hazlehursts filed a substantially similar motion to strike on September 4, 2007.

[208] The Petitioners' Steering Committee (PSC) is a designated group of petitioners' counsel representing the interests of petitioners in the OAP.

conducted there. Id. Without deciding the pending motion to strike, the undersigned and the special masters assigned to the other two test cases heard the testimony of the parties' witnesses, including the testimony of Dr. Bustin.

Although petitioners in the OAP were afforded a generous period of time within which to seek the release from the court in the United Kingdom of additional expert reports filed in connection with the MMR/autism litigation, petitioners declined to do so. In June 2008, nearly one year after the conduct of the Cedillo hearing, the first test case heard on petitioners' first theory of general causation, petitioners advised the special masters hearing the OAP test cases of their decision not to file an application with the court in the United Kingdom to obtain the release of additional expert reports. See Autism Update July 8, 2008, at 2.

In deciding the Hazlehursts' pending motion to strike, the undersigned is guided by Vaccine Rule 8©. Vaccine Rule 8© requires a special master to "consider all relevant and reliable evidence, governed by principles of fundamental fairness to both parties," when deciding vaccine claims. Rules of the Court of Federal Claims (RCFC), App. B, Vaccine Rule 8©. Consistent with Vaccine Rule 8© and for the reasons more fully addressed in the undersigned's ruling issued on February 12, 2009, petitioners' Motion to Strike Certain Testimony of Dr. Bustin is denied.

The undersigned will give due consideration to Dr. Bustin's testimony regarding the reliability of the test results obtained by the Unigenetics laboratory. The undersigned found Dr. Bustin to be a credible, knowledgeable, and persuasive witness, and his testimony about the proper conduct of PCR techniques was well-informed and helpful. Although the undersigned credits Dr. Bustin's testimony, the undersigned does not rely solely on his testimony in evaluating the reliability of the test results obtained by Unigenetics. The undersigned also considers the testimony of other witnesses and the filed scientific literature addressing Unigenetics' testing techniques.

The undersigned now turns to consider petitioners' theory regarding the causal connection between the MMR vaccine and autism, examining first the measles component of the MMR vaccine.[209]

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[209] The Petitioners' Steering Committee has 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 PSC Notice Re "MMR Only" Test Cases, dated August 7, 2008, located at http://www.uscfc.gov/node/2718 (follow "8/7/08 PSC Notice Re Theory 3" hyperlink) and Autism Update, dated September 29, 2008, located at http://www.uscfc.uscourts.gov/omnibus-autism-proceedings (follow "Autism Update-September 29, 2008" hyperlink) (last visited on 2/1/09).

2. Examining the Measles Component of the MMR Vaccine

MMR is a trivalent vaccine. The measles component of the vaccine is an attenuated form of the measles virus. The measles virus becomes attenuated by passing it through animal cells, in particular, chicken cells. See Cedillo Tr. at 1819A (Dr. Ward); Snyder Tr. at 831-832A (Dr. Rima); see also Cedillo Ex. V at 3 (Dr. Griffin's report).

In the United States, the MMR vaccine is administered usually between 12 and 15 months of age. See Morb. Mortal. Wkly. Rep. (MMWR) 55(22): 629-630 (2006). Petitioners argue that the vaccine strain of the virus is capable of behaving in the same manner as the wild or natural strain of the virus.[210] For this reason, an examination of the measles virus is helpful.

a. The Wild-Type Measles Virus

The measles virus is part of the paramyxovirus family in general (paramyxoviridae). Cedillo Tr. at 715 (Dr. Kennedy). Within the paramyxovirus family, there are subfamilies that differ from measles virus. Id. The measles virus belongs to the morbillivirus genus, one of the subfamilies of the paramyxovirus families. Id.

Measles is the morbillivirus that affects humans. Cedillo Tr. at 2754A (Dr. Griffin). Within the morbillivirus genus are a number of viruses that are similar to the measles virus and infect other hosts. Id. at 715 (Dr. Kennedy); accord id. at 2754A (Dr. Griffin). Among the viruses belonging to the morbillivirus genus is the canine distemper virus, a virus that affects primarily dogs and closely related species such as foxes, minks, and wolves. Id. at 715-716 (Dr. Kennedy). Found in the cerebral spinal fluid and in the brain of an affected dog, the virus adversely affects the temperament of the dog. See id. at 716. Another sub-type of the morbillivirus is the phocine distemper virus, which affects seals. Id. at 716. The virus is neurotropic (has an affinity for the neurological system). Id. Additionally, the dolphin morbillivirus infects dolphins and porpoises. Id. A morbillivirus can be found in the cerebral spinal fluid of the infected host and can cause neurological manifestations. Id. at 716, 735A. Dr. Kennedy asserted that morbilliviruses have a particular affinity for the neurological system (especially the brain). Id. at 735A.

b. The Structure of the Wild-Type Measles Virus

The measles virus is small and requires electron microscopy to be visible. Cedillo Tr. at 712 (Dr. Kennedy). It is comprised of a nonsegmented, negative single strand of RNA. Id. at 713. It carries its own RNA transcriptase, which is the important enzyme for replication of the virus. Id. The virus also contains a number of structural proteins,

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[210] Consistent with the experts' variable references to the wild strain of measles or to a natural measles infection, the undersigned uses the terms "wild-type" and "natural" interchangeably to refer to the measles virus that has not been attenuated to become the vaccine strain.

specifically, the phosphoprotein (P), the nucleoprotein (N), and the matrix protein (M), that permit the measles virus to produce new measles virus. Id. The virus also contains an envelope comprised of the hemoglobin protein (H) and the fusion protein (F) on the outer surface. Id. at 713.

The measles virus is comprised of an ordered sequence of genes. See Cedillo Tr. at 729; Cedillo Ps' Trial Ex. 8 at 16 (Dr. Kennedy's trial slides). As illustrated on a slide presented by Dr. Kennedy during the Cedillo hearing, the particular sequence of genes is designated from left to right as N, P, M, F, H, L. Cedillo Tr. at 729A; Cedillo Ps' Trial Ex. 8 at 16; see also Cedillo Ex. 61 DD at 1269 (1996 measles chapter in Fields' Virology, a textbook authored in part by respondent's expert Dr. Griffin[211]). This genetic sequence must be produced in the same orderly fashion, specifically from the left to the right of the genome, for viral replication (or productive infection) to occur. Cedillo Tr. at 729A (Dr. Kennedy); Snyder Tr. at 308A (Dr. Kennedy). As clarified by the testimony of Dr. Ward, the entire sequence must be present for replication or persistence because the virus is not segmented. Cedillo Tr. at 1820A-1821A (Dr. Ward). The individual genes of the viral genome for measles, specifically the N, P, M, F, H, L genes, cannot persist independently. See id. at 1821A (Dr. Ward).

Through the use of quantitative polymerase chain reaction (PCR), a standard technique for detecting and identifying particular gene sequences in tissue samples, the ordered sequence of the genes in the measles virus becomes detectable. See id. at 729A, 739 (Dr. Kennedy). Petitioner's expert Dr. Kennedy asserted that the detection in a tissue sample of a gene from the ordered sequence of genes that comprises the measles virus indicates that the sequence of genes that precede the detected gene must have been present. Cedillo Tr. at 732. He further asserted that such detection also indicates that replication is occurring. Id.

Dr. Kennedy also described how the measles virus infects and replicates, explaining the particular role of the specific genes in the measles virus. See Cedillo Tr. at 722-724 (Dr. Kennedy); Cedillo Ps' Trial Ex. 8 at 12-14 (Dr. Kennedy's trial slides). The measles virus begins the process of infection by attaching to a host cell. Dr. Kennedy identified the host cell receptor for the measles virus as CD46. Cedillo Tr. at 722 (Dr. Kennedy). But respondent's expert Dr. Ward explained that the cellular receptor for the measles virus widely believed to be more important than CD46 "is the so-called SLAM molecule, which is expressed on immune cells." Id. at 1822; accord id. at 2755, 2775 (Dr. Griffin). The SLAM molecule is also known as CD150. Id. at 2775 (Dr. Griffin). CD46 is the receptor recognized mainly by the measles vaccine attenuated virus and not the wild-type measles virus. Id. at 2775 (Dr. Griffin). The distinction between the choice receptors for the wild-type measles virus and the measles vaccine attenuated virus underscores one of key differences between the wild-type virus and the attenuated version of the virus contained in the vaccine.

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[211] D. E. Griffin and W. J. Bellini. Measles virus, in Fields' Virology 1267 (B. N. Fields et al., eds. 1996).

Dr. Kennedy further described the infection process, explaining that the H gene on the envelope of the measles virus attaches to that host cell receptor. Cedillo Tr. at 722. Once the H gene is attached to the host cell, the process of replication begins. Replication occurs in the cytoplasm of the measles virus. Cedillo Tr. at 723; Cedillo Ps' Trial Ex. 8 at 12 (Dr. Kennedy's trial slides). The negative strand RNA provides a template for messenger RNA synthesis. Cedillo Tr. at 723; Cedillo Ps' Trial Ex. 8 at 13. Messenger RNA is the positive strand that is generated by the RNA transcriptase contained within the virus and that will be translated into viral protein. Cedillo Tr. at 723. The messenger RNA "contains defined genes in a specific order." Cedillo Tr. at 727. The generation of more positive strand RNA is necessary to produce the negative strand RNA "to produce new virus." Cedillo Tr. at 723.

Each of the structural proteins of the measles virus has a particular job. The M gene works in the assembly of the virus to and the release of the virus from the cell that the virus is infecting. Cedillo Tr. at 723. The H gene attaches to the host cell. Id. at 722. The F gene assists the entry of the virus into the cell. See id. at 724, 725A. The N protein is involved in the process of viral replication within the cell. Id. at 724. Effectively, the measles virus takes over the host cell and "uses its synthesis machinery" to assist the measles virus in producing its protein. Id. at 728; accord id. at 1823A-1825A (Dr. Ward) (explaining that the measles virus makes more copies of itself by "us[ing] part of the host cell membrane as its own envelope, . . . [and] insert[ing] its [negative strand] protein into the host cell membrane" to which positive sense RNA protein can attach itself and begin the copying process). After infecting a cell, the virus exits (or "buds off") that cell to infect another cell. See id. at 1825A (Dr. Ward). If the immune system of the infected individual is functioning properly, the infected cells are killed by T cells known as "killer T cells" because of their assigned task in the immune system. See L. Sompayrac, How the Immune System Works at 65-66, 117.

A peculiarity of the measles virus "is that it transcribes the front end of its genome to RNA much more successfully than it does the back end of the genome." Id. at 1823A (Dr. Ward). Accordingly, there will be "many, many more copies of the RNA, for example, of the N gene than [there are] for the F or the H gene." Id. (Dr. Ward).

c. An Acute Wild-Type Measles Infection

Petitioners' expert Dr. Kennedy testified that there are various stages associated with a natural measles infection that inform where one might find the infection in the body. The initial stage involves infection of the host. Cedillo Tr. at 841-842 (Dr. Kennedy). There is also the droplet stage during which the infection can be spread through coughing. Id. at 841-842. There is a viremia stage during which the infection is found in the blood. Id. at 841. Additionally, active measles virus can be isolated from the lesions that occur. Id. at 842. Acknowledging, however, that respondent's expert Dr. Griffin has generated over 100 publications addressing the measles virus, petitioners' expert Dr. Kennedy openly deferred to her expertise on the subject of the measles virus. See Cedillo Tr. at 851A.

Concurring with Dr. Kennedy's description of the spread of the measles virus, Dr. Griffin testified that the measles virus is contracted by breathing in viral droplets. Cedillo

Tr. at 2750. Upon entry of the virus through the respiratory airways, the virus infects the epithelial cells lining the respiratory tract. Id.; Cedillo R's Ex. V at 2 (Dr. Griffin's report). The virus is "very infectious." Cedillo Tr. at 2750

Once the virus infects the epithelial cells (cells in the lining) of the respiratory tract, it is carried to the local lymph nodes. Id. at 2751. Dr. Griffin noted that the virus is "very lymphotropic" and the primary site of replication is in the lymphoid tissue. Id. at 2751, 2755. From the local lymph nodes, the virus spreads to the blood. Id. Contained within lymphocytic and monocytic cells, the virus circulates in the blood for a period of nine to 15 days before the immune system begins to clear the virus. Id. at 2752-2753; see also Cedillo R's Trial Ex. 23 at 1. This period of time is known as the viremia stage. Id. at 2752-2753 (Dr. Griffin); accord see id. at 1070, 1127 (Dr. Kinsbourne). During this period of time, the virus spreads to the skin and produces a rash. Id. at 2752 (Dr. Griffin). The virus can cause liver and heart "abnormalities." Id. The virus can also spread to the gut. Id. The virus spreads to lymphoid tissues throughout the body and also affects both endothelial and epithelial cells. Id. The virus causes a systemic infection throughout the body. Id. at 2756 (Dr. Griffin); accord see id. at 1127 (Dr. Kinsbourne). Dr. Griffin explained that during this time of peak viremia, "1/100-1/1000 of all circulating white blood cells are infected" with measles virus. Cedillo Ex. V at 2 (Dr. Griffin's report) (citing Cedillo Ex. V68 (1994 van Binnendijk article[212]) and Cedillo Ex. V3 (1999 Auwaerter article[213])).

Dr. Griffin noted that in her studies of acute measles infections in children in Peru, the virus was found only in the endothelial cells of the lining of the brain's blood vessels, but not in the actual brain tissue. Cedillo Tr. at 2756. Additionally, in patients suffering from post-infectious encephalomyelitis,[214] a complication following some measles infections, the measles virus was detectable in various organs, including the spleen, the lungs, the gut, and the skin but the virus could not be found in the brain. Id. at 2757. In acute measles infections, the measles virus was not found in astrocytes or in microglia or in any other cells in the brain other than the vascular endothelial cells. Id. at 2758.

Dr. Griffin described the clinical symptoms of an acute measles infection. Usually,

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[212] R. S. van Binnendijk et al., Viral replication and development of specific immunity in macaques after infection with different measles virus strains, J. Infect. Dis. 170:443 (1994).

[213] P. G. Auwaerter et al., Measles virus infection in rhesus macaques: altered immune responses and comparison of the virulence of six different virus strains, J. Infect. Dis. 180(4): 950-958 (Oct. 1999).

[214] One of the complications of measles is post-infectious encephalomyelitis. Cedillo Tr. at 2743A (Dr. Griffin). It is now understood to be an autoimmune disease that occurs in close association with measles. Id. at 2744. It is not a progressive disease. Id. Rather it is a characteristic disease that occurs primarily in patients who are older when they get measles, usually five or 10 years of age. Id. at 2744.

measles is recognized by a rash on the skin. Cedillo Tr. at 2758. In an outbreak situation, "an astute physician . . . may be able to see Koplik[] spots[,] which are little spots on the inside of [the] mouth[,] in children" who present with a fever. Id. The first symptoms of fever and rash appear at the peak of the viremia stage of the infection, which is 10 to 15 days after the initial viral infection. Id. at 2758-2759; see also Cedillo R's Trial Ex. 23 at 2 (Dr. Griffin's trial slides). The first 10 days of the infection are "relatively asymptomatic" even though there is a lot of viral replication occurring in the body. Id. During the first two weeks after infection, the measles virus "can be routinely isolated from blood." Cedillo Ex. V at 2 (Dr. Griffin's report) (citing Cedillo Ex. V68 (1994 van Binnendijk article)).

Dr. Griffin specifically addressed the occurrence of diarrhea following a measles infection. She stated that diarrhea is not a characteristic clinical symptom of measles. See Cedillo Tr. at 2760-2761 (Dr. Griffin). When it occurs in an infected child, the diarrhea can "almost always be ascribed to another diarrhea-causing agent that was there at the same time." Id. at 2760-2761. Although diarrhea can occur in an infected child, it is "not considered a common aspect of measles." Cedillo Tr. at 2761 (Dr. Griffin).

There is a prodromal period that occurs two to three days before the appearance of the rash. Id. at 2759. During the prodromal period, there may be conjunctivitis, cough, or fever. Id. at 2759, 2770. The rash typically lasts for three to five days. Id. at 2759. The onset of the rash correlates with the start of the clearance of the virus from the body as the adaptive immune system begins responding to the infection. Id. at 2759, 2770. The onset of fever followed by the rash is indicative of a proper immune response. See id. at 2770, 2781A.

By contrast, children who are immunosuppressed due to human immunodeficiency virus (HIV) infection (or for "whatever reason" they become clinically and significantly immunosuppressed) and then contract measles do not mount a good immune response to the measles infection. Id. at 2770, 2791 (Dr. Griffin). The failure to mount a good immune response may be evidenced by the failure to present with a rash. Id.

The immune response to a measles infection begins after the respiratory infection when the lymph nodes first become infected. Id. at 2761-2762 (Dr. Griffin); accord id. at 1067A, 1071 (Dr. Kinsbourne stating that the measles virus accumulates in the lymph glands, which are part of the body's immune system, and in the lymph glands, the measles virus preferentially seeks the dendritic cells which "take part in developing the [body's] immunity to the measles . . . virus"). The initiation of the immune response occurs in the initial phase of the infection. Id. at 2772-2773A (Dr. Griffin). Cells in the mucosal tissue in the respiratory tract and in other locations to which the viral particles have spread "pick up" the viral particles and present them to the lymph nodes. Id. at 2762. As the cells in which the virus is replicating move out into the blood stream, the immune system's response is mounting and is becoming specific for the antigen (foreign presence) of measles virus. See id. at 2762-2763.

During this time, there is an immune response, specifically, an antibody response in B lymphocytes and a T cell response in the CD4 T cells and CD8 T cells, that will assist in the viral clearance from the body. See id. at 2763-2764. Importantly, the T cells and the B cells are involved in making IgM, an antibody that can neutralize and restrict the spread of the virus in the body. See id. at 2765-2767. The T cells also are involved in the "differentiation" process that allows IgM to switch to IgG. Id. at 2765. It is the long-term secretion of IgG from the bone marrow that provides lifelong immunity to measles after recovery from the acute infection. Id. at 2765-2766, 2773A-2774.

The initial immune response involves the T cell response referred to as a TH1 response that produces cells that can kill virus-containing cells. See id. at 2802-2803. "The best way for the immune system to get rid of a virus is to kill the cell that the virus is in," id. at 2826A, and the cells known to become infected by the measles virus are rapidly replaced, id. at 2826A-2827A. As this process of viral clearance continues, the immune system's response to the measles virus then shifts to a TH2 response. See id. at 2806. The TH2 response is important for the production of antibodies. Id. at 2803.

Once the body's immune system has cleared the virus, the last phase of the infection, called the memory phase, begins. Id. at 2773A. During this phase, the population of cells that are specific for the measles virus decreases to a "much smaller population of cells than there was at the peak" of the immune response. Id. The memory cells that remain continue to circulate. Id. The memory cells include T cells and the antibody-secreting cells that "go mostly to the bone marrow." Id. A proper immune response to the measles virus may be confirmed by the presence of "satisfactory levels of antimeasles antibody." Id. at 1131 (Dr. Kinsbourne).

Interestingly, while the immune system is mounting a vigorous response to a natural measles infection, there is a period of time during which the immune system does "not respond[] normally to other challenges." See id. at 2767-2768A (Dr. Griffin). This concomitant period of immune suppression occurs during an acute measles infection and is the period of time during which infected children are more susceptible to other infectious diseases, such as bacterial pneumonia. See id. at 2768A-2769. This period of immunosuppression lasts longer than the period of maximum viremia (which lasts from nine to 15 days). Id. at 2799. The period of increased susceptibility to other infections may last for several months after the clearance of the rash associated with a natural measles virus. Id. at 2800A. During this period of time, specifically for a period of one to five months after the onset of the rash, the virus "can be detected by reverse transcriptase-polymerase chain reaction (RT-PCR)." Cedillo Ex. V at 2 (Dr. Griffin's report) (citing, among other articles, Cedillo Ex. V52 (2003 Permar article[215]), Cedillo Ex. V50 (2005 Pan article[216]), and Cedillo Ex. V57 (2005 Riddell article[217])). There is no correlative period of

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[215] S. R. Permar et al., The role of CD8 T lymphocytes in control and clearance of measles virus infection of rhesus monkeys, J. Virol. 77(7): 4396-4400 (Apr. 2003).

[216] C-H. Pan et al., Modulation of disease, T cell responses, and measles virus clearance in monkeys vaccinated with H-encoding alphavirus replicon particles, Proc.

(continued...)

immunosuppression, however, after a measles vaccination. Id. at 2799. Although "there are some immunologic changes that occur coincident with the [MMR] vaccinations," Dr. Griffin explained that there is no "clinically important . . . immunosuppression . . . that occurs with the vaccine." Id. at 2781.

Dr. Griffin described the measles virus as "lymphotropic" because it replicates in the lymphoid tissue throughout the body. Id. at 2819A. But, she explained, unlike an enterovirus, the measles virus has no "special predilection" for replicating "in the gut." Id. She discounted the likelihood that measles virus in the gut could attach to monocytes or macrophages in the blood and then enter the brain. See id. at 2782A. She stated

> I don't understand how that is going to happen. There[are] basically . . . antibodies present which [are] going to move to prevent the virus moving from one cell to another. That's an antibody's job . . . to neutralize that virus from infection. The thought that [the virus] would attach to the outside of a cell and then move into the brain, . . . I just don't see why that would be happening.

Id. at 2782A. Dr. Griffin did address, however, the rare but known biological complications associated with a contracted wild-type measles virus.

d. Recognized Complications Associated with Persistent Wild-Type Measles Virus

"There are [two] well[-]characterized diseases that are associated with [wild-type] measles virus persistence." Cedillo Tr. at 2785 (Dr. Griffin); see also id. at 1915 (Dr. Ward). The most "classic" of the diseases that can be caused by a persistent wild-type measles virus is subacute sclerosing panencephalitis (SSPE).[218] Id. at 2785 (Dr. Griffin).

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[216](...continued)
Natl. Acad. Sci. USA 102: 11481 (2005).

[217] M. A. Riddell et al., Slow clearance of measles virus RNA in children after acute measles, J. Clin. Virol. 39(4): 312-317 (Aug. 2007).

[218] The condition is defined as

> a rare chronic, progressive encephalitis that affects primarily children and young adults, caused by the measles virus. Characterized by a history of primary measles infection before the age of 2 years, followed by several asymptomatic years, and then gradual, progressive psychoneurological deterioration, consisting of personality change, seizures, myoclonus, ataxia, photosensitivity, ocular abnormalities, spasticity, and coma. Characteristic periodic activity is seen on EEG; pathologically, the white matter of both the hemispheres and brainstem are affected, as well as the cerebral cortex,

(continued...)

The condition is a relatively uncommon complication that occurs in children who have had a natural measles infection at a very young age (less than two years of age). Id. at 2785. This is the "only disease" known to be caused by a persistent measles infection in immunologically competent individuals. Cedillo Ex. V at 9 (Dr. Griffin's report).

The clinical symptoms of the condition do not appear for seven to 10 years after the measles infection. Cedillo Tr. at 2785 (Dr. Griffin, respondent's virologist); accord see id. at 1069A (Dr. Kinsbourne, petitioners' neurologist, stating that the latency period for SSPE is "anything from eight years to 30 years"). The children appear to be normal for years until the signs or symptoms of the disease manifest. Id. at 2786 (Dr. Griffin). The signs and symptoms of disease include intellectual deterioration (usually signaled by a decline in school performance), movement disorders (commonly involving myoclonus), characteristic electroencephalogram (EEG) abnormalities (known as a burst suppression pattern of brain wave irregularities[219]), "very[,] very high levels of antibody in the cerebrospinal fluid" indicating an immune response to the virus in the nervous system, and cell death (primarily of neurons) in the brain as evidenced by big ventricles and a shrinking brain on imaging (whether by computed tomagraphy study (CTS)--which provides internal body images--or by magnetic resonance imaging (MRI)--which permits a view of soft tissues).[220] Id. at 2786-2787, 2790. The affected children eventually become mute and bedridden. Id. at 2787. The children die within several years of the onset of their neurological symptoms. Id. at 2787-2788. At the time that the condition is diagnosed, the persistent infection is in the nervous system and is widespread. Id. at 2786.

Pathologically, there is a "very characteristic inclusion body formation" that can be seen, either by brain biopsy or at autopsy, in the infected cells in the nervous system. Id. at 2789A. Additionally, a stain for virus antigen is able to detect virus "everywhere." Id.

Children with SSPE typically have an elevated level of anti-measles antibodies in their brains and in their cerebrospinal fluid (CSF) as compared to the level of such antibodies in their blood. Cedillo Tr. at 1830A (Dr. Ward); see also Snyder Tr. at 841A-842A (Dr. Rima explaining that the antibody level in the brain is so high because resident B cells in the brains of SSPE patients make measles specific antibodies). A ratio of a higher CSF antibody level to a lower peripheral blood antibody level is a "very useful diagnostic criteri[on] for SSPE" because it is an inverted ratio of the anti-measles antibody levels detected in children who have had either a natural measles infection or a measles vaccination. Cedillo Tr. at 1830A-1831A (Dr. Ward). In children who have had either a

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[218](...continued)
and eosinophilic inclusion bodies are present in the cytoplasm nuclei of neurons and glial cells. Death usually occurs within 3 years.

Stedman's at 1141.

[219] A burst on an EEG is "any short waveform that has an abrupt onset and termination" and that differs from the background activity. See Dorland's at 266.

[220] See Dorland's at 908, 1919.

natural measles infection or a measles vaccination, the immune response occurs in the peripheral tissues and not in the brain. Accordingly, the anti-measles antibody level is higher in the peripheral blood than in the CSF, and any antibody that gets into the brain is derived from the peripheral blood rather than the presence of infection in the brain. Id. at 1831A (Dr. Ward).

The measles virus is thought to have entered the brains of the children affected with SSPE at the time of the original infection. Id. at 2786 (Dr. Griffin). Replicating "very slowly" and spreading "very slowly" through the nervous system, the virus is thought to achieve a "threshold" that is enough to cause symptoms and damage. Id. at 2786-2787. The infection causes "profound and progressive change" over a period of time. Id. at 2787 (Dr. Griffin). Notably, in cases of SSPE, the measles virus persists "in a heavily mutated form that is clearly abnormal. It is not present in a normal replicating form." Id. at 1830A (Dr. Ward). Nor is the measles virus in the brain of an SSPE patient limited to particular areas; instead, the infection is diffuse in the brain. Snyder Tr. at 842A (Dr. Rima).

Another recognized complication of persistent wild-type measles virus is measles inclusion-body encephalitis (MIBE). See Cedillo Tr. at 1068 (Dr. Kinsbourne); accord see Cedillo R's Ex. V at 10 (Dr. Griffin's report). This complication occurs in persons (including children) who have "profound immunosuppression" and are immunologically compromised due to HIV infection, congenital immunodeficiencies, cancer, or chemotherapy. Cedillo Tr. at 2790-2792 (Dr. Griffin). In the "profoundly immunocompromised," measles virus can persist and cause disease associated with giant cell pneumonia or measles inclusion-body encephalitis. See Cedillo R's Ex. V at 10 (Dr. Griffin's report). As evidence of their severely compromised immunological states, the profoundly immunocompromised often do not manifest a rash after contracting a measles virus infection because the persons are unable to "mount an adequate immune response." Cedillo Tr. at 2791 (Dr. Griffin). The affected persons characteristically develop a "progressive measles virus disease" that manifests within months. Id. at 2791-2792A. The most common symptoms when they present are neurologic deterioration and respiratory problems. Id. at 2792A. Induced by a persistent measles infection, the MIBE condition is progressive and fatal. See id.; Cedillo Tr. at 1828 (Dr. Ward). The persons die within weeks or months after the recognized exposure to the wild-type measles virus. See id. This disease progresses much more rapidly than SSPE. See id.

Dr. Griffin explained that in MIBE cases, the ongoing replication of the measles virus "is easily and reproducibly demonstrated by a wide variety of techniques," including PCR methods, immunocytochemical staining for proteins, and "routine histology for giant cells or inclusion bodies" in the lungs and/or in the brain. Cedillo R's Ex. V at 10 (Dr. Griffin's report). The giant cells are indicative of an acute and persistent measles infection of the lungs and lymphoid tissue, id., and the inclusion bodies are indicative of a persistent measles infection of the brain, id.

Dr. Griffin noted that in certain circumstances, however, even the severely immunocompromised are urged to receive the MMR vaccine. She testified that "because wild-type measles is such a severe disease in HIV[-]infected children, it is generally recommended that children receive the measles virus vaccine even though [they are] HIV[-]infected." Cedillo Tr. at 2794 (Dr. Griffin). She observed that in Africa, the age of

vaccination for HIV-infected children has been lowered to the range of six to nine months from the range that is recommended in the United States. Id. She explained that because "immune suppression for HIV is progressive over time[,]" administered immunizations while the children's immune systems "are still in fairly good shape" may provoke a good immune response without complications. Id. at 2794-2795A; see also id. at 1804-1807A (Dr. Ward). Moreover, for the same reasons that the MMR vaccine is recommended for HIV-infected children in Africa, the Advisory Committee on Immunization Practices, an advisory body with the Centers for Disease Control in the United States, has recommended that asymptomatic HIV-infected adults and severely immunocompromised HIV-infected patients receive the MMR vaccine. See Cedillo Ex. V14 at 3-4[221] (1996 CDC case report[222]). And petitioners' expert Dr. Byers acknowledged during her testimony that it is "possible" for the body to clear the measles virus even in circumstances involving systemic immunosuppression. See id. at 968-972A (Dr. Byers referring to study indicating that an HIV-infected person cleared the measles virus in six months).

Dr. Griffin testified that there has never been a reported case of a neurological outcome of autism for either the wild-type measles virus or the vaccine strain. Id. at 2795A. Although there are neurological complications that are associated with a natural measles infection and, in the limited circumstances described by Dr. Griffin, there are also neurological complications associated with a persistent natural measles infection, Dr. Griffin asserted that autism is not one of the recognized complications. Id.; see also id. at 1826A (Dr. Ward). There is a lot of scientific and medical knowledge "about what measles virus does when it gets in the brain and none of it is autism." Id. at 2796 (Dr. Griffin).

Echoing Dr. Griffin's testimony, respondent's expert Dr. Ward testified that SSPE and MIBE are the "only two" conditions known at the present time to occur as a result of a persistent wild-type measles virus in the brain. See id. at 1915 (Dr. Ward). What is known to the medical community about both persistent wild-type measles infections is that the infections are readily measurable by a number of different methods. Moreover, both persistent measles infections lead to progressive neurological disease over weeks or months once symptoms begin to appear, and both diseases are fatal.

During the Cedillo hearing, petitioners presented to Dr. Griffin, for her consideration and comment, the editorial opinion of Dr. Paul Dyken, a pediatric neurologist claiming to maintain the SSPE registry for the United States and offering a comparison between the disease SSPE and a disorder he described as measles-induced neuroautistic encephalopathy (or MINE). Dr. Griffin did not recognize him, the disorder he described, or the registry he claimed to maintain. See id. at 2850-2853 (referencing

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[221] The pages of the document are unnumbered. The citation refers to the third and fourth pages of that unnumbered document.

[222] Centers for Disease Control and Prevention. Measles pneumonitis following measles-mumps-rubella vaccination of a patient with HIV infection,1993 Morb. Mortal. Wkly Rep. (MMWR) 45(28): 603-606 (Jul. 1996).

Cedillo Ps' Trial Ex. 17 (2004 Dyken editorial[223])). Based on her extensive research and work with the measles virus, Dr. Griffin declined to accept Dr. Dyken's theory that autism results from a measles-induced brain injury as anything other than a personal opinion because he offered the theory, without any supporting data, as an "opinion" only. Id. at 2852. Respondent's expert Dr. Ward further observed that after Dr. Dyken published his editorial "in a fairly obscure medical journal," the problems with his hypothesis were exposed. See Snyder Tr. at 943A (Dr. Ward).

e. The Attenuated Vaccine-Strain Measles Virus

The vaccine strain of the measles virus is an attenuated form of the wild-type strain. Cedillo Tr. at 713. All measles vaccines come from the Edmonston strain of measles virus. See Snyder Tr. at 832A (Dr. Rima). Petitioners' expert Dr. Kennedy explained that the attenuation process involves passing the wild-type virus through host cell tissue culture multiple times. Id. at 771 (Dr. Kennedy). He stated that typically, the host cell is "some sort of a monkey kidney [cell]." Id. As the virus passes through the host cell, it replicates, and as it continues to replicate, it becomes "less virulent, less pathogenic, and [more] attenuated." Id. The current version of the measles vaccine administered in the United States was developed in the late 1960s or early 1970s and is better attenuated than its predecessor. Snyder Tr. at 833A (Dr. Rima).

Dr. Kennedy asserted that the structure of the vaccine strain of measles virus is essentially the same as the wild-type virus. Id. at 714A. But, he acknowledged the attenuated vaccine strain does not replicate as readily or as well as the wild-type strain. Id. at 715, 771; see also id. at 978 (Dr. Byers); id. at 1071 (Dr. Kinsbourne stating that the vaccine strain of the measles virus has the same properties as the live virus, "although much attenuated").

Among other similarities between the vaccine and the natural infection that Dr. Kennedy noted is the induced immune response. The measles vaccine induces an immune response that is similar "for the most part" to the immune response induced by a natural measles infection. Cedillo Ex. 112 at 5 (Dr. Kennedy's report). The interval of time between the particular exposure and the induced immune response, however, is different for the vaccine and for the natural infection. Id. The immune response time for the vaccine is shorter. Id.

Respondent's experts Dr. Griffin and Dr. Ward corrected Dr. Kennedy's testimony that presently the measles virus is passed through chicken cells, and not monkey cells, as part of the attenuation process. Cedillo Ex. V at 3 (Dr. Griffin's report); Cedillo Tr. at 1819A (Dr. Ward); see also Snyder Tr. at 831-832A (Dr. Rima). Dr. Griffin further explained that the process of passing measles virus through non-human cells permits the

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[223] P. Dyken, Some aspects about the clinical and pathogenetic characteristics of the presumed persistent measles infections: SSPE and MINE, an editorial appearing in the Journal of Pediatric Neurology 2(3):121-124 (2004).

virus to adapt, by changing its properties, to grow very well in non-human cells and no longer to grow well in human cells. See id. at 2774-2775 (Dr. Griffin). Dr. Griffin testified that

> paradoxically, if you look at [vaccine strain measles virus] in tissue culture [(for an in vitro study),] it replicates better than the wild-type virus . . . . But if you look at it in a person . . . , the replication is almost . . . undetectable for a vaccine strain of virus compared to the wild-type strain which causes this huge viremia. . . . [O]ne of the things . . . accomplished with attenuation . . . [which] is probably the most critical [is] that [vaccine strain measles] no longer really caused measles, but it replicated enough that it induce[s] an immune response to measles.

Id. at 2776-2777. The immune response that follows a measles vaccination is similar to the immune response to a natural measles infection, but the response is "greatly attenuated." Id. at 2812; accord id. at 978A (Dr. Byers). The difference is one of considerable degree. See id. As Dr. Griffin pointed out during her testimony, the amount of antibody generated in response to the measles vaccine "is about ten-fold lower than . . . [the] response to wild-type infections." Cedillo Tr. at 2812 (Dr. Griffin).

Dr. Griffin identified and addressed with specificity the differences between the wild-type strain and the vaccine strain of measles. First, the routes of entry into the body are different. The vaccine strain enters the body by subcutaneous inoculation whereas the natural infection enters the body by a respiratory route. Id. at 2778A. Second, the strains are recognized by different host cell receptors (CD150 for the wild-type strain and CD46 for the vaccine strain). See id. at 2775. Third, unlike the wild-type strain, the vaccine strain generally does not cause disease. Id. at 2778A. Fourth, there is no evidence of transmission of the vaccine strain of the measles virus from person to person as has occurred with other vaccines containing attenuated viruses, but a person with a natural infection becomes infectious to others "just a few days before the rash onset." Id. Fifth, there is no clinically important immunosuppression that occurs with the vaccine strain that would permit an increased susceptibility to other infections or impede the body's efforts to clear the vaccine virus while the body is mounting a lasting immune response to the virus. Id. at 2779A-2781A; see also Snyder Tr. at 590A (Dr. Zweiman describing, based on his own research with colleagues of the immunological effects of an administered "attenuated measles vaccine," a "moderate transient decrease in . . . cellular reactivity to certain antigens" but otherwise a normal "antibody formation to [the] measles . . . virus itself, and to other antigens" following a measles vaccination).

Additionally, Dr. Griffin testified that while most children develop a fever following a measles vaccine, a "small percentage" develop fever of 103 degrees or more (in Dr. Griffin's estimate, the percentage is "five to fifteen percent" of immunized children), and a small percentage develop a rash after the vaccine (in Dr. Griffin's estimate, the percentage is "maybe ten percent"). Cedillo Tr. at 2779A (Dr. Griffin); see also id. at 2206 (Dr. McCusker testifying that while not a common occurrence, "fever does occur" after a MMR vaccination, and a high fever occurs "more rarely"). If a fever or a rash appears following a measles vaccination, it "usually" occurs five to 10 days after the measles vaccination. Id. at 2817-2818A (Dr. Griffin); accord id. at 1070 (Dr. Kinsbourne

stating that if fever occurs after an MMR vaccination, it occurs in the "second week after the vaccination").

Based on Dr. Griffin's experience of more than 25 years studying the measles virus, see id. at 2743A, she would expect the complications associated with the vaccine strain to be "dramatically diminished" from the complications associated with a natural infection, id. at 2779A; accord id. at 978 (Dr. Byers). Moreover, she would not expect the complications associated with the vaccine strain to be different from the recognized complications of the wild-type strain. Id. at 2779A (Dr. Griffin); accord see Snyder Tr. at 363A-364A (Dr. Kennedy acknowledging that wild-type measles virus is not known to cause autism). On review, Dr. Griffin concluded that "the most important components of measles and the complications of measles don't occur with the vaccine." Cedillo Tr. at 2779A (Dr. Griffin).

3. Petitioners' Claim that the Administration of the Vaccine Strain of the Measles Virus can cause Immunosuppression in a Vaccinee

Petitioners' expert Dr. Kennedy identified immune suppression as "one of the environmental requirements or factors . . . necessary to allow persistence of the [measles] virus." Cedillo Tr. at 760. He stated in his expert report that the wild-type measles virus is a known immunosuppressive agent. Cedillo Ex. 112 at 5 (Dr. Kennedy's report). He also stated that measles vaccine "can induce immunosuppression of an important component of the acquired immune response." Id. He noted that one of the contraindications for the MMR vaccine is the administration of the vaccine to an immunosuppressed individual. Cedillo Tr. at 759. When questioned at the Cedillo hearing, however, he acknowledged that neither of the two articles that he had cited in his report, particularly the 1969 Fireman article and the 1994 Plotkin article,[224] offered support for the proposition that the measles vaccine can cause immunosuppression of any clinical relevance. See Cedillo Tr. at 769-770.

Dr. Kennedy conceded that in his view, petitioners' theory that an MMR vaccine given to an immunosuppressed child can lead to a persistent viral infection in the child's gut tissue and chronic inflammation that in turn can lead to a neurological impairment that manifests as autism is "less likely" in the absence of immune suppression. See Cedillo Tr. at 760-761, 772A, 777, 786, 800; Cedillo Ps' Trial Ex. 8 at 21-22 (Dr. Kennedy's trial slides).

Respondent's expert Dr. Griffin testified that there is no period of "clinically significant" immunosuppression after a measles vaccination that is correlative to the period of immunosuppression that follows a natural infection. Id. at 2799A. Accordingly, there is no increased susceptibility to other infections associated with the vaccine strain of

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[224] Filed as Cedillo Ex. 112D is P. Fireman, et al., Effect of measles vaccine on immunologic responsiveness, Pediatrics, 43(2): 264-272 (Feb. 1969). Filed as Cedillo Ex. 112N is S. A. Plotkin and E. A. Mortimer, eds., Vaccines 229-276, 907, 916 (1994).

measles. Id. at 2779A-2781A (Dr. Griffin); accord id. at 1890 (Dr. Ward) (testifying that although a number of changes in immune cell function can be measured transiently following vaccination, "[t]here is no clinical evidence that measles virus vaccine causes immunosuppression; and therefore, . . . there is no clinical evidence that measles virus vaccination results in enhanced susceptibility to any organism"). The body is able to clear the vaccine virus while mounting a lasting immune response to the virus. Id. at 2779A-2881A (Dr. Griffin).

Respondent's expert Dr. Ward observed during his testimony that there is a reluctance to vaccinate individuals with other attenuated live viral vaccines after administering a measles vaccination. Cedillo Tr. at 1890-1891. He explained, however, that the reluctance does not stem from a fear that the live virus vaccines might "overgrow and cause problems" such as immunosuppression, but rather the reluctance is based on a concern that the "antiviral state initiated by [the measles virus vaccine] might decrease the ability of the other vaccine strains to replicate and grow and induce an immune response." Id. Dr. Ward testified that 50 years of experience with the measles vaccine has not shown the measles vaccine to cause any clinically relevant immunosuppression. Cedillo Tr. at 1919. Respondent's expert Dr. Rima concurred, acknowledging that he is not a physician but based on his nearly 33 years of experience with the measles virus, he has "never seen any clinically relevant immunosuppression after vaccination." Snyder Tr. at 826A, 831.

With decades of experience working with the measles virus, respondent's experts consistently testified that there is no period of clinically relevant immunosuppression that follows a measles vaccination. In this significant respect, the wild-type virus and the vaccine strain virus behave very differently. Petitioners assertions to the contrary are unsupported and ignore the well-known distinctions between the two different strengths of the measles virus. Petitioners have failed to persuade that the administration of the vaccine strain of the measles virus can cause immunosuppression in a vaccinee.

4. Petitioners Assert that the Vaccine Strain of the Measles Virus can Persist in a Vaccinee

a. Characteristics of Viral Persistence

Dr. Byers testified on petitioners' behalf that if a child has a dysfunctional immune system at the time of the administration of the MMR vaccine, the child's ability to clear the measles virus will be affected. Cedillo Tr. at 915 (Dr. Byers). Dr. Byers identified a child's impaired ability to clear the measles virus as a factor that could contribute substantially to the persistence of the measles virus in the child. Id.

In further support of their theory that an administered MMR vaccine can lead first to a persistent measles virus and then to the development of an autistic spectrum disorder, petitioners relied on several introductory remarks in a review article of scientific literature addressing viral persistence. The review article on which petitioners relied was authored by the virologist Dr. Michael Oldstone. See Cedillo Ex. 61VV (2006 Oldstone review

article[225]). The particular statements in the 2006 Oldstone review article on which petitioners relied were the following: (1) viral persistence rests, in part, on the failure of the host's immune system either to form an immune response or to purge the virus; (2) "viruses can acquire unique component(s) or strategies of replication;" (3) the diseases that result from persistent viruses are "often novel and unexpected;" and (4) persistent viral material "can selectively disorder the functions of that cell without destroying it." Cedillo Ex. 61VV at 111. Respondent's expert Dr. Griffin specifically addressed the significance of these statements in the 2006 Oldstone review article and explained that the statements have more limited application than petitioners have urged. She stated that the comments by Dr. Oldstone, a well-known virologist and a colleague personally known by Dr. Griffin for a long time, did not apply to viruses generally or to the measles virus in particular, but rather pertained very particularly to certain very specific viruses. See id. at 2844-2846A (quoting Cedillo Ex. 61VV at 111 (2006 Oldstone article)).

Dr. Oldstone himself subsequently confirmed Dr. Griffin's interpretation of the statements made in the 2006 Oldstone review article in a letter filed into the record of the Snyder case. He wrote:

> I recently became aware that my work in the field of viral persistence is being quoted in support of the hypothesis that the measles virus component of the [MMR] vaccine is supposedly associated with the development of [ASD].
>
> Measles virus has been a focus of my laboratory for many years, so this autism/measles link has been of interest to me. Further, I should state up front that I see at present no evidence whatsoever for such a link.

Snyder Ex. AA. Without relying on Dr. Oldstone's letter as evidence on the ultimate issue of causation in this case, the undersigned views the document as evidence that Dr. Oldstone's statements in the 2006 review article were not intended to apply as broadly as petitioners here assert.

Petitioners' expert Dr. Kennedy testified during the Cedillo hearing that viral persistence does not "necessarily" mean that more virus is being produced. Cedillo Tr. at 730. Viral persistence can occur with portions of the measles virus that may "at some point . . . be able to reactivate and produce new [viral material]." Id. at 731A. According to Dr. Kennedy, the length of time within which measles proteins can persist within a cell in unknown. See Cedillo Tr. at 733.

In general, Dr. Kennedy testified viruses persist in a host because the host's immune response is ineffective. Cedillo Tr. at 736. In individuals with normally functioning immune systems, there should be no problem in clearing either the wild-type measles virus or the vaccine strain from the body. Cedillo Tr. at 717 (Dr. Kennedy). An

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[225] M. Oldstone, Viral persistence, parameters, mechanisms and future predictions, Virology 344: 111-118 (2006).

ineffective immune system, however, reflects a problem with the immune system. Dr. Kennedy defined the term "immune dysfunction" to include problems that are associated with a normal immune function. Cedillo Tr. at 735A, 736. Dr. Kennedy also defined the term "immune suppression" to include "anything that would affect the induction of an effective vaccine, [particularly a] MMR-induced, protective immune response." Cedillo Tr. at 761. There are "a number of serologic, virologic, and immunologic assays that can be used" to measure an effective immune response to a vaccine. Cedillo Tr. at 763.

Addressing the viral persistence of the other sub-types of morbillivirus in dogs, seals, and dolphins, Dr. Kennedy acknowledged that the persistence of those viruses usually leads to the death of the animals. Cedillo Tr. at 790. But, in support of petitioner's theory that measles virus could persist following a MMR vaccine without causing death but causing autism instead, Dr. Kennedy pointed out that a bad temper and deranged behavior are among the neurological manifestations that precede deaths associated with morbillivirus infections in dogs. See id.

The most critical support for the offered opinion of petitioners' expert Dr. Kennedy regarding vaccine causation, however, is the reported recovery of measles virus genomic material from tissue in the body because the recovered material is an indication that the persistent viral material is in the body. See Cedillo Tr. at 794-795. Dr. Kennedy testified that in the absence of viral persistence, it is possible that the measles component of the MMR vaccine could "set up an inflammation" that "allow[s] the immune system to get haywire" and produce the neurologic disorder of autism. See Cedillo Tr. at 801-803. But, he acknowledged that the described sequence of events without a persistent measles virus is a "less likely" possibility. Id. at 803.

With respect to the theory that measles vaccine can persist in a vaccinee, Dr. Griffin stated in her filed report that there is some evidence indicating that the attenuated measles vaccine virus can "cause progressive fatal respiratory or neurological disease in severely immunocompromised individuals" months after immunization. Cedillo R's Ex. V at 10 (Dr. Griffin's report) (emphasis added). The "severely immunocompromised" are those who have HIV infection or a congenital immunodeficiency or those who are receiving immunosuppressive chemotherapy. See id. Dr. Griffin explained that a causal relationship between the measles vaccine virus and the progressive vaccine-induced disease in the severely immunocompromised has been accepted based on: (1) the vaccinee's receipt of the vaccination; (2) the evidence of tissue damage, in particular, evidence of inclusion bodies and/or giant cells, that is typical of damage caused by a wild-type measles infection; (3) the detection of the measles virus by electron microscopy; (4) "the frequent ability to isolate replicating virus from the affected tissue;" and (5) the "confirmation of these findings by independent laboratories." Id. (citing the 1999 Bitnun

article,[226] the 1971 Mawhinnery article,[227] and the 1996 CDC article[228]). Although there is some evidence that supports the finding of a causal association between an administered measles vaccination and the development of a progressive and fatal respiratory or neurological disease, the cases involve seriously immunocompromised persons, not those with selective immune dysfunction.

Contrary to Dr. Kennedy's assertions regarding the immunological requirements for viral persistence, Dr. Griffin testified that immune dysfunction is not required for viral persistence. Cedillo Tr. at 2820; accord id. at 1923-1924 (Dr. Ward). She observed that many viruses are known to persist in persons who were immunologically normal prior to the viral infection. Id. at 2820 (Dr. Griffin); accord id. at 1924 (Dr. Ward). Such persistent viral infections include HIV, hepatitis C, and herpes. Id. at 2820-2821A. Moreover, Dr. Griffin explained that there can be different types of immunosuppression that may increase the risk of persistence for some viral infections but not others. Id. at 2821A. Observations pertaining to viruses that are known to persist in the body, such as HIV and herpes, cannot be extrapolated to the measles virus in the absence of any evidence to date that the measles virus similarly persists in the human body. Cedillo Tr. at 1927 (Dr. Ward).

Having studied the persistence of the wild-type measles virus, Dr. Griffin explained that true viral persistence is distinguishable from the process of viral clearance that, as is better understood now, takes a period of time and could be misconstrued as evidence of viral persistence. See Cedillo Tr. at 2822-2823A. She stated in her report that with a "truly persistent infection, infectious virus is continuously produced and the viral proteins and RNA are abundant and easy to detect." Cedillo R's Ex. V at 5 (Dr. Griffin's report) (emphasis added). But viral clearance is the process of ridding the body of the virus. With "more and more sensitive techniques," including various PCR techniques, measles virus "can still [be found] at three months." Cedillo Tr. at 2823A. However, the virus cleared after five or six months. Id.

Regarding the period of time during which a persistent measles virus might be measured in an infected individual, Dr. Griffin testified that the natural measles virus can be recovered from the blood for a period of five to seven days during the viremia period, which is the period of time that corresponds to the initiation of the infection (generally nine to 14 days). See id. at 2840A-2842A. After the onset of rash, however, which

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[226] A. Bitnun, et al., Measles inclusion-body encephalitis caused by the vaccine strain of measles virus, Clin. Infect. Dis. 29:855 (1999). The article was filed as Cedillo Ex. V5.

[227] H. Mawhinnery, et al., Dysgammaglobulinaemia complicated by disseminated measles, Brit. Med. J. 2(5758): 380-381 (May 15, 1971). The article was filed as Cedillo Ex. V41.

[228] Centers for Disease Control and Prevention. Measles pneumonitis following measles-mumps-rubella vaccination of a patient with HIV infection:1993, Morb. Mortal. Wkly Rep. (MMWR) 45:603-606 (1996). The article was filed as Cedillo Ex. V14.

corresponds to the initiation of the immune response, recovery of the measles virus is more difficult. Id. at 2843A. But, Dr. Griffin observed that if the measles virus is thought to persist as petitioners assert, one ought to be able to recover the persistent virus "whenever." Id. She explained that the period of time during which one can recover a persistent measles virus should not matter because with truly persistent viruses, the virus can "always" be recovered. Id. Dr. Griffin testified that nothing in her nearly 30 years of studying the measles virus has led her to believe that a persistent measles virus would result in autism. Id. at 2865.

Respondent's expert Dr. Ward offered the further observation that in the presence of a truly persistent infection, the administration of powerful immunosuppressive drugs would actually worsen rather than improve the host's condition. See Cedillo Tr. at 1815-1816 (Dr. Ward). He noted that there is evidence in the medical literature that persons with persisting infections–whether viral, intracellular, bacterial or parasitic–who receive potent immunosuppressive drugs experience a worsening of the infection that leads to death. Id. at 1815-1816.

Respondent's expert Dr. Rima also addressed the issue of measles virus persistence. He noted that measles virus is an RNA virus, and he explained that RNA viruses are very unstable. Snyder Tr. at 837A (Dr. Rima). He testified that, contrary to Dr. Kennedy's assertions that measles virus can persist without actively producing more virus, see Cedillo Tr. at 730-731A (Dr. Kennedy), the measles virus cannot remain in a latent state for a period of time, unlike DNA viruses which are much more stable. Snyder Tr. at 837A (Dr. Rima). Rather, the measles virus must be able "to replicate constantly in order to maintain [itself]" because RNA viruses are so unstable. Id. Dr. Rima stated that "an active replication process . . . needs to be there to sustain the virus throughout the period of symptoms." Id. at 838A.

b. Evidence of Viral Persistence

As evidence that the measles virus can persist and replicate after vaccination, petitioners and their experts rely primarily on the 2000 Kawashima article[229] and the 2002 Uhlmann article[230] in which investigators reported that they had detected, by various laboratory techniques involving PCR, persistent measles in blood and in the intestinal tissues of autistic children who had received the MMR vaccine. Among the authors of the 2000 Kawashima article was Dr. Andrew Wakefield of the Royal Free Hospital in London. Among the authors of the 2002 Uhlmann article were Dr. Andrew Wakefield of the Royal Free Hospital School of Medicine at the University of London, and Drs. Orla Sheils and John O'Leary of the Unigenetics laboratory. See Cedillo Ex. BB95 (2002 Uhlmann

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[229] H. Kawashima et al., Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism, Dig. Dis. Sci. 45(4): 723-729 (Apr. 2000). The article was filed as Cedillo Ex. BB55.

[230] V. Uhlmann, et al, Potential viral pathogenic mechanism for new variant inflammatory bowel disease, Mol. Pathol. 55(2): 84-90 (Apr. 2002). This article was filed as Cedillo Ex. BB95.

article).

Before addressing the articles on which petitioners relied in support of the viral persistence component of their vaccine causation theory, the undersigned turns first to address the various laboratory techniques that were employed by the investigators in the articles on which petitioners rely.

c. PCR-Based Laboratory Techniques

Petitioners' expert Dr. Hepner testified concerning the PCR-based techniques employed in the 2002 Uhlmann paper. As a preliminary matter, she described the different types of techniques and how the techniques are applied. Cedillo Tr. at 584A.

PCR-based techniques are used in molecular biology to analyze protein molecules. See id. at 586. Proteins are important to the functioning of a cell, and each protein is specifically designed for a specific function. Id. The specific design of a protein is determined by its genetic code. See id.; see also Cedillo Ps' Trial Ex. 7 at 2 (Dr. Hepner's slides). The genetic code for a protein is found in the DNA (deoxyribonucleic acid) molecule of the protein. Cedillo Tr. at 584A. The DNA of a protein is located in the nucleus of the protein. Id. at 587A.

The DNA molecule is a double-stranded helical molecule comprised of nucleotides that have letter designations, As, Cs, Gs, and Ts. Id. at 586. The nucleotides bind together in particular ways; the T nucleotides always bind to the A nucleotides and the G nucleotides always bind to the C nucleotides. Id. A particular string of As, Cs, Gs, and Ts provides the code for a particular gene that, in turn, provides the code for a particular protein. Id. at 587A; see Cedillo Ps' Trial Ex. 7 at 1 (Dr. Hepner's slides). Whether the specific gene (comprised of an ordered string of As, Cs, Gs, and Ts) corresponds to a protein of interest may be determined from a standardized and computerized database that is available to scientists. Cedillo Tr. at 587A, 589A; see Cedillo Ps' Trial Ex. 7 at 2 (Dr. Hepner's slides). The database permits a scientist to identify a detected gene by source--whether human, plant or virus--and by name--if the genetic sequence has a name. Id. at 588A-589A. The database can provide additional information about what is known about the gene. Id.

To see a particular gene requires the use of particular laboratory techniques to "amplify" or to "copy . . . multiple times" the DNA of interest. Id. at 589A-590A. The DNA source is put into a machine that has certain parameters and that effectively functions as a copying machine to produce an exponential number of copies of the DNA. Id. at 589A-590A. The copying occurs by DNA replication. Id. at 590A; see also Cedillo Ps' Trial Ex. 7 at 3 (Dr. Hepner's slides).

Not only can the process of DNA replication be effected by scientists using PCR-based techniques in a laboratory, the process also can occur naturally in the body. Cedillo Tr. at 591-592. The first step involved in the natural process of DNA replication is the separation of the two strands that comprise the DNA helix. Id. at 590A. The two strands are separated by a naturally occurring enzyme found in the body called helicase. Id. at 590A-591. Another naturally occurring enzyme found in the body called polymerase

attaches to the separated strands and begins to add nucleotides, one by one along the strand, until a complementary strand is formed. Id. Through this naturally occurring process, what began as one strand of DNA becomes two strands of DNA. Id. at 591.

When the process of DNA replication occurs in a laboratory rather than naturally and when the source of the gene to be replicated is a virus, a preliminary manipulation is necessary before the laboratory copy technique can be applied. The preliminary manipulation is required because the genomic material for a RNA virus, such as the measles virus, is not contained in double-stranded DNA, but rather in single-stranded RNA (ribonucleic acid). Id. at 602A, see also Cedillo Ps' Trial Ex. 7 at 7 (Dr. Hepner's slides). As a single-stranded molecule, RNA is chemically unstable (also described as "labile," see Dorland's at 987). Cedillo Tr. at 603A; accord Snyder Tr. at 837A (Dr. Rima testifying that RNA viruses, unlike DNA viruses, cannot remain in a latent state for a period of time, but rather must be able "to replicate constantly in order to maintain themselves" because the RNA viruses are so unstable). The unstable nature of an RNA virus necessitates that the integrity of the RNA be tested before it can be subject to laboratory copying techniques. Cedillo Tr. at 615A (Dr. Hepner). In addition, before PCR techniques can be applied to detect measles virus RNA, the RNA must undergo a process of reverse transcription, which is the process of."tak[ing] an RNA molecule and mak[ing] it look like a DNA molecule." Id. at 603A (Dr. Hepner); accord id. at 1975A-1976A (Dr. Bustin stating that "to be able to amplify an RNA molecule[,] you have to convert the RNA to DNA" and "you must use a[] R[everse]T[ranscription] step to detect the measles virus RNA" using PCR techniques).

The purpose of reverse transcription is to make a copy of the RNA strand, called cDNA, that has "the features of a DNA molecule." Cedillo Tr. at 603A. The copy of the RNA strand must be double-stranded and must contain a DNA base (a base pair that is different between RNA and DNA). Id. (Dr. Hepner). The quality of the sample can be evaluated with a cellular reference gene. Id. at 1974A-1975A (Dr. Bustin describing the use of GAPDH, which is a reference or target cellular gene, for which investigators might look to confirm the presence of RNA). The process of reverse transcription is effected by using an enzyme called reverse transcriptase and using a primer that is complementary to the targeted segment of the RNA. A primer is a nucleotide sequence that is complementary to a nucleotide sequence of about 20 bases that is specific to the ends of the targeted gene. Id. at 593A (Dr. Hepner); accord id. at 1942A (Dr. Bustin); see also Dorland's at 1506 (defining a primer as a "short piece of DNA or RNA [that is] complementary to a given DNA sequence and acts as the point from which replication proceeds during the process of polymerase chain reaction"). The targeted segment of the RNA is its "poly A tail," which is a string of As at the end of the RNA. Id. At 604A (Dr. Hepner); see also Cedillo Ps' Trial Ex. 7 at 8 (Dr. Hepner's slides). The primer generates a complement to the targeted string of As and the reverse transcriptase enzyme generates a complementary strand that is a copy of the original RNA. See id. at 604A-605A. The generated product cDNA can be replicated for analysis using PCR techniques. Good laboratory practice counsels that after making the cDNA copy of the RNA and before applying PCR techniques to replicate the cDNA, an investigator should verify that the generated cDNA does not contain a degraded version of the original RNA. See Cedillo Ex. QQ at 2 (Dr. Chadwick's report). An investigator may make this determination by checking for the presence of a particular housekeeping gene in the cDNA. Id.

Investigators can replicate DNA or cDNA using the laboratory process called PCR. See Cedillo Tr. at 592. The process occurs either in special laboratory equipment or in a tissue sample resting on a slide. Rather than using an enzyme, as the body does naturally, to separate the double-stranded DNA molecule, investigators in the laboratory process apply heat to the DNA which causes the strands to separate. Id. The process of causing the strands to separate is referred to as denaturing. Id.

Once the strands are separated, the target gene that is to be copied must be delineated. To delineate (or define the beginning of and the end of) the target gene that is to be copied using a PCR-based technique, an investigator uses "primers." Primers are stretches of DNA that are complementary to a nucleotide sequence of about 20 bases that are specific to the ends of the targeted gene. Id. at 593A; accord id. at 1942A (Dr. Bustin). If an investigator knows what region of a targeted gene is of interest, the relevant nucleotide sequence at the ends of the targeted gene may be determined by consulting the computerized database containing such information. Id. at 593A-594 (Dr. Hepner). Once identified, the nucleotide sequences of interest are forwarded to a commercial entity that, for a fee, designs and develops a set of primers to correspond to the provided nucleotide sequences. Id. at 595A. If the designed primers are not specific enough to the target gene, however, an investigator risks amplifying genes other than the targeted gene and obtaining spurious results. See id. at 596A; accord id. at 1942A (Dr. Bustin).

With primers in place, the polymerase chain reaction is put into motion by allowing, after the separation of the DNA strands by heat, the polymerase enzyme to copy the DNA strand to generate a copy of a two-stranded DNA molecule. Id. at 597A (Dr. Hepner). The process of DNA replication occurs in cycles. See id. at 597A-598A. Typically, 35 to 40 cycles of DNA replication by polymerase chain reaction are run. Id. at 598A-599A; accord id. at 1942A (Dr. Bustin) (stating that "[f]or conventional PCR you conduct 20, 30, 40 cycles of the polymerase chain reaction").

This described technique is referred to as conventional or solution-based PCR. Id. at 599A (Dr. Hepner). The technique yields a tube of clear liquid. Id. at 599A-599B. To examine the DNA contained in the PCR product and to confirm that the PCR process has amplified the targeted gene and not some other material, an investigator may conduct gel electrophoresis. Id. at 601A-602A.

The gel electrophoresis technique involves adding DNA that has been amplified by the PCR process to an agarose gel in the wells of the equipment. Id. at 600. Current is applied to the gel, and because DNA is negatively charged, it begins to run down the various lanes of the PCR laboratory equipment toward the "positive pulse." Id. The DNA runs down each lane at a rate that is "inversely proportional to its size." Id. Because smaller material travels more quickly than larger material, the smaller material clusters at the bottom and the larger material remains closer to the top. Id. A stain is applied to the gel mixture "that basically inserts itself" between the base pairs of the DNA, fluoresces under ultraviolet light, and permits measurement of the number of base pairs. See id.; see also Cedillo Ps' Trial Ex. 7 at 6 (Dr. Hepner's slides). This technique yield what looks like a bar code. From the measured number of base pairs and the design of the primers for the targeted gene, the size of the amplified DNA can be examined to determine whether the amplified product is the correct size. Cedillo Tr. at 601A; accord id. at 1942A (Dr.

Bustin) (stating that "you look for bands on gels").

Another technique used to determine that what was amplified during PCR is what was intended is the Southern blot technique. See id. at 606A-608 (Dr. Hepner). The technique involves adding a solution to the agarose gel containing the DNA to denature, or separate, the DNA strands again. Id. at 606. The strands are separated and placed into a particular filter. The addition of either a radioactive label or a colorimetric label to a piece of DNA that is complementary to the targeted gene creates a probe. Id. at 606A-607A. The probe is then introduced to the separated strands of DNA. Id. at 607A. If the probe binds to the DNA, its complement is present. Id. at 607A-608. This described technique is another method for checking that the amplified material is the material that is intended to be amplified. Id. at 608; see also Cedillo Ps' Trial Ex. 7 at 9 (Dr. Hepner's slides).

The described solution-based PCR technique is just one of various PCR-based techniques. Another PCR-based technique is TaqMan PCR. Id. at 609A. TaqMan PCR requires the design of a probe that is complementary to one of the DNA strands in addition to the primers that are complementary to the ends of the targeted gene. Id. at 609A. The probe gives off a fluorescent signal when it binds to its target. Id. TaqMan PCR adds another level of specificity by adding a probe that binds to another part of the targeted gene sequence. Id. at 610A; see also Cedillo Ps' Trial Ex. 7 at 10 (Dr. Hepner's slides); accord id. at 1943A (Dr. Bustin) (stating that "TaqMan PCR . . . provides an additional probe that would be very specific for the target [you are] amplifying . . . [and that additional probe] binds to the amplified DNA only if the correct target is being amplified). The software associated with TaqMan PCR is able to identify the number of cycles, usually 15 to 20, that are required before exponential amplification of the target occurs that permits detection of the DNA by the fluorescent signal. Cedillo Tr. at 611 (Dr. Hepner). This cycle number is referred to as the cycle threshold. Id. at 612A.

In-situ PCR is a technique that involves amplification "directly in the tissue." Id. at 613A. After the collection of biopsy tissue, the tissue is placed on a slide. Id. The PCR reaction occurs in the tissue itself on the slide rather than in a tube. Id.; see also Cedillo Ps' Trial Ex. 7 at 11 (Dr. Hepner's slides).

Nested PCR is a technique that involves conducting a number of cycles of PCR, referred to as primary PCR. See Cedillo Tr. at 660A-661 (Dr. Hepner). After the primary PCR is run using a primer, an amount of the material subject to the primary PCR is then run through an additional number of cycles using a different primer that is specific for the same target. Id.; accord id. at 1958A (Dr. Bustin) (explaining that "nested PCR is where you take a PCR reaction and do a second PCR reaction on top of the first one").

There is variability in the detection thresholds of the different PCR-based techniques. Id. at 650 (Dr. Hepner). The detection threshold is the number of cycles of PCR that is required before the investigator begins to detect the presence of the targeted product and the results of the test become positive. Different PCR techniques do not yield the same results. Id. But within a particular assay (which is the group of samples tested at one time during a run of a particular PCR experiment), a particular sample should be consistently positive or consistently negative in each run. Id. Due to differences in the detection thresholds of different PCR techniques, however, a different result might be

obtained when the assay is run applying a different PCR technique. Id.

Another technique used to detect protein is immunohistochemistry. Cedillo Tr. at 614. The technique may generate a colormetric reading that indicates the presence of a protein if a particular color appears in the immunohistochemical stain, and conversely, the absence of a protein if the particular color is absent. Id.; see also Cedillo Ps' Trial Ex. 7 at 12 (Dr. Hepner's slides). The results obtained by immunohistochemistry are not questioned generally, but may be questioned in detail. Cedillo Tr. at 615A.

d. The Difficulties Associated with PCR Technology

Respondent's experts Dr. Ward and Dr. Bustin addressed some of the difficulties associated with PCR technology. See Cedillo Tr. at 1840A-1845 (Dr Ward); id. at 1944A (Dr. Bustin).

As discussed in Section III.C.4.c., above, performing PCR on RNA material (such as the measles virus), requires the preliminary step of reverse transcription. The quality of the sampled RNA affects the validity of the obtained PCR test results. Cedillo Tr. at 1840B-1841 (Dr. Ward).

Dr. Bustin elaborated on Dr. Ward's testimony concerning the quality of the RNA. He explained in his testimony during the Cedillo hearing that the results of PCR testing can vary considerably depending on whether the biopsied tissue to be PCR-tested was "fresh-frozen" tissue or was "formalin-fixed, paraffin-embedded" tissue. Cedillo Tr. at 1946; see also id. at 1840A-1841A (Dr. Ward) (stating that the quality of the RNA sample is affected by how the RNA sample was preserved). As implied in the name, "fresh-frozen" tissue is biopsied tissue that is put into liquid nitrogen and frozen immediately following the surgery or the colonoscopy. See id. This type of tissue yields "very good" quality RNA if the RNA is extracted and handled carefully. Id. By contrast, formalin-fixed, paraffin-embedded tissue yields poorer quality RNA because the process of formalin fixation and paraffin embedding degrades the RNA, making it less available for the reverse transcription process that is required before PCR techniques can be applied. See id. at 1947. Because the quality of the RNA differs depending on whether the tissue samples were fresh-frozen or were paraffin-fixed and formalin-embedded, the results of PCR testing obtained from the two types of differently preserved tissue samples should not be compared. Id. at 1947; see also Cedillo R's Trial Ex. 13 at 5-7 (Dr. Bustin's slides) (showing difference in RNA quality depending on the type of tissue from which the RNA is extracted).

Dr. Ward also emphasized the importance of having standard operating procedures to which laboratory personnel rigorously adhere to ensure that the PCR methods yield results that can be confirmed and therefore are reliable. See id. at 1842-1843A. Such standard operating procedures must address how to handle the contamination that can occur in laboratories and how to analyze the PCR results. Id. at 1843A. To avoid "jigger[ing]" the results, the initial machine settings for a PCR assay must not be adjusted during a PCR run. Id. at 1843A. As explained during the Cedillo hearing, a "run" is a single assay during a PCR experiment that can involve 96 wells, which is the number of wells or lanes in the piece of equipment used to conduct PCR. Id. at 1977A (Dr. Bustin).

Only 90 of those wells are used for samples during a typical run. Id. at 1977A-1977B.

The primers and probes that are used in the PCR reactions must be specific. Id. at 1842 (Dr. Ward). If the primers are not "absolutely specific for the target" that is to be amplified, the PCR reaction can generate "misinformation." Id.

PCR can be used as a research tool and as a diagnostic tool. Id. at 1846 (Dr. Ward). Particularly when using PCR as a diagnostic tool, measures must be taken to ascertain that the product that is amplified during the PCR process is actually the targeted product. See id. at 1846. The use of proper controls, both positive and negative, is important for internal consistency. Id. at 1843A (Dr. Ward); see also id. at 617-619A (Dr. Hepner). Dr. Ward cautioned that primers that give non-specific results in any tissue are suspect in all tissues. See id. at 1858A. To ensure that what is being amplified is the targeted material, experts for both parties in the OAP litigation agreed that sequencing is the "gold standard." Id. at 1856A (Dr. Ward); see also id. at 673 (Dr. Hepner noting that "[f]or [PCR] specificity, . . . the gold standard would be to sequence . . . the results"); id. at 1942A (Dr. Bustin explaining that "getting a DNA sequence" (or sequencing) is the "best way" to confirm that the obtained test results are the target product); see Snyder Tr. at 847-848A (Dr. Rima explaining that sequencing is distinguishable from allelic discrimination, which involves testing for chromosomal mutations in genetic sequences (or alleles)). Sequencing is the process of confirming that the obtained product through PCR techniques contains the proper nucleotide composition for the targeted product. See Dorland's at 1683.

e. Published Articles addressing Reported Findings of Persistent Measles Virus in Autistic Children

Following the publication of Dr. Wakefield's article in 1998 purporting to link the MMR vaccine to autistic disorders, two additional articles were published that reported findings of persistent measles virus in tissue samples taken from autistic children. Of note, Dr. Wakefield was listed among the named authors of the two additional articles.

As reported in the 2000 Kawashima article, investigators used nested PCR assays to detect the presence of measles genomic material in the peripheral blood mononuclear cells (PBMC) taken from three of nine patients with autistic enterocolitis. Cedillo Ex. BB55 at 723, 726 (2000 Kawashima article). The investigators stated that they had confirmed the persistence of both measles vaccine virus and wild-type measles virus (described as "sporadic") in peripheral blood in some patients with chronic intestinal inflammation. Id. at 727-728.

As reported in the 2002 Uhlmann article, the investigators used in situ PCR and real-time in situ PCR to examine the ileal biopsies of 91 children with autism spectrum disorder and gastrointestinal complaints, and 70 children without autism spectrum disorder as controls. Cedillo Ex. BB95 at 87 (2002 Uhlmann article). The investigators reported the detection by real-time PCR of measles virus genomic material in 75 of the 91 ASD children but only five of the 70 controls. Id. The investigators also reported that by in situ RT-PCR, 42 of the 57 ileal biopsies from the ASD children were positive for measles while only one of five of the controls was positive. Id. Similar findings also were

reported in a less detailed manuscript authored by the same investigators named in the 2002 Uhlmann article. See Cedillo Ex. BB67 (2002 Martin article[231]). Of note, the lead investigator, Dr. Uhlmann was a post-doctoral student in Dr. O'Leary's laboratory. See Cedillo Tr. at 1938A (Dr. Bustin); Cedillo Ex. BB95 at 89 (2002 Uhlmann article).

In 2004, however, 10 of Dr. Wakefield's 12 co-authors on the 1998 Wakefield article published in the Lancet issued a retraction of the findings set forth in that article.[232] The co-authors of the article who issued the retraction explained that "[t]he main thrust of [the 1998 Wakefield article] was the first description of an unexpected intestinal lesion in the children reported." Cedillo Ex. P114 at 750 (2004 Lancet commentary). Stating that further studies had been conducted "to support and extend the[] [reported] findings" and that "much uncertainty remains about the nature of the[] [discovered intestinal] changes, the co-authors expressed their desire "to make it clear that in [the 1998 Wakefield paper] no causal link was established between MMR vaccine and autism as the data were insufficient." Id. (emphasis added). Aware of the "major implications for public health" that resulted from their prior interpretation as evidence of a possible causal link between the MMR vaccine and autism, the authors decided to "formally retract the interpretation placed upon these findings in the paper, according to precedent." Id.

Additional studies were conducted thereafter by different investigators. But, subsequent efforts to replicate the findings reported in the 2000 Kawashima article, the 2002 Martin article, and the 2002 Uhlmann article were not successful. See Cedillo Ex. BB4 (2006 Afzal article[233]); Cedillo Ex. BB30 (2006 D'Souza article[234]). As stated in the 2006 Afzal article, the investigators designed a study, using blood samples of children with confirmed autism diagnoses and MMR vaccination histories, for the purpose of replicating the methodology used in the 2002 Uhlmann article about gut biopsies. Cedillo Ex. BB4 at 629 (2006 Afzal article). The investigators noted that the high detection level reported in the 2002 Uhlmann article reported for measles virus genome sequences "is not achieved often with conventional molecular diagnostic methods applied routinely in public health laboratories to acute measles infections." Id. at 623 (emphasis added). The investigators therefore sought to examine whether "the high positivity reported [in the 2002 Uhlmann article] was due to the high sensitivity of the method used or [was due to] .

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[231] C. M. Martin et al., Detection of measles virus in children with ileo-colonic lymphoid nodular hyperplasia, enterocolitis and developmental disorder, Mol. Psychiatry 7 Suppl 2: S47-48 (2002).

[232] The title of that article is "Ileal-Lymphoidnodular Hyperplasia, Non-Specific Colitis, and Pervasive Developmental Disorder in Children."

[233] M. A. Afzal et al., Absence of detectable measles virus genome sequence in blood of autistic children who have had their MMR vaccination during the routine childhood immunization schedule of UK, J. Med. Virol. 78(5): 623-630 (May 2006).

[234] Y. D'Souza et al., No evidence of persisting measles virus in peripheral blood mononuclear cells from children with autism spectrum disorder, www.pediatrics.org/cgi/doi/10.1542/peds.2006-1242.

. . cross-contamination of samples and/or false positive scoring." Id. The investigators described the primers and probes used and the PCR techniques used in the experiment. See id. at 624-627. The investigators found that their study "failed to verify the finding of previous studies that predicted persistence of measles virus in autistic children with development regression." Id. at 630. Instead, the investigators found that the "children examined in th[e] study responded positively to MMR vaccine and developed a normal immune response to the measles component of the vaccine." Id.

As reflected in the published 2006 D'Souza article and as described during Dr. Ward's testimony at the Cedillo hearing, Dr. Ward's lab made an effort to replicate the Uhlmann results by getting data that would be informative on the question of whether the measles virus can persist in the tissues of autistic spectrum disorder children. Cedillo Tr. at 1848 (Dr. Ward). But, Dr. Ward and his fellow investigators were unable to replicate aspects of the findings reported in either the 2002 Uhlmann article, specifically the reported finding of detectable measles in gut biopsies, or the 2000 Kawashima article, specifically the reported finding of detectable measles in the peripheral blood mononuclear cells. Id. at 1848, 1903A.

Like the study performed by Dr. Afzal, Dr. Ward's study (which was published as the 2006 D'Souza article, see Cedillo Ex. BB30) targeted peripheral blood mononuclear cells (PBMCs) rather than the gastrointestinal tissue studied by Uhlmann. See Cedillo Ex. BB4 (2006 Afzal article) (examining leukocytes, a type of peripheral mononuclear blood cell, because "[i]t was difficult to obtain ethical permission for the collection of gut biopsies and CSF from the patients studied here, as collection would involve highly invasive procedures."). Advised that endoscopies are rarely necessary medically for autistic children who have gastrointestinal complaints, Dr. Ward declined to obtain samples of gastrointestinal tissue for testing. See Cedillo Tr. at 1899A-1901A. Compared to the examined control population, twice the number of the autistic children from whom peripheral blood mononuclear cells were taken had reported gastrointestinal problems. See id. at 1901A. But Dr. Ward clarified that the "bar" for gastrointestinal complaints was "very low" and included complaints of modest constipation and abdominal discomfort. Id. The reported gastrointestinal complaints did not satisfy the medical criteria for performing endoscopic procedures. Id.; see also Hazlehurst Tr. at 627A (Dr. MacDonald stating that it is "unethical to [perform an] endoscopy on children with autism whose primary problem is constipation").

Dr. Ward explained that peripheral blood mononuclear cells (PBMCs) are what is "left over when you take out the red blood cells, platelets, and the neutrophils from the peripheral blood." Cedillo Tr. at 1848 (Dr. Ward). PBMCs are composed primarily of macrophages, dendritic cells, and lymphocytes. Id. The hypothesis underlying Dr. Ward's experiment was that if measles virus is replicating in the gut and causing inflammation, then white blood cells or immune cells must be summoned to the gut to "deal with the inflammation." Id. at 1849. The immune cells that are summoned to the gut are "fully susceptible to" the measles infection. Id. at 1849-1850. The summoned immune cells do not remain in the gut, however, but move through the body carrying replicating measles virus and encountering peripheral blood cells. See id. at 1850. The encountered peripheral blood cells, therefore, should make an adequate tissue to test for the presence of measles virus. Id. at 1850.

Using the Uhlmann primers for the F, H, and N genes of the measles virus, and the Kawashima primers, and primers developed in Dr. Ward's lab for the F-gene, Dr. Ward's lab tried to identify measles virus material in the blood cells of children with inflammatory bowel disease. See id. at 1859A-1860A. The lab obtained a lot of positive results from the applied PCR technique. Id. at 1860. The positive results appeared to have been confirmed by the appropriate melt curve analysis and by the correct gel size on electrophoresis. Id. But when the material was sequenced, the material was determined to be human genetic material rather than viral genetic material. Id. While some of the detected genes were similar to the human genes found in children with autism, others were different from the human genes found in children with autism. Id. As described in the article detailing this study, Dr. Ward and his colleagues found no evidence of persisting measles virus in the peripheral blood mononuclear cells taken from children with autism spectrum disorder. See Cedillo Ex. BB30 at 1671-1674 (2006 D'Souza article).

Dr. Ward explained that sequencing is the "gold standard" in PCR. Cedillo Tr. at 1853A. When developing a PCR test, a researcher first develops primers that are "perfectly homologous" or identical to the unique protein sequence of the targeted product, such as the measles virus. Id. at 1854-1855. The researcher must also generate sequencing information. Id. at 1856A. Sequencing is the only way to be certain that the amplified material is the targeted material. Id. at 1853A. To Dr. Ward's knowledge, Dr. Uhlmann has never published any sequencing information in connection with the 2002 Uhlmann article. Id. at 1857A.

The findings of persisting measles virus reported in these articles were obtained through various forms of PCR. In part, the criticisms in the medical literature of the reported positive findings (and, as set forth in the next discussion section, the criticisms by respondent's experts in the OAP litigation of the reported positive findings) are based on the inability of other research laboratories to replicate the reported findings. As the investigators observed in the 2006 D'Souza article:

> The alleged link between measles/MMR vaccination and development of autism in children has been controversial for a number of years. The laboratory studies which reported the persistence of measles virus in autism cases were either carried out by a single study group or through collaborations where all investigators used clinical samples from a single laboratory source. The findings have not been verified independently by any other study groups using assays reported to detect measles virus in autism cases with gut related complications.

Cedillo Ex. BB4 at 629 (2006 Afzal article).

f. Petitioners' Reliance on the Reported Findings of Measles Virus Persisting in the Tissues of Autistic Children

Relying on the published 2002 Uhlmann article, petitioners' expert Dr. Kennedy stated that the detection of the measles virus in gut tissue (particularly the presence of the H and F genes, which are proteins that occur after the N, P, and M genes in the measles

protein sequence) is evidence that supports a finding that the measles virus is persisting and replicating in the intestinal tissue in autistic children who have certain gastrointestinal difficulties, the type of children described in the 2002 Uhlman article as having autistic enterocolitis. See Cedillo Tr. at 736-738A, 743A.

Petitioners' expert Dr. Hepner also expressed confidence in the findings reported in the 2002 Uhlmann article. She testified that the results reported in the 2002 Uhlmann paper were both valid and reliable. See Cedillo Tr. at 616A-617, 639. She based her opinion regarding the validity of the results on the design of the experiments and the manner in which the experiments were conducted. Id. at 616A-617, 639. She explained that, as an initial matter, the PCR-based techniques were the appropriate experiments to run to detect measles RNA. See id. Moreover, she asserted, the experiments were conducted properly. See id. at 616A-619A, 639.

Proper conduct of PCR-based techniques involves the use of controls. See id. at 617-619A. There are two categories of controls. Id. at 618A. The first level of control includes both positive and negative controls. See id. at 618A-619A. A positive control is a sample that contains the measles virus. Id. at 618A. The sample must be positive every time the experiment is run. Id. at 618A-619A. If the positive control is negative, there is a flaw in the experimental design, and no information can be obtained. Id. at 618A-619A. A negative control (also referred to as a "no-template control") is a sample in which measles virus is not present. Id. at 619A. The sample must be negative every time the experiment is run. See id. If the negative control is positive, there is either a flaw in the experimental design (such as a primer that is not sufficiently specific to the desired target) or cross-contamination between the negative control and the measles virus. Id. The negative samples within the experiment function as a control for contamination. Id. at 621A. Dr. Hepner testified that when the controls do not function true to designation, confidence in the results obtained from the experiments diminishes. See id. at 654.

The second level of control includes the experimental subjects and the normal controls. Id. at 619A-620A. In the Uhlmann paper, the experimental group consisted of the ASD patients with idiopathic bowel disease. See id. The control group consisted of developmentally normal children who had received endoscopies and bowel biopsies. Id. at 620A. By design, the control group has to be similar to the experimental group but has to differ by the variable of interest. Id. at 620A.

In running an experiment, the investigator must run all four controls (the positive, negative, experimental and control samples) at the same time. Id. at 620A, 677. The controls must be run every time an experiment is conducted. Id. at 627. "That is standard laboratory practice." Id. at 621A.

Dr. Hepner opined that because both the positive and the negative controls acted "true to designation" during the Uhlmann experiments, she has a level of confidence that the experiments were working properly. Id. at 623A. Moreover, the use of the Southern blot technique to confirm the specificity of the targeted genes that were amplified,

specifically the F and H genes of the measles virus virion,[235] enhanced Dr. Hepner's confidence that the results of the experiments were valid. Id. at 624A-625A. Finally, the use of the TaqMan PCR technique further increased Dr. Hepner's confidence in the results from the Uhlmann experiments. See id. at 625A-627A. As part of the TaqMan PCR, Dr. Uhlmann and his colleagues used multiple primers and probes to make sure that the obtained results were not caused by "some sort of technical flaw." Id. at 626A. But, Dr. Hepner acknowledged that as reported in the published article, the results in Uhlmann were not confirmed by immunohistochemistry. Id. at 652A. She also acknowledged that the data for each of the controls that Uhlmann used in the 2002 study were not presented in the study. Id. at 653.

Dr. Hepner noted that the principal criticism of the 2002 Uhlmann article is the inability of other labs to reproduce the findings. Id. at 628. But, she explained that with any attempt to reproduce a study, all of the variables of that study must be reproduced. Id. at 629A. Changes in the design of the experiment can affect the results of the experiment. Id. at 669.

Dr. Hepner specifically addressed the 2006 Afzal and the 2006 D'Souza studies that were unable to replicate the Uhlmann findings. She stated that in the Afzal study, the investigators "neglected to use the same starting material," using peripheral blood mononuclear cells instead of gastrointestinal biopsy tissue. Id. at 629A. She added that the study was not "restricted to ASD patients with GI disease" but included patients with "just ASD[s]" Id. By testing the peripheral blood cells, Dr. Hepner asserts, the investigators were testing a different hypothesis than the Uhlmann group, and the results of the Afzal group's study indicate that either measles virus is not in the blood cells or measles virus is there but at undetectable levels. Id. at 630A. Additionally, Dr. Hepner viewed the use of primers that were different from the Uhlmann primers as a design flaw in the Afzal experiment. Id. at 643.

Dr. Hepner observed that similar to the Afzal study, the D'Souza study used peripheral blood mononuclear cells rather than gut biopsies, and the population of interest was not restricted to ASD patients with bowel disease. Id. at 629A. Rather, the population of interest was ASD patients. Id. at 631. Dr. Hepner noted that in the D'Souza study, the investigators were able to amplify measles virus successfully from the positive control cDNA using the primers that were used in the Uhlmann paper. Id. She stated that the successful amplification of measles virus from the positive control indicated that the primer was specific for measles virus, and she attributed the inability to detect measles virus in the experimental samples directly to the selection of experimental samples that were not restricted to ASD patients with gastrointestinal disease, a selection that she viewed as flawed. Id. In the D'Souza study, the investigators found that the amplified material in the peripheral blood was not measles virus. Id. at 645. And Dr. Hepner acknowledged during her testimony that if measles virus were present in the body, it could also be in the blood. Id. at 647.

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[235] A virion is a complete virus that is able to survive and infect a living cell. Dorland's at 2041.

Dr. Hepner added that the failure to detect measles virus in studies seeking to replicate the Uhlmann findings may be attributable in part to the variability in detection limits between different laboratories. In support of her position, Dr. Hepner pointed to another Afzal study that was a collaborative effort between seven different laboratories that were looking for measles virus in the same set of samples. Id. at 632A (citing Cedillo Ex. 63B (2003 Afzal article[236])). Some of the samples were positive while others were negative. Id. at 633. The samples of interest were divided into seven batches which were sent to seven laboratories that were blind to the nature of the sample. Id. at 632A-632B. The laboratories easily detected the RNA in samples that had high levels of measles virus. Id. at 633. There was, however, "about a thousand-fold difference in the detection threshold" for samples with low levels of RNA. Id. Dr. Hepner opined that the differences in detection thresholds between the laboratories may be due to "differences in . . . the people who are conducting the study and . . . a difference in reagents and technical design" of the experiments. Id. at 633. Based on the difference in detection limits between different laboratories that was exposed in the 2003 Afzal study, Dr. Hepner reasoned that the failure to replicate the Uhlmann findings in subsequent studies did not diminish the validity of the Uhlmann results. See id. at 634A.

In addition to recognizing the differences between laboratories in detection thresholds, Dr. Hepner recognized the difficulties associated with interpreting PCR results that hover around the detection limit of a particular laboratory. Id. at 672. She stated that if the obtained results "hover[] around [the] detection threshold" and the material of interest in the tested sample is "in low abundance," repeated runs of a PCR experiment may yield results that are alternately positive and negative. See id. In such circumstances, Dr. Hepner cautioned against interpreting the results as positive. Id. She testified that such results would prompt an investigator to examine how the experiment is being run and to run the experiment again. Id. at 672-673.

Dr. Hepner identified other factors that could affect the reliability of PCR-obtained results. Such factors include the specificity and sensitivity of the primers used in the experiments and any contamination of the experiment. Id. at 670. She stated that inconsistent outcomes for the positive controls and the negative controls affect the interpretability of the results and would cast doubt on the reliability of the obtained experimental results. Id. at 671.

Special masters routinely rely on the published findings of laboratories. However, evidence presented during the hearings in the test cases called into question the reliability of these particular laboratory findings of measles virus persistence in the gastrointestinal tissues of autistic patients. The evidence that raises questions about the reliability of the published findings pertaining to persisting measles virus requires closer examination.

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[236] M. A. Afzal et al., Comparative evaluation of measles virus specific RT-PCR methods through an international collaborative study, J. Med. Virol. 70: 171–176 (2003).

g. Examining the Reliability of the Published Articles concerning Measles Virus Persistence

Respondent's experts challenged the reliability of the series of Wakefield articles as well as the 2000 Kawashima article and the 2002 Uhlmann article (as well as the less detailed 2002 Martin article) on which petitioners relied. Respondent offered the expert testimony of experts, Dr. Bustin and Dr. Griffin, and the fact testimony of Nicholas Chadwick, Ph.D, a post-doctoral research assistant, to address the flawed testing methods that underlay the reported findings.

During the Cedillo hearing, respondent's expert Dr. Chadwick testified about his experience as a doctoral student working in Dr. Wakefield's laboratory at the time that the lab began testing tissue samples from autistic patients.[237] Dr. Chadwick was present as the endoscopies were performed on the subject children, and "his role was to take the [collected] material . . . to the lab[,] process it by extract[ing] RNA[,] and then look for evidence of measles virus." Cedillo Tr. at 2284. Using PCR techniques, he personally tested the gut biopsy samples, the cerebral spinal fluid samples, and the peripheral blood mononuclear cell samples obtained from autistic children. Id. at 2284-2286. He sequenced the products from the PCR tests to identify the source of the amplified products. Id. at 2285. Dr. Chadwick testified that of the sequenced products, none of the products "match[ed] up with" any known wild-type measles virus or vaccine strain measles virus. Id. Rather, each sequenced product from the PCR testing was "in every case . . . a lab strain [measles] virus." Id. Of the nine positive PCR results he obtained for measles, Dr. Chadwick stated that after sequencing, "all" of the positive test results were "false positives." Id. at 2288. According to Dr. Chadwick, he informed Dr. Wakefield of the negative PCR test results. Id. at 2286.

Dr. Chadwick also sent coded and randomized samples in test tubes to the lab of Dr. Kawashima for PCR testing. Id. Based on Dr. Chadwick's coding of the samples, Dr. Kawashima did not know which samples he was testing. Id. at 2286-2287. Dr. Chadwick explained that "some of the samples . . . sent over [to the Kawashima lab] . . . [were] duplicate samples so if one of them was to come up positive[,] then we would expect the other sample to come up positive as well." Id. at 2287. But, "[i]n every case where [Dr. Kawashima] did have a positive result[,] the duplicate didn't match that, which led . . . me

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[237] Dr. Chadwick is currently a postdoctoral research associate at the University of Manchester in England. Cedillo Ex. QQ at 1 (Dr. Chadwick's report). He obtained his doctorate in 1998 under the supervision of Dr. Andrew Wakefield at the Royal Free Hospital School of Medicine, Faculty of Medicine, University of London. Id. He began working in Dr. Wakefield's laboratory in 1994, and he continued to work there when the laboratory began testing biopsied gastrointestinal tissues, cerebral spinal fluid samples, and peripheral mononuclear blood cell samples of autistic children. Cedillo Tr. at 2283, 2285. Dr. Chadwick personally ran experiments and conducted testing to detect the presence of the vaccine strain of the measles virus while in Dr. Wakefield's laboratory. See id. at 2285-2286. Dr. Chadwick testified by telephone during the Cedillo hearing. Dr. Chadwick testified credibly.

to question [Dr. Kawashima's test] results." Id. Again, Dr. Chadwick informed Dr. Wakefield of the problems with the results, which in this instance had been obtained in the Kawashima lab. Id.

During his time in Dr. Wakefield's lab, Dr. Chadwick also expressed reservations about the immunohistochemistry testing done to detect measles virus. Id. at 2288. Dr. Chadwick's concern was that the antibody used in the testing appeared to cross-react with bacterial proteins that may have been present in the gastrointestinal systems of the biopsied patients rather than reacting to the presence of measles virus. Id. at 2288-2289A. Such a cross-reaction would skew the results of the test.

Dr. Chadwick testified that based on his own work in the lab, he believes that Dr. Wakefield was aware of the negative test results when he submitted the paper that was published as the 1998 Wakefield article. Id. at 2289A. Dr. Chadwick explained that because none of his data appeared in the 1998 Wakefield article, his name did not appear. Id. Moreover, Dr. Chadwick testified that he asked to have his name removed from any publication by the Kawashima lab addressing PCR testing results because Dr. Chadwick was not comfortable with the quality of the PCR-obtained data. Id. at 2290A. Dr. Chadwick's work experience did not extend to the Unigenetics lab. Id. at 2292-2293.

Respondent's expert Dr. Griffin offered additional criticism of the reported findings in the Uhlmann article. She testified that the biggest problem with the results presented in the Uhlmann paper is that the investigators did not "do [a] sequencing of their product." Id. at 2835A. Such sequencing is the only way to detect whether the amplified viral material is the vaccine strain or is the wild-type virus due to contamination. See id. at 2836. Dr. Griffin testified that the presence of RNA alone is insufficient to indicate that viral protein is being made. Id. at 2830A-2831. She explained that RNA can either make protein or not depending on what type of RNA it is. Id. at 2831. What indicates that the RNA is coding for viral protein is the presence of B cells, which are the components of the antibody response. See id. at 2824-2831; see also Cedillo Ex. V64 (1992 Thyor article[238]) (addressing the sindbis virus, which, unlike the measles virus, infects the neuronal cells in the brain, a cell type that is not replaced once it is destroyed). Although Dr. Griffin's testimony was entirely consistent with the testimony of the other witnesses regarding the importance of sequencing, she stated that she is not an expert on PCR. Cedillo Tr. at 2835B.

Respondent's expert Dr. Bustin also offered testimony regarding the reliability of the articles on which petitioners rely for the concept of measles virus persistence. Dr. Bustin explained in his testimony during the Cedillo hearing that Dr. Uhlmann, who was one of the authors of the 2002 Uhlmann article on which petitioners rely, was a postdoctoral student in Dr. O'Leary's laboratory and the methods used for PCR testing in the 2002 Uhlmann article "would have been used on the [PCR] testing carried out . . . at the Unigenetics laboratory." Cedillo Tr. at 1938A. Dr. Bustin stated that the 2002

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[238] W. Thyor et al., Long term parenchymal Ig secretion after acute viral encephalitis in mice, J. Immunol. 149(12): 4016-4020 (1992).

Uhlmann article provided "very little information about how the assay was performed, [and] about what the results actually were." Id. at 1940. Moreover, the 2002 Uhlmann article does not allow for an evaluation of "how reliable and consistent the results are." Id. There is no discussion in the article about how the RNA was handled. Id. at 1945A. There is no information about which samples and controls were fresh-frozen and which were formalin-fixed paraffin-embedded. See id. at 1947A-1948A. Although there is information about which genes were targeted in the Uhlmann experiments, specifically the F, H, and N genes in the measles virus, the Uhlmann paper does not distinguish what results were obtained from the PCR testing. See id. at 1950A.

Petitioners have relied heavily on the findings of persisting measles virus in the tissue samples of autistic children that were reported in the published 2000 Kawashima article, the 2002 Uhlmann article, and the 2002 Martin article (that was authored by the Uhlmann authors but contained less detail). The chief criticisms of those reported findings by respondent's experts and in the scientific literature are consistent and twofold. First, the reported positive findings of measles virus have not been replicated by laboratories independent of Dr. Wakefield and his colleagues. See Cedillo Ex. B30 (1996 D'Souza article); Cedillo Ex. BB4 (1996 Afzal article). Second, the published articles on which petitioners rely do not include sufficient laboratory data to evaluate the conducted testing procedures and the validity of the test results. The dearth of reported laboratory data in the published articles impairs the scientific community's ability to scrutinize the reported findings for methodological errors. See Daubert, 509 U.S. at 592-594. And failed efforts to replicate the reported findings diminish the confidence of the scientific community in the validity of the reported findings. See id. The evidence before the undersigned indicates that the positive measles findings reported in the published articles on which petitioners rely are unlikely to be scientifically sound or reliable.

h. Petitioners' Reliance on Unpublished Findings concerning Measles Virus Persistence

I. The Preliminary Findings of the Walker Study

Petitioners also rely on unpublished findings of measles virus in tested bowel tissues taken from autistic children as support for their claim regarding measles persistence. Petitioners' expert Dr. Hepner expressed the opinion that the published 2002 Uhlmann findings are "reliable," see Cedillo Tr. at 639, and her confidence in the reported positive findings of measles virus is bolstered by the preliminary findings of a study on which she is working. Dr. Hepner discussed her current work with a team of investigators in the laboratory of Dr. Stephen Walker at Wake Forest University in Winston-Salem, North Carolina. Dr. Hepner described the project as a study "to create a highly reproducible, highly sensitive, very specific . . . experimental design to detect [measles virus] RNA in the bowel biopsies of ASD patients." Id. at 634A-635A. She stated that the preliminary findings of the study, which were presented as an abstract at the June 2006 International Meeting for Autism Research (IMFAR), confirm the presence of vaccine strain measles virus in some of the bowel biopsies that were tested. Id. at 635.

Dr. Hepner stated that while positive controls (specifically "an artificial laboratory

construct" of wild-type measles virus) have been run in each experimental run in the study, no negative controls have been run to date because the investigators are still looking for suitable negative controls. Id. at 658, 663, 674-675. The experimental controls are patients who do not have ASDs but have gastrointestinal symptoms. Id. at 675. The experimental group includes ASD patients who have "[inflammatory bowel disease]-like symptoms, but not all of whom have received the MMR vaccine." Id. at 676. She described the preliminary results of the experiments as "a technical achievement" because the investigators "believe that they have developed some assays to detect [measles virus] in this cohort of patients in biopsied tissue that is vaccine strain specific." Id. at 682. But Dr. Hepner declined to "draw any conclusions about the biological significance" of the investigators' findings. Id.

However, respondent's expert Dr. Bustin expressed some concern about the preliminary PCR results reported in the Walker abstract presented at the IMFAR conference and discussed in Dr. Hepner's testimony. Dr. Bustin's chief concern after reviewing the slides from the poster presentation is that there is evidence from the location of the bands in the experimental gel that the obtained results are not specific for the intended target. See id. at 1955A-1958A. Because the experiment did not include a negative control, a proper determination of what the observed bands show cannot be made. See id. at 1958. In the absence of both positive and negative controls during a PCR run, Dr. Bustin stated that he "[could not] have any confidence" in the test results. Id. at 1959A.

The testimony during the Cedillo hearing of the parties' experts, Dr. Hepner for petitioners and Dr. Bustin and Dr. Ward for respondent, made clear that standard laboratory practice requires that positive samples (that always contain the targeted material), negative samples (that never contain the targeted material), experimental samples (the subjects with an exposure of interest tested for the presence of the targeted material), and control samples (the subjects without the exposure of interest tested for the presence of the targeted material) are run during each experiment. See Cedillo Tr. at 620A, 621A, 627A, 677 (Dr. Hepner); id. at 1842 (Dr. Ward); id. at 1959A (Dr. Bustin). The use of the positive and negative controls provides information about the internal consistency of the experiments. Informed that test results without the use of these controls during PCR experiments may not be reliable, the undersigned cannot place much weight on the preliminary findings of Walker study (addressed by petitioners' experts Drs. Corbier, Hepner, and Krigsman), specifically the alleged findings of vaccine-strain measles virus in some of the bowel biopsies that were tested.

ii. Test Results Obtained from the Unigenetics Laboratory

Petitioners have relied, in part, on the findings of the Unigenetics laboratory to support the aspect of their general causation theory that measles virus persists in the tissues of some children who have received the MMR vaccine. Petitioners' reliance on the findings of the Unigenetics laboratory is based on the positive test results obtained from Unigenetics indicating the presence of measles virus in the gastrointestinal tissues of some of the children involved in the OAP litigation. As petitioners' expert virologist Dr. Kennedy testified during the Cedillo hearing, his opinion about the likelihood of the

vaccine strain of the measles virus persisting in a vaccinee was bolstered by the reported detection by the Unigenetics Laboratory of the vaccine strain of the measles virus in the gut tissue and in the cerebrospinal fluid of some autistic children. Cedillo Tr. at 817. Moreover, as petitioners' expert neurologist Dr. Kinsbourne testified during the Cedillo hearing, his opinion depended upon the reported positive findings of measles virus in the tissue samples obtained from autistic children. Id. at 1179.

Several of respondent's witnesses, however, expressed concerns in the OAP litigation about the reliability of the test results produced by the Unigenetics laboratory. Because petitioners have relied on the Unigenetics' findings and because the reliability of the results of laboratory tests performed by Unigenetics has been challenged in this case, the undersigned must consider, with more scrutiny than generally occurs in vaccine proceedings, the reported test results and the laboratory practices of that particular laboratory. See 42 U.S.C. § 300aa-13(b)(1) (providing that no test result is binding on a special master and directing the special master to consider the record as a whole).

Located in Ireland, the Unigenetics laboratory was a for-profit entity that was operated by molecular biologists, Dr. John O'Leary and Dr. Orla Shiels. See Cedillo Tr. at 808, 811A-813 (Dr. Kennedy); see also id. at 738A (Dr. Hepner). The two, who were also colleagues at Trinity College, operated the Unigenetics lab to support the litigation in the United Kingdom examining whether there exists a causal connection between the MMR vaccine and autism. See Cedillo Tr. at 812, 856 (Dr. Kennedy). Additionally, tissue samples from children who are involved in the OAP litigation currently pending before the Office of Special Masters were sent to the Unigenetics laboratory for testing. In 2002, the Unigenetics lab was the only laboratory performing PCR testing for the presence of measles virus.[239] See Snyder Tr. at 927A-928A (respondent's expert Dr. Rima explaining that the work of Dr. O'Leary's lab was singular because there was no confidence in the scientific community that the technology he employed was doing what Dr. O'Leary claimed it was doing). The lab was never accredited and declined to participate in a quality control program in which various laboratories in Europe and the United States participated. Cedillo Tr. at 2034 (Dr. Bustin). After the discontinuation of the action brought by claimants in the United Kingdom alleging that the MMR vaccine caused autism, however, and without an ongoing source of support, the Unigenetics lab ceased to exist. See Cedillo Tr. at 855-856 (Dr. Kennedy).

Petitioners offered the expert testimony of Dr. Kennedy to address the reliability of the methods employed by the Unigenetics lab. Dr. Kennedy testified that he was invited to attend a meeting that was arranged by the lawyers for the claimants in the United Kingdom litigation. Cedillo Tr. at 810. That meeting took place in late 2001 or early 2002. Cedillo Tr. at 809. Dr. Kennedy received his invitation from a professor of microbiology and immunology at the University of Arizona, namely Dr. John Marchulonis, who was

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[239] Dr. Rima indicated that when the tissue samples from Michelle Cedillo and Colten Snyder, the children of interest in the two other test cases, were sent to Unigenetics for PCR testing for measles virus, Unigenetics was the only lab performing that type of testing. See Snyder Tr. at 927A. The undersigned understood Dr. Rima to mean that Unigenetics was the only lab using PCR for diagnostic testing.

working with the solicitors and barristers (the British lawyers) for the claimants in the United Kingdom litigation. Cedillo Tr. at 810. The purpose of the meeting was to evaluate the data gathered by the Unigenetics lab. Cedillo Tr. at 809. After the meeting, Dr. Kennedy met with the litigators who subsequently retained him as an expert witness for the claimants. Cedillo Tr. at 809-810.

Dr. Kennedy described a four-to five-hour meeting with Dr. Shiels at Unigenetics that Dr. Kennedy attended with a select group of others that included: (1) a pediatrician and two molecular biology experts from Ireland, (2) Dr. Richard Tedder, a professor of clinical virology in the United Kingdom, (3) Dr. Stephen Jacobson, a branch chief at the National Institutes of Neurologic Disorders and Stroke, and (4) Dr. Marchulonis, who had extended the invitation to Dr. Kennedy to participate in the meeting. See Cedillo Tr. at 844-845. Dr. O'Leary was not present physically for the meeting but was later available for a teleconference. Cedillo Tr. at 810-811.

The attendees at the meeting with Dr. Shiels were provided with protocols and other information about Unigenetics' operation as well as the test results that the lab had obtained. Cedillo Tr. at 813-815. Although the attendees did not see the physical layout of the lab, the attendees talked with Dr. Shiels about the lab layout, the lab equipment, the manner of preparing the tested samples, the specificity of the primers used in connection with the testing, and the procedure for addressing contamination. See Cedillo Tr. at 814-815.

Dr. Kennedy identified a number of standard practices that a lab should observe when conducting experiments using PCR. He testified that the lab must develop first a standard operating procedure to which the lab would adhere. Cedillo Tr. at 818. All the samples should be run at the same time with both a positive control and a negative control. Cedillo Tr. at 821A. There should be a standard curve that defines the range within which the tested samples are expected to fall. See Cedillo Tr. at 821A (Dr. Kennedy); accord id. at 1988-1993 (Dr. Bustin describing the procedure for generating a standard curve). The test results for a negative test should be consistently negative. Cedillo Tr. at 823. When performing quantitative PCR, multiple primer pairs should be used, and when a sample tests positive, sequencing should be performed to verify that the sample contains the product for which the lab is testing. See Cedillo Tr. at 824A.

Dr. Kennedy identified some of the concerns that the attendees raised at the meeting. One of the identified issues was the lab's practice of "pushing the sensitivity" of the PCR equipment at the very low end by using a non-standard cycle number to determine whether a sample was positive or negative. See Cedillo Tr. at 816A, 848 (questioning Unigenetics' practice of "stretching the limits of sensitivity of the assay and trying to pick up . . . very low copy numbers"). The attendees also expressed concern about the lab's use of a particular polychronal antibody to detect the measles virus because that antibody may be cross-reacting with the tested samples rather than detecting the measles virus protein. Cedillo Tr. at 853A. Additionally, Dr. Kennedy stated that the attendees inquired about and were provided data that is "standard" in a research paper but was not contained in the 2002 Uhlmann article. See Cedillo Tr. at 815. The 2002 Uhlmann article has been criticized for the omission of standard data pertaining to the conducted experiments. Cedillo Tr. at 825. To date, the missing laboratory data that was provided to the meeting

attendees has not been published. Cedillo Tr. at 825-827.

Asked to address the significance of a test result obtained from the Unigenetics laboratory that reflected a copy number for vaccine strain measles virus that was higher than the detected copy number for a natural measles infection during the peak time of an infection, Dr. Kennedy expressed no concern about the validity of the test result. See Cedillo Tr. at 828A-831. He attributed the high copy number to "a lot of inflammation" in the tissue sample. Cedillo Tr. at 830. He stated that the copy number did not necessarily relate to the amount of measles virus present. Id. at 831. Rather, the copy number indicated the presence of protein that was confirmed by the immunohistochemistry of the samples from autistic children with gastrointestinal problems, which had been provided to the Unigenetics lab. See id.

Respondent's experts offered a different view of the test results produced by the Unigenetics lab based on the experts' personal experiences with measles virus, PCR techniques, Dr. Wakefield, or the scientists at the Unigenetics lab. Drs. Griffin, Bustin, and Rima, in particular, offered testimony challenging the reliability of the lab's PCR testing methods.

Dr. Griffin testified that at Dr. Wakefield's invitation in 1998, Dr. Griffin attended an open scientific meeting. Id. at 2862. Dr. Wakefield was "just beginning to implicate MMR as a cause of autism" and the team with whom he was working at the lab "did not have a hypothesis . . . [about] the connection between MMR and measles and autism and were sort of looking for something that would link them." Id. at 2862-2863. She recalled that "the people in the lab . . . [working with Dr. Wakefield] were having a lot of trouble trying to make their PCR work." Id. at 2862. She testified that the Unigenetics lab (operated by Drs. O'Leary and Shiels) did not enjoy a good reputation in the scientific community. Id. at 2866.

Dr. Griffin found the copy numbers reported by the Unigenetics lab as test results to be highly questionable. See id. at 2783. She testified:

> That many copy numbers of a virus in the amount [of] tissue that they looked at would mean that it would have to be an overwhelming infection. It would have to be more virus replicating in that piece of gastrointestinal tissue that was biopsied than is present at the peak of wild-type measles virus infection.

Id. at 2783-2784. She explained that:

> [M]easles pathology is very characteristic. It causes syncytia[,] [(or certain small masses formed by merged cells)[240]][.] [I]t causes inclusion body formation[.] [I]t would cause inflammation. There are a lot of things you would expect to see if you have that much measles virus infection in a piece of tissue. . . . If they had that much virus they ought to be able to easily amplify it from other portions of the genome, not just that one primer set that

[240] See Dorland's at 1808.

> worked. . . . You ought to be able to see it by lots of different ways than just a PCR number.

Id. at 2784 (footnote added); see also Cedillo Ex. V at 8-9 (Dr. Griffin's report); Cedillo Ex. BB at 12 (Dr. Ward's report) (stating that "[i]f measles virus genomic material w[ere] truly present at the[] concentrations in the gut tissues of ASD children] [reported by the Unigenetics lab], one would logically expect to see virtually every cell infected with massive disruption of tissue integrity"). Dr. Griffin opined that the reported copy numbers from the Unigenetics lab "[just weren't] . . . biologically plausible number[s]." Cedillo Tr. at 2783-2784.

Dr. Bustin had an opportunity to examine the testing methods used by the Unigenetics laboratory as part of the United Kingdom litigation. He was approached by the solicitors and barristers representing the pharmaceutical companies involved in the MMR trial in the United Kingdom to serve as an expert witness in the litigation. See id. at 1962A-1963A. As explained to Dr. Bustin, his overriding duty as an expert witness was to assist the court in evaluating the 2002 Uhlmann paper and the documentation submitted from Unigenetics in the litigation. Id. at 1963A. In connection with that litigation, Dr. Bustin was granted physical access twice to the Unigenetics laboratory. Id. at 1964A. During his visits to the laboratory, Dr. Bustin used the instruments and the computers that were used in the laboratory to run PCR experiments and to analyze the test results. See id. at 1964A-1967. Dr. Bustin estimates that he spent approximately 1500 hours analyzing data from the laboratory and reviewing the standard operating procedure for the laboratory, the laboratory notebooks, the operator sheets generated during the laboratory experiments, and the generated reports for the experiments. See id. at 1966A-1968.

Among the findings that Dr. Bustin found troubling was the finding that Unigenetics used different procedures than those set forth in its standard operating procedure. See id. at 1973-1974A. Dr. Bustin explained that the standard operating procedure is a detailed document that describes, among other things, the manner in which an investigator obtains samples for testing, describes the process of preparing the RNA, and describes how the quality of the RNA is assessed. See id. at 1969A. The interpretation of the final data from real-time PCR is a subjective process, see id. at 2017, and having a standard operating procedure and adhering to the detailed procedures is important for a laboratory to ensure consistency in its laboratory procedures and thereby ensure that the results of any performed tests are replicable. See id. at 1969A-1970A. Adherence to the standard operating procedure to ensure the consistency and reproducibility of the obtained results becomes of critical importance when several investigators perform the tests in the laboratory, as was the practice at Unigenetics. Id. at 2024. But contrary to the standard operating procedure in place at Unigenetics, the investigators used different procedures for RNA extractions and used different ways to check the quality of the extracted RNA. Id. at 1974A.

Moreover, in contravention of the laboratory's own standard operating procedure, operators at Unigenetics tested samples containing degraded RNA in which the target gene GAPDH (used to confirm the presence of RNA in the sample) was missing. Id. at 1978A-1979A (Dr. Bustin). The standard operating procedure required that such samples be discarded. Id. at 1979A. Dr. Bustin explained that amplifying the degraded RNA through

PCR would yield results that did not come from RNA material but from DNA material. Id. Dr. Bustin further explained that results obtained from the amplification of DNA material cannot be measles virus because measles virus is not a DNA strand but a RNA strand. Id. at 1979A, 1983A (stating that "measles virus doesn't exist as a DNA molecule"); see also id. at 602A (Dr. Hepner explaining that the genomic material for measles virus is not contained in double-stranded DNA, but rather in single-stranded RNA). In the couple of runs in which Dr. Bustin suspected that a DNA contaminant had been amplified rather than RNA, he determined from examining Unigenetics' own instruments that the reverse transcription step that is necessary to prepare RNA for the application of PCR techniques had been "forgotten" for those particular runs. Id. at 1980A; see also Cedillo R's Trial Ex. 13 at 8 (Dr. Bustin's slides) (showing results of two particular runs from the Unigenetics laboratory). As a possible source of the DNA contamination, Dr. Bustin noted that the room next to the area in which the PCR experiments were conducted was the DNA plasmid room where the target F gene and H gene for the measles virus were cloned to generate lots of DNA for laboratory use. Id. at 2021-2022; see also Snyder Tr. at 853A (respondent's expert Dr. Rima stating that "if you have in your laboratory a large number of plasmids that are of a particular virus, then you have a much greater chance of contamination than if you have the actual virus itself"). These cloned genes assist the investigators in making RNA to develop the standard curves for the PCR experiments. Cedillo Tr. at 2022 (Dr. Bustin).

Dr. Bustin discussed the various instances in which the obtained test results were inconsistent with one another. He pointed to the instances in which one gene in the targeted measles sequence tested positive while another gene in the same sequence tested negative. See id. at 1985A-1986A; see also Cedillo Tr. at 729A (Dr. Kennedy); Cedillo Ps' Trial Ex. 8 at 16 (Dr. Kennedy's slides[241]) (identifying the genetic sequence for measles virus as N, P, M, F, H, L). Specifically, the F gene tested positive and the H gene tested negative. Cedillo Tr. at 1985A (Dr. Bustin). Yet in other instances, the F gene tested negative and the H gene tested positive. See id. Of the primers and probes that Unigenetics designed for the F gene and the H gene of the measles virus, the F-gene assay was less sensitive than the H-gene assay. See id. Although the F-gene assay lacked the sensitivity of the H-gene assay, the operators reported positive findings in the laboratory notebook in instances where the F-gene assay was positive and the more sensitive H-gene assay was negative. Id. at 1985A-1986A. Dr. Bustin explained that instead of reporting positive findings, "they should [have] redesign[ed] the F-gene assay because [they] were looking for concordance." Id. at 1986A.

After determining that a result is positive, an investigator typically refers to the standard curve that he has established for a particular product to quantify the amount of obtained product.[242] See id. at 2064A-2065A. The standard curve permits the investigator

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[241] Dr. Kennedy's trial slides are unnumbered, but the title slide is identified as the first of 22 slides. The undersigned uses that "numbering" convention for citations to the trial slides.

[242] Dr. Bustin described in considerable detail how a standard curve is generated. (continued...)

to quantify the copy numbers of the product, which in this instance is the number of targeted genes in the measles virus sequence. See id. at 1988. Dr. Bustin pointed out that the standard curve generated in the Unigenetics laboratory for the F gene did not permit proper quantification of the amplified PCR product. Id. at 1987A–1995. "[P]roduced using optimal conditions," the standard curve is a type of positive control in the experiments. Id. at 1987A-1988. But the standard curve generated by the Unigenetics lab for the F gene was not sensitive enough to be an effective positive control. Id. at 1994-1995; see also Cedillo R's Trial Ex. 13 at 9-10 (Dr. Bustin's slides). Dr. Bustin observed that the generated standard curves did not comport with standard practice or with best practice. See id. at 1994-1995 (Dr. Bustin). Without a proper standard curve, an investigator cannot have confidence in the apparent copy numbers for a product. See id. at 2064A.

With respect to the negative controls that Unigenetics used in the PCR experiments, "[a]pproximately one-third of the runs had positive results in the negative controls." Id. at 1995. These results suggest that contamination was present because negative controls are designed not to contain any of the target material. Id. at 1995-1996.

In addition to not following the laboratory's own standard operating procedure and not adhering to certain standard laboratory practices, Unigenetics failed to comply with the standards set forth by the manufacturer of the PCR equipment pertaining to the use of the equipment. See id. at 2002-2010A. For example, Unigenetics failed to heed the manufacturer's instruction to exclude from the PCR analysis the first three cycles of amplification, an "ABI-recommended" practice. See id. at 2008-2010A. The failure to comply with the manufacturer's recommended setting for the threshold cycle (which is the number of amplification cycles that is required before the presence of the targeted material, if any, can be detected) affected certain of the test results, changing negative results to what appear to be positive results. See id. at 2009-2010A.

Dr. Bustin testified that generally PCR assays are run in duplicate or triplicate at the same time to verify that the duplicate or triplicate assays are yielding the same results. See id. at 2013-2014. The reproducibility of the results of the experiment is an indication that the obtained results are genuine. Id. Dr. Bustin found that when Unigenetics ran duplicate assays at the same time and obtained discordant results for the F gene, specifically one positive result and one negative result, the test results were reported as positive rather than questioned. See id. at 2013-2015A. Unigenetics did not run the discordant assays again.

Particular efforts were made during the litigation in the United Kingdom to reproduce the positive results that Unigenetics obtained. The claimants in the litigation instructed Professor Finbarr Cotter, who trained as a molecular biologist and currently heads the Experimental Haematology and Functional Genomics laboratories at Barts and

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[242](...continued)
See Cedillo Tr. at 1987A-1995, 2022, 2062A-2064A; see also Cedillo R's Trial Ex. 13 at 10-11 (Dr. Bustin's slides).

the London School of Medicine and Dentistry,[243] to try to reproduce the results obtained by the Unigenetics laboratory. See id. at 2015A (Dr. Bustin); Snyder Tr. at 347A (Dr. Kennedy). Professor Cotter had the same PCR instrument in his laboratory as did Unigenetics. Cedillo Tr. at 2015A (Dr. Bustin). Endeavoring to replicate the Unigenetics results, Professor Cotter extracted RNA from samples that Unigenetics had tested previously, but Professor Cotter did not get the positive results that Unigenetics had. Id. Rather Professor Cotter's results were negative. Id. Professor Cotter reported his findings in the report he prepared for the claimants in the United Kingdom litigation. Id. at 2016.

Among other detected problems at the Unigenetics laboratory, Dr. Bustin stated that he found irregularities in the keeping of at least one set of laboratory notebooks that he had an opportunity to review on two separate occasions. Id. at 2027. In particular, he found additions to the reviewed lab notebook that had occurred between the first and second disclosure of the notebook, a practice that he described as "highly unusual" because the notations in lab notebooks "tend to be sacrosanct" as a record of what happened during an experiment.[244] See id. at 2027-2028.

Based on his review of the laboratory and the underlying data at Unigenetics, Dr. Bustin opined that what was detected by the investigators at the laboratory was DNA

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[243] See http://www.icms.qmul.ac.uk/Profiles/Haematology/Cotter%20Finbarr.htm (Dr. Cotter's biography) (last visited on 2/1/09).

[244] Dr. Bustin described during his testimony at least two other irregularities in Unigenetics' practices. First, he noted that when conducting the Taqman PCR procedure, the investigators did not use the same amount of reference dye for the fluorescent probes from well to well (sample to sample) in the experiment. Cedillo Tr. at 2025A-2026. Such inconsistency is a deviation from the standard operating procedure and introduces variability in the test results that affects the reliability of the results. See id. at 2026.

Second, Dr. Bustin expressed particular suspicion about the high copy numbers (reportedly of the targeted material) obtained as a result of multiple runs (or cycles) of a PCR experiment when, as in Unigenetics' circumstances, contamination is suspected and the generation of standard curve for the experiment is compromised. Id. at 2064A-2067A. A laboratory generates a standard curve by defining how much of a targeted material must be present in a sample to generate a particular copy number after a certain number of experiment runs. Id. at 2062A-2063. The laboratory then uses the standard curve "to quantitate copy numbers." Id. at 2062A. If the standard curve has not been generated properly, however, the measure of copy numbers is not reliable. Id. at 2063-2064A. A properly generated standard curve should define "the linear range of the assay [of interest that] includes all of the possible concentrations of your unknown samples." Id. at 1988. Dr. Bustin pointed to examples from the Unigenetics lab where the purported measles virus concentrations in the tested samples were outside of the range of the defined standard curve. Id. at 1991A-1994. Dr. Bustin explained that what this information "tells you [is] that the assay is working very poorly and that you can place no reliance whatsoever on any quantification of any of these samples." Id. at 1995.

contamination rather than the measles virus. Id. at 2036. Dr. Bustin testified that the discovered problems with the testing methods at Unigenetics diminished the reliability of the obtained test results purporting to find the presence of measles virus in the gastrointestinal tissue of autistic children and in the cerebral spinal fluid of autistic patients. Id. at 2036-2037.

Respondent's expert Dr. Rima also testified about problems with laboratory procedures at Unigenetics based on his experience as an expert witness for the vaccine manufacturers in the MMR/autism litigation in the United Kingdom. See Snyder Tr. at 828-829A. Dr. Rima identified a number of the problems that Dr. Bustin had identified.

The undersigned found the testimony of Drs. Bustin, Rima, and Ward, respondent's experts who addressed the standard practices for conducting PCR experiments, the reportedly positive measles test results obtained through PCR techniques, or the laboratory practices of Unigenetics, to be knowledgeable, consistent, credible, and persuasive. The undersigned further considered that petitioners' experts Dr. Hepner and Dr. Kennedy did not disagree with the testimony of respondent's experts regarding the standard practices for conducting PCR experiments. On the contrary, Dr. Hepner and Dr. Kennedy identified a number of the same practices identified by respondent's experts that would increase the likelihood that the obtained test results are, in fact, what they purport to be. Based on the extensive experience of respondent's witnesses with PCR techniques and the depth of their understanding of the procedures associated with PCR experiments as reflected in the witnesses' testimony, the undersigned gave more weight to the testimony of the respondents' witnesses Drs. Bustin, Rima, and Ward than to petitioners' experts Drs. Hepner and Kennedy on the issue of the reliability of the Unigenetics testing and the reported test results. Based on all of the evidence presented, the undersigned finds that the laboratory practices at Unigenetics differed considerably not only from the standard practices for conducting PCR testing but also differed considerably from the operating procedures established within the laboratory. The expert witnesses for both parties testified that the confidence that can be placed on the test results obtained from a laboratory is reduced considerably when the laboratory fails to follow certain standard operating procedures when conducting sensitive PCR experiments. The published reports of the findings on which petitioners rely in this litigation were conducted at the Unigenetics laboratory or in cooperation with colleagues of either Dr. Wakefield or Dr. O'Leary. Critical details pertaining to the conduct of the PCR experiments in question have never been released publicly. The laboratory practices while conducting the PCR experiments in question were not scientifically sound, and the reported positive findings have not been replicated by researchers unaffiliated with the laboratories of either Dr. Wakefield or Dr. O'Leary. Having carefully considered the record on this subject, the undersigned concludes that the published reports of findings of measles virus in the tissues of autistic children and the positive test results obtained from the Unigenetics laboratory were obtained through flawed laboratory practices and are therefore scientifically unreliable.

5. Petitioners' Claim that the Vaccine-Strain Measles Virus can Cause Inflammation

Testifying on petitioners' behalf, Dr. Kennedy stated that the measles virus can

cause the dysregulation of dendritic cells, suppress T lymphocyte responses, and delay the production of specific antibodies. Cedillo Tr. at 712, 720. He added that after exposure to either the wild-type measles virus or the vaccine strain, the immune system remains dysfunctional for three to six months. Id. at 717A-718, 720 (Dr. Kennedy).

Another of petitioners' experts, Dr. Byers, testified that receipt of the MMR vaccine after a child's immune system has been affected by the mercury in thimerosal-containing vaccines "could" cause the child to have difficulty clearing the measles virus. Id. at 917. In Dr. Byers' view, the affected child's difficulty clearing the measles virus would be expected to result in a "persistent measles virus which would continue to produce an inflammatory response and ultimately an autoimmune condition." Id. at 918. The inflammatory response would become systemic as the affected child began the systemic release of cytokines. Id. at 918-919 (Dr. Byers).

"As a rule of thumb," Dr. Byers "use[s] fever" as evidence of the "activation of the innate immune system" and evidence of an inflammatory response in the body. Id. at 948-949. Dr. Byers stated that evidence that an inflammatory immune response had become a systemic response might be supplied by the development of either an inflammatory bowel disease or recurrent infections, or by evidence of an aberrant response to the measles virus (such as measles virus persistence in the body). See id. at 950-955 (Dr. Byers). Dr. Byers explained that evidence of either systemic inflammation or measles virus persistence would be suggestive of an immunodysfunction that would be sufficient, in her view, to implicate the MMR vaccine in the development of autism. See id. at 950-951.

Dr. Byers addressed how systemic inflammation and the release of cytokines affects the central nervous system. See Cedillo Ps' Trial Ex. 9 at 26 (Dr. Byers' slides). She testified that inflammation permits cytokines to move more freely across the blood-brain barrier. Cedillo Tr. at 919 (Dr. Byers); see also Cedillo Ps' Trial Ex. 9 at 29 (Dr. Byers' slides). The blood-brain barrier is the barrier system of proteins that separates the blood in the body from the key components of the central nervous system. See Dorland's at 202. Respondent's expert Dr. Ward explained more particularly that it is "local inflammation [that] damages the blood brain barrier badly, and peripheral inflammation can influence the blood brain barrier in more subtle ways." Cedillo Tr. at 1897A (Dr. Ward).

Dr. Byers addressed other effects of cytokines on the central nervous system. She stated that after learning "to produce cytokines in a commercial formulation" as a drug therapy, investigators have observed certain effects of the administered cytokines that merited a black box warning to doctors in the 2007 Physicians' Desk Reference (PDR). Cedillo Tr. at 921A-922; see also Cedillo Ps' Trial Ex. 9 at 31 (Dr. Byers' slides). Among the observed effects of administered cytokines on the central nervous system are a "change in mental status, speech difficulties, cortical blindness, limb or gait ataxia, hallucinations, agitation, [and] obtundation [(or the clouding of consciousness[245])]. . . . [C]oma may result, and [the cytokines] may cause seizures." Cedillo Tr. at 922 (Dr. Byers). These particular effects have been observed following the therapeutic administration of interleukin-2 (IL-2). Id. at 921A-922 (Dr. Byers). "[O]ne of the main cytokines released

[245] See Dorland's at 1298.

by T cells," the cytokine IL-2 also can cause fever. Id. at 921-922.

Dr. Byers also described the observed effects of other therapeutically administered cytokines, in particular, interferon-alpha (IFN-α). Id. at 922-923. The cytokines are "secreted by various members of both the adaptive and the innate immune system." Id. at 922 (Dr. Byers). Interferon-alpha "produces depression, psychosis, nervousness, anxiety, emotional lability[,] and agitation. . . ." Id. at 922-923 (Dr. Byers); Cedillo Ps' Trial Ex. 9 at 32 (Dr. Byers' slides). Because the observed problems resolve when the cytokines are no longer administered, investigators have inferred a causal association between the administered cytokines and the observed effects on the central nervous system. See id.; see also Cedillo Ps' Trial Ex. 9 at 33 (Dr. Byers' slides).

Respondent's expert Dr. McCusker subsequently clarified, however, what Dr. Byers did not make clear in her testimony. Dr. McCusker explained that the administered doses of therapeutic cytokines to which Dr. Byers referred are considered "supernormal" doses that far exceed the small amount of cytokine secretion that would naturally occur in a lymph node that is responding to an infection. See id. at 2239 (Dr. McCusker).

Dr. Byers testified that cytokines have an effect on the neurological system because there "is a very close interaction between the immune system and the neurologic system." Cedillo Tr. at 923. She explained that the immune system produces cytokines that "act[] on" the neurologic system, and conversely, the neurologic system produces cytokines that "interact with" the immune system. Id. at 923-924. Of particular importance to petitioners' theory is the relationship between cytokines from the immune system and the molecules responsible for the "development, synaptogenesis and regeneration" of nerves. Id. at 924 (Dr. Byers).

Of additional importance are the proinflammatory cytokines (specifically the IL-2 proinflammatory cytokines) that are present in the hippocampus of the brain and that "contribut[e] to [the] regulation of neurotransmission in that same area" of the brain. Id. at 924-925 (Dr. Byers). Neurotransmission refers to the signals that neurons send to each other as a means of talking to each other. Id. at 925. One of the known effects of IL-2 in the hippocampus is the provocation "of schizophrenia-like symptoms in humans" as one of its side effects. Id. (Dr. Byers).

Another proinflammatory cytokine of importance to petitioners' theory is IL-6. Stress receptors for IL-6 are located in the hippocampus of the brain. See id. at 926. Dr. Byers testified that the hippocampus is important in cognitive function, and that area of the brain has been found to be abnormal in autistic patients. Id.; Cedillo Ps' Trial Ex. 9 at 37 (Dr. Byers' slides). Dr. Byers described stress receptors as "receptors that will dysregulate and cause abnormal function of the neurons." Cedillo Tr. at 926A. She noted that elevated levels of IL-6 have been found in the hippocampal region of the brain in patients with Alzheimer's disease. Id.; Cedillo Ps' Trial Ex. 9 at 37 (Dr. Byers' slides).

Dr. Byers also testified that there are cytokines that can cause inflammation in the brain, specifically by "activat[ing] the microglia and . . . increas[ing] the expression of multiple . . . pro-inflammatory factors" in the brain. Cedillo Tr. at 927; Cedillo Ps' Trial Ex. 9 at 38 (Dr. Byers' slides). In support of her testimony, Dr. Byers relied on the 2007

Qin article in which the investigators injected a powerful stimulant (known as lipopolysaccharide or LPS[246]) into the brains of mice. See Cedillo Ps' Trial Ex. 9 at 38 (Dr. Byers' slides) (citing 2007 Qin article[247]). The investigators found that in response to the injected stimulant, elevated levels of proinflammatory cytokines remained in the brain for 10 months while the levels in the periphery, specifically in the serum and the liver, decreased more quickly. Id. The levels in the serum decreased within nine hours. Id. The levels in the liver decreased within one week. Id. Dr. Byers apparently referred to the article to support the proposition that inflammation may be present in the brain even if no longer detectable in the periphery. See Cedillo Tr. at 928-929.

Critical to petitioners' theory regarding viral persistence and systemic inflammation following a measles vaccination is a finding that an affected child has a dysfunctional immune system that is further dysregulated after receiving thimerosal-containing vaccine and the MMR vaccine. With respect to the immunological effects of the measles virus, petitioners' and respondent's experts agreed that wild-type measles virus can cause dysregulation of the immune system. Compare Cedillo Tr. at 710, 712 (Dr. Kennedy) with Cedillo Tr. at 2767-2769 (Dr. Griffin). Contrary to petitioners' loose characterization, however, immune dysregulation is distinguishable from immunosuppression. See Cedillo Tr. at 1801A-1804 (Dr. Ward); see also id. at 2820-2821A (Dr. Griffin).

Immune dysregulation or immune imbalance can be genetically influenced. Id. at 1809 (Dr. Ward). When a person has a genetically influenced immune imbalance that produces a state of either TH1 or TH2 predominance, that person has a tendency to respond to every pathogen "in either a TH1 or TH2 way." Id. at 1808. Even with an immune imbalance, both a cellular response and an antibody response are generated, but the generated response leans toward one of them. See id. at 1810A-1811A. An immune imbalance or an abnormality of the immune system is not equivalent to immunosuppression. See id. at 1817 (Dr. Ward).

Immunosuppression is a "big deal" medically. Id. at 1802 (Dr. Ward). Immunosuppressive agents target cellular immunity while "relatively" sparing antibody-type immunity. Id. Powerful immunosuppressive agents include high dose steroids and azathioprine (the generic form of Imuran[248]). Id. "Prior to the discovery of HIV, measles virus was considered to be the most potent immuno[]suppressive virus known in its wild type form, but not [in the] measles virus vaccine [form]." Id. Although the measles vaccine causes changes in the functioning of some cells, it does not cause clinical immune

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[246] Dr. Byers explained that LPS is a component of several of the cellular walls in bacteria. See Cedillo Tr. at 1006; accord id. at 2234A (Dr. McCusker).

[247] L. Qin et al., Effective Inflammation on the Microglia of the Brain, Glia 55(5): 453-462 (2007). Dr. Byers cited this article in her trial slide presentation. See Cedillo Ps' Trial Ex. 9 at 38 (Dr. Byers' slides). But petitioners did not file it in the record. The undersigned does not rely on this article in reaching her decision.

[248] Among other noted uses, this powerful immunosuppressant medication may be used in patients to prevent the rejection of a transplanted organ. See Dorland's at 187.

suppression. Id. at 1803A (Dr. Ward).

The undersigned finds several critical problems with petitioners' claim that vaccine-strain measles virus can cause inflammation. The first problem with this aspect of petitioners' theory is that it hinges upon a finding of a persistent measles virus in the body after the administration of a measles vaccine. As addressed in Section III.C.4 of this decision, the published reports and laboratory test results on which petitioners rely for a finding of measles virus persistence are flawed and unreliable.

The second problem rests with the type of evidence that petitioners presented in support of this aspect of their claim. Testimony about the adverse neurological effects and the inflammation caused by the therapeutic administration of massive doses of cytokines provided little guidance to the undersigned regarding the effects of the more limited cytokine secretions that follow either a viral infection or a vaccination, and petitioners failed to show how that testimony made petitioners' claim that vaccine-strain measles can cause inflammation more likely than not.

The third problem with the aspect of petitioners' theory regarding the systemic inflammation resulting from measles virus persistence is that it requires a state of immunosuppression in the vaccinee. Although petitioners' experts loosely referred to various states of immune dysregulation, there is a distinction between abnormalities and dysfunction of the immune system and the grave state of immunosuppression. A person who is in a state of immunosuppression is not only vulnerable to the measles virus, but to other viral infections as well. While it is true that a period of immunosuppression may follow a wild-type measles infection, there is no correlative state of immunosuppression that follows a measles vaccine.

In the view of the undersigned, the identified problems with this aspect of petitioner's general theory of causation make the plausibility of this aspect of petitioners' proposed theory less than likely.

a. The Claim that Vaccine-Strain Measles can Cause Gastrointestinal Inflammation

Petitioners' expert Arthur Krigsman, M.D., a pediatric gastroenterologist, testified on petitioners' behalf that measles vaccine can cause gastrointestinal problems in autistic children. He explained how he became persuaded of a causal connection between the MMR vaccine, the disorder of autism, and the gastrointestinal problems that some autistic children experience.

Dr. Krigsman testified that he first saw autistic patients with gastroenterological problems in the year 2000 on referral from an allergist within the pediatric practice of which he was a member. Cedillo Tr. at 411-412. The children were referred to him because they had "chronic diarrhea and abdominal pain," two clinical indications for a gastroenterological referral. Id. at 412. Dr. Krigsman was unable to identify any infectious causes for the diarrhea. Id. at 413-414. Some of the parents of the children claimed that certain foods would aggravate the diarrheal condition and the abdominal pain, but Dr. Krigsman found that "standard dietary changes that a pediatric gastroenterologist

would put in place" and the dietary interventions "circulating amongst the autism community" did not result in any improvement. Id. at 414-415. Unable to help the patients following his routine gastroenterological testing, he dismissed the referred patients. See id. at 415.

Subsequently in 2001, the allergist who had made the earlier referrals of the autistic children to Dr. Krigsman presented to Dr. Krigsman a copy of the 2000 Wakefield article[249] that describes autistic children who had the same gastroenterological complaints as the children that Dr. Krigsman had seen on referral. Cedillo Tr. at 415. As reported in the 2002 Uhlmann article, the investigators had performed the same battery of tests that Dr. Krigsman had performed and were unable to make a diagnosis. Id. However, unlike Dr. Krigsman, the investigators considered the possibility of an inflammatory bowel disease. Id. Dr. Krigsman explained that he had not considered the possibility of an inflammatory bowel disease because the conventionally taught symptoms of inflammatory bowel disease, specifically, bloody diarrhea, weight loss, and recurring fever, were not present in the children that he had examined. Id. at 416A, 559A-560.

Dr. Krigsman stated that, as documented in the 2002 Uhlmann article, the investigators performed diagnostic colonoscopies on the 62 children involved in the study. Cedillo Tr. at 416A. What the investigators found was "nonspecific inflammation of the colon and of the very end of the ileum." Id. at 416A. After reviewing the article, Dr. Krigsman made an effort to contact the referred patients whom he had dismissed earlier and offered to perform diagnostic colonoscopies.[250] Id. at 417-418. Dr. Krigsman also obtained biopsied gut tissue samples from the children for review by a pathologist. See id.

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[249] As a point of clarification, Dr Krigsman refers to this article in his testimony "as the article written by Professor John Walker-Smith, amongst others." Cedillo Tr. at 415. The article is, in fact, the 2000 Wakefield article, and Professor Walker-Smith is one of the named co-authors of the article. See Hazlehurst Ex. 37D at 2286 (2000 Wakefield article). The undersigned has used a citation convention in this decision, however, that refers to the lead author of an article.

[250] The colonoscopies that Dr. Krigsman performed on children during his employment with Lenox Hill Hospital were the subject of litigation between Dr. Krigsman and the hospital. Cedillo Tr. at 500. The hospital expressed concern that the children on whom the colonoscopies were being performed did not have the proper clinical indications to warrant the colonoscopies. See id. at 500, 558-559A. Based on the expressed concern that the procedures were not medically indicated but were being performed for research-related purposes, the hospital prevented Dr. Krigsman from scheduling and performing any further colonoscopies at the hospital. Id. at 558-559A, 561. Dr. Krigsman filed suit against the hospital claiming that the hospital had imposed improper restrictions on his conduct of colonoscopies. See id. at 500, 558-559A. The hospital instituted disciplinary action against Dr. Krigsman, for which he was subsequently fined. See id. at 499A-500; see also Cedillo R's Trial Ex. 2 at 2 (Texas State Board of Medical Examiners, Licensure Committee Meeting Minutes, August 25, 2005, addressing the $5000 fine imposed on Dr. Krigsman (applicant #391), in part, due to the disciplinary action instituted by Lenox Hill Hospital).

at 420-421.

Dr. Krigsman explained during the hearing that during a colonoscopy, the endoscopist is examining the appearance of the mucosa or lining of the bowel. Cedillo Tr. at 420; see also Cedillo Ps' Trial Ex. 2 at 8 (Dr. Krigsman's trial slides). Of interest to the endoscopist are the color of the lining and the smoothness of the lining's surface. Cedillo Tr. at 420. A pink lining is healthy; a red one is unhealthy. Id. Typically, the lining is smooth. Id. at 445A. The presence of ulcers (which appear as either shallow or deep holes) in the lining indicates that shedding or sloughing off of inflammatory necrotic (or dead) tissue occurred to create the ulcer. See id. at 443-444; see also Cedillo Ps' Trial Ex. 2 at 2 (Dr. Krigsman's trial slides). An aphthous ulcer is a lesion surrounded by a red (erythema) halo, and that type of ulcer generally occurs over a lymphoid nodule (a small nodule beneath the surface of the lining of the bowel). Cedillo Tr. at 445A, 448A-449; see also Cedillo Ps' Trial Ex. 2 at 3, 7 (Dr. Krigsman's trial slides). An aphthous ulcer is the "earliest characteristic lesion of Crohn's Disease." Cedillo Tr. at 448A; see also Cedillo Ps' Trial Ex. 2 at 4-5 (Dr. Krigsman's trial slides).

Dr. Krigsman explained that the appearance of lymphoid nodules in the lining of the bowel indicates that lymphonodular hyperplasia is present. Cedillo Tr. at 445A. The presence of lymphonodular hyperplasia "suggests that the immune system is recognizing something and [is] responding to it appropriately." Id. at 447-448A. The lymphoid nodules are part of the bowel's "overall immune system" that detects anything it perceives as foreign, such as a virus, a bacterium, a fungus, or a food allergen. Id. at 446A. The nodules are primarily a collection of B lymphocytes, which are antibody-producing cells. Id. at 446A-446B; Cedillo Ps' Trial Ex. 2 at 6 (Dr. Krigsman's trial slides). See also L. Sompayrac, How the Immune System Works at 79, 81.

Dr. Krigsman stated that biopsied tissue is examined for evidence of inflammatory cells and, if so, where those cells are located. Cedillo Tr. at 420. The clustering of the inflammatory cells allows the pathologist to determine whether the inflammation is acute or chronic. Id. at 420-421.

Dr. Krigsman further stated that the observed findings from the colonoscopies and the microscopic findings in the biopsied samples of the autistic children referred to him indicated that there was inflammation in both the small intestine (enteritis) and the colon (colitis), a condition he described as enterocolitis. Cedillo Tr. at 420-422; accord Hazlehurst Tr. at 663-64 (testimony of respondent's expert Dr. MacDonald that enterocolitis is inflammation of the large and small intestine). Dr. Krigsman defined autistic enterocolitis as a "nonspecific enterocolitis . . . that we see in autistic children." Cedillo Tr. at 519A.

Dr. Krigsman distinguished children with autistic enterocolitis from autistic children with gastrointestinal problems (denoted as children with ASD-GI). Id. at 523-524A. Autistic enterocolitis "describes bowel disease of the small intestine and of the colon" in autistic children. Id. at 524A. ASD-GI involves more than the small bowel and the colon; it may involve the esophagus and the stomach as well. Id. Dr. Krigsman stated that there is a substantial portion of children with ASDs who also have gastrointestinal symptoms, and there is a subpopulation of those autistic children with gastrointestinal

disease. Id. at 523. Dr. Krigsman acknowledged during his testimony, however, that the terms "autistic enterocolitis" and "ASD-GI" are used by the people who medically treat children with autism and gastrointestinal problems, but the terms do not appear in the authoritative gastroenterology textbooks. See id. at 523-525A.

Having detected enterocolitis in the referred autistic children on whom he performed colonoscopies and from whom he obtained biopsied tissue, Dr. Krigsman decided to treat the children's condition with oral anti-inflammatory drugs. Id. at 421-422. Dr. Krigsman opined that the improvement in the children's symptoms after starting the anti-inflammatory drugs was evidence that the children were suffering from intestinal inflammation, even if not from a form of inflammatory bowel disease.[251] Id. at 422.

Dr. Krigsman stated that inflammatory bowel disease is "an umbrella term" that encompasses a number of different diagnoses. Id. at 428. The two principal diagnoses are Crohn's disease and ulcerative colitis. Id. Crohn's disease can occur anywhere in the gastrointestinal tract, between the mouth to the anus. Id. at 430A. The disease is not limited to the lining of the intestines but can penetrate deeper than the intestinal lining and can perforate the bowel. Id. Additionally, the affected areas can be interspersed with areas that appear normal. Id. By contrast, ulcerative colitis involves inflammation that is limited to the lining of the colon. Id. at 429A. It does not penetrate into the deep muscular layer of the bowel and the inflammation, which always begins at the anus and then extends proximally to varying lengths. Id. If unable to confirm with certainty a diagnosis of either Crohn's disease or ulcerative colitis, an examining gastroenterologist gives a diagnosis of indeterminate colitis. Id. at 429A.

After performing 22 colonoscopies on autistic children who had been referred to him through his pediatric practice group, Dr. Krigsman concluded that there was "probably" a connection between the children's autism and their gastrointestinal problems. Cedillo Tr. at 419. To explore further whether an association exists between autism and gastrointestinal symptoms after receipt of the MMR vaccine, Dr. Krigsman is working with several others on a study approved by the Institutional Review Board (IRB)[252] to see whether there is "any evidence of measles RNA" in the bowels of autistic children with

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[251] Dr. Krigsman noted that, in his view, the particular diagnosis given a child–whether indeterminate colitis or Crohn's disease or autistic enterocolitis–"makes no difference because the treatment approach would be the same." Cedillo Tr. at 520. The treatment approach involves the use of anti-inflammatory drugs, the use of drugs that affect the microbial flora content in the bowel, and the use of certain nutritional feedings. Id. at 520-522A.

[252] An IRB is a "committee set up or used by an institution to ensure the protection of human subjects by independently approving, modifying, or disapproving research protocols. IRBs can be domestic or foreign and must follow federal regulations and local institutional policy. Frequently, foreign entities that conduct IRB functions are called independent ethics committees." See http://www.niaid.nih.gov/ncn/glossary/default4.htm#iec.

gastrointestinal problems and to compare the findings in the autistic children with the findings in "neurotypical children." Id. at 473A-474A, 483A. He testified that he presented by poster at the June 2006 International Meeting for Autism Research (IMFAR) the preliminary findings of the study. Id. at 474A. That study was referenced in Section III.C.4.h.1 of this decision as the preliminary Walker study and was discussed as well by petitioners' expert molecular biologist Dr. Hepner. Dr. Krigsman stated that the preliminary findings of that study show that based on the obtained PCR results, measles virus is present in the biopsied gastrointestinal tissue taken from patients with autism and bowel disease and examined by Dr. Krigsman. Id.; see also Cedillo Ex. 59K (abstract of IMFAR poster presentation); Cedillo Ps' Trial Ex. 3 at 8-90 (IMFAR poster presentation). Dr. Krigsman acknowledged, however, as did Dr. Hepner, that not all of the samples had been sequenced for vaccine strain measles. See Cedillo Tr. at 485A-487A.

Dr. Krigsman primarily sees autistic patients in his current practice. See id. at 574A. He expressed the opinion in the Cedillo case, that an administered MMR vaccine can contribute significantly to the development of autistic enterocolitis in a child and that the persistence of the measles virus in the lymphoid tissue causes the ongoing enterocolitis. See Id. at 525A; Cedillo Ex. 59 at 8 (Dr. Krigsman's report). Based on the 2004 Ashwood article (filed as Cedillo Ex. 61B),[253] Dr. Krigsman suspects that the measles virus persists in the lymphoid tissue of a child after the MMR vaccination because the child has a dysregulated immune system that permits "a skewed inflammatory response in favor of pro-inflammatory cytokines." See Cedillo Tr. at 530A-531. In Dr. Krigsman's opinion, gastrointestinal problems that develop in autistic children within six months after the administration of the MMR vaccine are vaccine-related. See id. at 536A-537A.

To address and expound upon a number of issues that petitioners' expert Dr. Krigsman raised, respondent presented the expert testimony of Stephen Hanauer, M.D. Dr. Hanauer is a gastroenterologist with a specialty in inflammatory bowel disease. See Cedillo Tr. at 2077A-2082. As part of his clinical practice, he performs 12 or more colonoscopies a week. Id. at 2082.

Dr. Hanauer described inflammatory bowel disease as "a spectrum of inflammatory disorders of the digestive tract." Id. at 2088A. He explained that "anything that produces inflammation of the digestive tract" constitutes an inflammatory bowel disease. Id. The nature of the disease, however, varies according to the location of the inflammation within the digestive tract. Id.

The causes of inflammation in the digestive tract are diverse.[254] Acute infections, including viral agents like salmonella and rotavirus, are the most common causes. Id. at

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[253] P. Ashwood et al., Spontaneous mucosal lymphocyte cytokine profiles in children with autism and gastrointestinal symptoms: Mucosal immune activation and reduced counter regulatory interleukin-10, J. of Clin. Imm. 24: 664-673 (2004).

[254] Dr. Hanauer noted that gastrointestinal reflux disease is not an inflammatory disease or an immunologic injury. Cedillo Tr. at 2095A. Rather, it is an acid-related injury to the lower esophagus. Id.

2088A-2089. Radiation or medication are among the other causes. Id. at 2089. Dr. Hanauer noted that autistic enterocolitis is not a recognized inflammatory bowel disease in the standard gastroenterology textbooks. See id. at 2143. But he concurred with Dr. Krigsman that the main forms of chronic inflammatory disease of the intestines are Crohn's disease and ulcerative colitis. Id. at 2089. The cause of these inflammatory diseases is unknown (idiopathic). Id.

Dr. Hanauer explained that inflammatory bowel disease is not the same as irritable bowel syndrome. Id. at 2089. Inflammatory bowel disease is characterized by inflammation. Id.; see also id. at 2092A (Dr. Hanauer explaining that in medicine, the suffix "itis" denotes inflammation). Signs and symptoms of inflammatory bowel disease may include diarrhea, weight loss, fever, rectal bleeding, or abdominal pain. Id. at 2095A. Alternating diarrhea and constipation are not characteristic evidence of inflammatory bowel disease. Cedillo Tr. at 2107-2108A (Dr. Hanauer). Inflammatory bowel disease produces "persistent diarrhea with inflammation in the stool." Id. at 2105A. Stool that contains blood may be a sign of inflammation; stool that contains white blood cells or "pus cells," but not mucous, is evidence of inflammation. Id. at 2142-2143.

Distinguishable from inflammatory bowel disease is irritable bowel syndrome. Irritable bowel syndrome is a group of symptomatic disorders resulting from increased motility and pressure within the digestive tract as well as an increased perception of that motility within the digestive tract. Id. at 2089-2090A. The symptoms of irritable bowel syndrome are abdominal pain with either diarrhea or constipation; more often, however, the abdominal pain is accompanied by alternating diarrhea and constipation. Id. at 2090A. Irritable bowel syndrome is "[t]he only condition[] that produce[s] diarrhea alternating with constipation." Id. at 2105A. With irritable bowel syndrome, the produced stool is often mucousy. See id. at 2109. Symptoms of irritable bowel syndrome do not progress to inflammatory bowel disease. See id. at 2167, 2190A.

Explaining that the liquidity or solidness of stool depends on how long the material is in the colon (less time produces looser stool while more time permits firmer stool) and on the motility (or spontaneous movement)[255] of the intestine, Dr. Hanauer discussed how diarrhea could be caused in the presence of constipation. See id. at 2103A-2104A.

Dr. Hanauer also addressed possible causes of diarrhea other than inflammation. He noted that ordinary emotional responses such as fear or nervousness involve a connection between the brain and the intestine that can affect the motility of the intestine and produce a sensation of "butterflies" in the stomach or a sense of bowel urgency. See id. at 2106A. Diet and food allergies also can affect the motility of the intestine. Id. at 2106A-2107. Prescribed antibiotics can cause diarrhea. Id. at 2146; accord Hazlehurst Tr. at 510A (Dr. Rust). Additionally, children typically experience "three to five bouts of diarrhea a year." Hazlehurst Tr. at 510A (Dr. Rust).

Turning to address the characteristics of inflammatory bowel disease, Dr. Hanauer agreed with Dr. Krigsman's description of the two main forms of chronic inflammatory

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[255] Definition of motility according to Dorland's at 1175.

bowel disease, Crohn's disease and ulcerative colitis. Cedillo Tr. at 2090A. Crohn's disease involves a patchy pattern of inflammation that can affect any portion of the digestive tract between the mouth and the anus. Id. at 2091A. The inflammation is deep, penetrating the various layers of the lining of the digestive tract and, in severe cases, affecting adjacent organs through holes in the digestive tract known as fistulas. See id. at 2091A-2092A. By contrast, ulcerative colitis involves superficial and continuous inflammation of the lining of only the large intestine (also known as the colon). Id. at 2090A. With ulcerative colitis, the inflammation always begins at the "anal verge, at the bottom of the colon" and can extend proximally along the length of the colon. Id. at 2090A-2901A. Through a scope, the lining of the colon affected by ulcerative colitis "looks like someone took sandpaper and rubbed the lining of the colon so it looks granular." Id. at 2091A.

Dr. Hanauer explained that the diagnosis of indeterminate colitis is appropriate in a "patient[] who ha[s] such severe ulceration of [his] large intestine" that the endoscopist cannot separate the pattern of ulcerative colitis from Crohn's disease. Id. at 2092A. Because severe ulceration and inflammation are present in a case of indeterminate colitis, Dr. Hanauer does not regard the condition as a minor one. Id.

A diagnosis of inflammatory bowel disease is made by a combination of endoscopic examinations of the tissues and biopsies from the tissues. Id. at 2096. Alternatively, if the tissues cannot be reached by scope, a diagnosis of inflammatory bowel disease may be made by x-rays or CT scans of the affected areas. Id.

The combination of endoscopic examinations to which Dr. Hanauer referred is the combination of an upper endoscopy and a lower endoscopy. Id. An upper endoscopy is performed by inserting a tube in the mouth, down the esophagus, into the stomach and into the first part of the small intestine. Id. The lower endoscopy (also referred to as a colonoscopy) is performed by inserting a tube into the rectum, through the large intestine and into the bottom of the small intestine (an area referred to as the terminal ileum). Id. at 2096-2097A. The inserted tubes take pictures of the gastrointestinal tract that permit a diagnostic evaluation to be made.

The gastrointestinal tissue that is obtained by biopsy is examined microscopically (also referred to as a histopathological examination). Id. at 2097A. The microscopic (or histopathologic) analysis of the tissue permits the classification of the type of inflammation that is present. Id. For example, eosinophils are a type of white blood cell that may be detected microscopically. Id. at 2112A-2113A. Eosinophils, however, are "not specific in any way for inflammatory bowel disease." Id. at 2113A. Rather, they are indicative of an allergic-type reaction. Id.

Different types of inflammatory bowel disease have different types of microscopic inflammation. Id. at 2097A. Dr. Hanauer testified that because the appearance of the intestine may look different on endoscopic examination according to how traumatic the examination is, the histopathologic findings are important to a proper diagnosis of inflammatory bowel disease. See id. at 2097A-2099.

Dr. Hanauer explained that there is a continuous underlying layer of chronic

inflammatory cells along the lining of the intestine. Id. at 2115. The cells are organized into lymphoid aggregates or microscopic lymph nodes "that line the entire digestive tract" and assist in processing foreign material. Id. When the lymphoid tissue appears enlarged, it is described as lymphoid hyperplasia. Id. at 2115-2116. It can be a normal finding in children. Id. at 2116. In fact, an increased presence of lymphoid hyperplasia is common in children. Id. at 2150.

Dr. Hanauer observed that "the digestive tract is actually our immunologic eye to the world. More of our environment is sampled through our intestinal tract than the rest of the body. Most of the foreign material we sample is actually through the digestive tract, so there is more lymphoid tissue or immune tissue in the gut than any other portion, so the number one function is the immune function of the gut." Cedillo Tr. at 2100A-2101A.

Additionally, Dr. Hanauer described aphthous ulcers in the intestines as "pinpoint, barely visible erosions over a lymphoid aggregate that can be due to trauma, medications [such as nonsteroidal anti-inflammatory drugs], bowel preparation itself [for a colonoscopy], infection or part of the normal intestinal lining." Id. at 2126, 2128A. Dr. Hanauer agreed with Dr. Krigsman that an aphthous ulcer can be the first sign of Crohn's disease, but Dr. Hanauer clarified that an aphthous ulcer is not specific for Crohn's disease. Id. at 2126. He added that the aphthous ulcer by itself has "no specificity whatsoever" and is not indicative of inflammation. See id. at 2127-2128A.

Dr. Hanauer testified that there is no evidence that viral infections cause chronic inflammatory bowel disease. See id. at 2093. Viral infections that cause inflamation of the small and large intestines (or enterocolitis) are self-limited. See id.; Cedillo Ex. X at 3 (Dr. Hanauer's report). For example, a stomach virus that causes diarrhea lasts between 24 to 72 hours. Cedillo Tr. at 2093. Rotavirus, the most common viral cause of diarrhea in children, causes diarrhea for three to seven days. Id. When the intestines encounter these viruses, the intestines develop acute inflammation to get rid of the viruses, and after the viral organisms are eradicated, the intestines return to their normal physiologic state with the number of chronic inflammatory cells that typically line the intestines. Id. at 2094A. Viral infections do not lead to chronic gastrointestinal symptoms. See id. at 2093, 2161A.

Other than the findings presented by the Royal Free group (a reference to Dr. Wakefield and his colleagues), Dr. Hanauer knows of no evidence that the measles virus can cause inflammatory bowel disease. Id. at 2094A. Nor is he aware of any specific neurologic complications associated with inflammatory bowel disease. Id.

The undersigned found the testimony of respondent's witness to be significantly more persuasive than the testimony of Dr. Krigsman. Informed by his extensive clinical experience and his well-developed expertise on the subject of inflammatory bowel disease, Dr. Hanauer ably distinguished those symptoms, both clinical and pathological, that are not characteristic of inflammatory bowel disease from those symptoms that are. He testified that the term autistic enterocolitis is not a recognized inflammatory bowel disease in gastroenterological texts, and Dr. Krigsman did not disagree. Dr. Hanauer acknowledged that connections between the brain and the intestines can create sensations in the stomach or a sense of bowel urgency. But he stated that there is no evidence that

viral infections cause inflammatory bowel disease or that inflammatory bowel disease causes specific neurological problems. Petitioners' claim that vaccine strain measles virus can cause gastrointestinal inflamation is supported only by the work of Dr. Wakefield and his colleagues. That work has been discredited by the scientific community including 10 of Dr. Wakefield's 12 co-authors who collaborated on the 1998 Wakefield article. As discussed in Section III.C.1 of this decision, that body of work lacked sound methodology and scientific validity. Because the evidentiary support for petitioners' claim is unreliable, the undersigned cannot find that vaccine strain measles virus can cause gastrointestinal inflammation.

b. The Claim that Vaccine-Strain Measles can Cause Neuroinflammation

An aspect of petitioners' claim that the MMR vaccine contributes to the development of autism is the claim that vaccine strain measles can cause neuroinflammation. Petitioners' expert neurologist Dr. Kinsbourne addressed the mechanism by which viruses, including the measles virus, can persist in the brain and cause inflammation. He stated that "the dominant way for [a] virus to persist is within cells" and that a virus could persist within the cells in the brain. Cedillo Tr. at 1074.

Relying on the 2006 Oldstone review article discussed in Section III.C.4.a, above, Dr. Kinsbourne asserted that a virus can live within a cell without destroying the cell. Cedillo Tr. at 1077- 1079A. But the function of the infected cell "is likely to be impaired." Id. at 1079A. As he gleaned from the 2006 Oldstone review article, Dr. Kinsbourne stated that "more diseases are probably caused by viruses persisting inside cells, including cells of the nervous system, than we currently appreciate and that a mechanism that invokes viruses persisting in cells is a biologically plausible, medically reasonable mechanism to invoke when trying to explain disease." Id. at 1081.

Dr. Kinsbourne explained that the two main categories of cells in the brain are the neurons and the glia. Id. at 1074. The neurons "do the basic work of the brain and . . . control [the] organs." Id. at 1074-1075A. The glia function "more like connective tissue cells" and include the cells of the immune system that are present in the brain. Id. at 1075A.

Of the glia, there are several subsets that are important to petitioners' theory. Id. First, the astroglia are star-shaped cells that are prevalent in the brain and are scattered among the neurons. Id. Second, the oligodendroglia are the cells that produce myelin, the fatty sheaths that surround the axons[256] and permit the neurons to communicate with each other at long distances. Id. Third, the microglia are part of the innate immune system and are the cells "that become activated if there is an immune challenge." Id. When activated by an immune challenge, such as the presence of a foreign antigen, the microglia increase the expression of proinflammatory cytokines in the brain. Id. at 1083-1084A (referencing Cedillo Ps' Trial Ex. 9 at 38 (2007 Qin article)).

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[256] The word that appears in the transcript is "axous." Context, however, strongly suggests that "axous" is a misspelling of the word "axons."

Dr. Kinsbourne explained that a local infection can become a systemic infection through blood circulation. Id. at 1084A-1085. With respect to the measles virus, Dr. Kinsbourne testified that once an infection occurs, the virus travels first to reside in the lymphoid tissue and then travels, through circulation of the blood, to the lining of the gut before traveling to the brain. Id. at 1135A, 1137A, 1139. He indicated that the measles virus could persist in the gut of a person with an immune dysfunction without continuing to circulate in the blood. Id. at 1140A-1141. He stated that the measles virus "can take months or years . . . to reach the brain from its source." Id. at 1143. Dr. Kinsbourne did not identify the "source," and he did not know specifically how that time period is "modified if the gut is the source." Id. He conceded that he has not independently studied the portion of his opinion pertaining to the enterotropic properties of the measles virus, but that he relies instead on the expressed opinion of Dr. Kennedy, petitioners' virologist. See id. at 1144A.

Dr. Kinsbourne observed that the brain generally is protected from a systemic infection by the blood-brain barrier, but certain systemic infections, including a persistent infectious measles virus, can cause a breach of the blood-brain barrier. Id. at 1085-1086. A breach of the blood-brain barrier can be caused by the circulation of proinflammatory cytokines that are generated at a particular site in the body and then "reach[] the blood vessels that irrigate the brain." Id. at 1082. Once the blood-brain barrier is breached, the infectious agent that has created the systemic infection can be found in both the cerebrospinal fluid and in the brain itself. See id. The infectious agent in the brain would be found in the glial cells, specifically, the astroglia and the microglia, and in the neurons. Id. at 1086, 1147-1149A. Dr. Kinsbourne testified that there are circumstances in which measles virus can cause the death of cells in the brain (also described as cytolysis[257]) and there are other circumstances in which the measles virus remains within a cell damaging only the functioning of the cell but not the integrity of the cell. Id. at 1149A, 1151.

Dr. Kinsbourne opined that when the measles virus enters the brain, the innate immune system of the brain responds quickly. Id. at 1151-1152A. Specifically, the microglia are activated and begin to produce proinflammatory cytokines that generate inflammation in the brain. Id. Dr. Kinsbourne stated that the immune system response that he described when measles virus enters the brain is a proper immunological response. Id. at 1152A-1153.

Relying on the 2005 Vargas article,[258] in which the investigators noted areas of inflammation in the brains of autistic patients on autopsy, Dr. Kinsbourne reasoned that contrary to earlier thinking that autism is a static brain injury, the finding of inflammation and activated microglia in the 2005 Vargas article is evidence of an ongoing disease process in the autistic patient. Cedillo Tr. at 1090-1091. Dr. Kinsbourne acknowledged,

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[257] This term appears misspelled in the transcript as "cytolosis."

[258] Filed as Cedillo Ex. 61MMM, the citation for the article is D.L. Vargas, et al., Neurological activation and neuroinflammation in the brain of patients with autism, Annals of Neurology. 10: 1002-1013 (2005).

however, that microglial activation can occur "in a variety of circumstances," such as in Parkinson's disease and Alzheimer's disease, but the interpretations of the microglial activation "are debated." Id. at 1091.

Dr. Kinsbourne addressed the further impact on the brain of measles virus in the brain that is causing either the dysfunction or the destruction of the astroglia (also referred to as astrocytes and one of the subsets of the glial cells in the brain). See id. at 1092A. He explained that when the proper functioning of the astroglia becomes impaired, the astroglia are unable to maintain the proper balance between the excitatory and the inhibitory chemical messengers that help neurons to communicate with each other. Id. at 1092A-1094; see also id. at 1157A.

The chemical messengers that help neurons communicate with each other are known as neurotransmitters. Id. at 1092A. The excitatory ones cause the receiving neurons to become activated. See id. The most prevalent excitatory neurotransmitter is glutamate. Id. at 1094. The inhibitory neurotransmitters cause the receiving neuron to become inhibited. Id. at 1092A-1093. Maintaining the balance between excitatory and inhibitory neurotransmitters is important for proper brain activity and is an important function of the astroglia. See id. at 1093-1095; see also id. at 1157 (Dr. Kinsbourne describing the "skew[ing] to the excitatory extreme" when the balance between the excitatory and inhibitory influences shift in the brain). When the functioning of the astroglia becomes impaired, the astroglia are unable to "mop up the excess glutamate," an excitatory neurotransmitter, that can become excitotoxic to neurons when present in excess. See id. at 1095, 1153, 1155A. Dr. Kinsbourne stated that the pyramidal cells (the large neuronal cells that are characteristically depleted in autistic brains observed on autopsy), are particularly vulnerable targets for cytotoxic damage due to glutamate. Snyder Ex. 29 at 18-19 (Dr. Kinsbourne's report); see also Hazlehurst Tr. at 488A-489A (Dr. Rust describing the noted loss of pyramidal cells in autistic brains). Dr. Kinsbourne further stated that the depletion of Purkinje cells in the cerebellum and frontal cortex of autistic brains examined on autopsy may be due to the cytotoxic effect of glutamate. Snyder Ex. 29 at 19 (Dr. Kinsbourne's report). In Dr. Kinsbourne's view, it is the presence of excess glutamate that creates the state of "overanxiety and arousal" that characterizes the autistic state. Id. at 1096-1098A (citing Cedillo Ex. 61CCCC (2003 Rubenstein article[259])).

Moreover, Dr. Kinsbourne opined that the inflammation in the brain (that results from persistent measles virus accessing the brain and infecting neurons) contributes to the disorganization of the critical circuits in the brain and disrupts communication between various areas of the brain in a manner that limits the type of mental operations that can be performed. See id. at 1098A-1099. Dr. Kinsbourne stated that this disruption in the brain explains why autistic children have more problems with complex mental operations than with simple ones. Id. at 1099; see also id. at 1159A-1160A (describing the propensity in autistics toward "the more simplistic local selective patterns such as . . . obsessing in one's

[259] J. Rubenstein and M. Merzennich, Model of autism: increased ratio of excitation /inhibition in key neural systems, Genes, Brain, and Behavior 2:255-267 (2003).

mind with one thought over and over and over, or engaging in a particular activity again and again and again as opposed to flexibly moving from one thought to another, one perception to another, one memory to another, one activity to another, as is required by the contingencies of normal living"). Dr. Kinsbourne could offer no opinion on the period of time between the entry of the measles virus into the brain and the skewing of the brain function toward an excitatory state. See id. at 1156-1157A.

Dr. Kinsbourne opined that a persistent measles virus is more likely than not the cause of the encephalopathic process that results in autistic behavior when the onset of the autistic disorder occurs within three months following the receipt of the MMR vaccine. See id. at 1161A, 1178A; see also Snyder Tr. at 531A-532A. Dr. Kinsbourne indicated that a key component of his causation opinion was evidence of the recovery of measles virus genomic material from an autistic patient. See Cedillo Tr. at 1179. In the absence of such a finding, however, he would offer no opinion of causation. Id. at 1180A, 1183A. Moreover, Dr. Kinsbourne indicated that if the results of testing performed by the Unigenetics laboratory that were presented as positive findings of measles virus genomic material in tissue samples obtained from autistic children were shown to be of questionable reliability, his opinion of MMR vaccine-caused autism would change. Id. at 1196A.

Dr. Kinsbourne specifically limited his opinion to the relationship between the MMR vaccine and the development of autism. Id. at 1172. He offered no opinion on the role of the thimerosal-containing vaccines in causing an autistic injury, deferring instead to the toxicology opinion offered by Dr. Aposhian on petitioners' behalf. Id. at 1125A, 1172.

Respondent's expert Dr. Wiznitzer challenged the mechanism proposed by Dr. Kinsbourne that would allow persistent measles virus to breach the blood-brain barrier and cause neuroinflammation that leads to the development of autism. Dr. Wiznitzer indicated that he was not familiar with any literature that proposes a scientifically proven model for autism induced by the measles virus. Cedillo Tr. at 1630.

Dr. Wiznitzer testified that the hypothesis put forth by petitioners' expert Dr. Kinsbourne, specifically that overexcitation in the brain causes autism, is not a new theory. Id. at 1631. The aspect of the hypothesis that is new, however, is the aspect that excessive glutamate levels in the brain cause the overexcitation. Id. at 1632. Addressing the 2003 Rubenstein article on which Dr. Kinsbourne relied for his excess glutamate/overexcitation hypothesis, Dr. Wiznitzer explained that the authors identified a number of different theoretical mechanism by which overexcitation could occur. Id. at 1632-1633A. The postulated mechanisms considered the different ways that an imbalance could occur between the excitatory and the inhibitory neuronal circuits in the brain. Id. at 1633A; see also Cedillo Ex. 61CCCC (2003 Rubenstein article). The excitatory neurons include glutamate, the "primary excitatory neurotransmitter in the brain." Cedillo Tr. at 1634A (Dr. Wiznitzer); Snyder Tr. at 691A (Dr. Wiznitzer). The inhibitory neurons include GABA (gamma-aminobutyric acid), the "primary inhibitory neurotransmitter in the brain." Cedillo Tr. at 1634A-1635 (Dr. Wiznitzer); Snyder Tr. at 691A (Dr. Wiznitzer). Normally the systems of excitation and inhibition are "in a reasonable balance." Cedillo Tr. at 1633A (Dr. Wiznitzer). But factors that can cause either excessive excitation or deficient inhibition disrupt the neuronal balance. See id. at 1633A-1637. As Dr.

Wiznitzer pointed out during his testimony, the authors of the 2003 Rubenstein article "were very careful" about stating their conclusions and noting that the presented models of mechanisms for autism are "theoretical" and requires further investigation. See id. at 1636A-1637; see also Cedillo R's Trial Ex. 11 at 21-24 (Dr. Wiznitzer's slides). Dr. Wiznitzer testified that the authors' postulates must "be further proven before . . . th[e] information [can be used] in a clinically meaningful manner." Cedillo Tr. at 1637. Dr. Wiznitzer observed that the authors did not mention either the measles virus or the MMR vaccine playing a role in the presented models. Id. at 1784A-1785.

Dr. Wiznitzer also discussed the 2005 Vargas article to which Dr. Kinsbourne referred as support or the proposition that inflammation has been found in the brains of autistic subjects on autopsy. See id. at 1783A-1784A. He indicated that the Vargas article did not address chronic viral infections, the measles virus, or the MMR vaccine in any of the examined subjects. Id. at 1783A. Nor did the authors in the Vargas study address glutamate, the hypothesis regarding the role of glutamate in the development of autism, or the role of the discovered inflammation in the autistic brain. Id. at 1784A.

Dr. Wiznitzer testified that Dr. Kinsbourne's theory about the cytotoxic effect of glutamate causing the loss of cells in autistic brains is "conjecture and speculation." Snyder Tr. at 694A. Dr. Wiznitzer stated that "[t]he evidence that we have about this kind of cytotoxic effect is that there is no evidence of scarring in the region, suggesting that more likely than not, the phenomenon may occur prior to birth before the scarring system is in place in the brain." Id. at 695. He added that "we just don't know whether or not [the cells] [we]re there" in the first place. It's a presumption that [the cells are missing] due to cytotoxicity." Id.

Dr. Wiznitzer also disagreed with Dr. Kinsbourne's theory that excess glutamate may cause the loss of synaptic connections and diminished dendritic growth in the hippocampus in autism.[260] Id. at 695-696. Dr. Wiznitzer reasoned that "if you get enough cytotoxic effect, you're going to kill the cell. It's not going to change the number of synaptic connections. It's not going to decrease the amount of dendritic growth. You're going to kill the cell." Id. at 696. He elaborated:

> [The hypothesis] that there is going to be excessive glutamate in the synaptic cleft just enough to overexcite the cell but not enough to kill it doesn't make sense. If you really have a fine-tuned mechanism, which is what [Dr. Kinsbourne] says has been lost, that control mechanism . . . has been lost, you're going to get too much glutamate building up, and there is going to be [a] cell death period. It's not going to stay at a certain level. It's going to get worse and worse and worse because there are no cleanup components there, because [Dr. Kinsbourne] stated that [is what's] missing.

Id. at 697A. In a chronic state of low level overexcitation, the state contemplated in Dr.

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[260] Dendrites are the branch-like fibrous extensions from the axons that permit cells in the brain to communicate with each other. See Hazlehurst Tr. at 461A (Dr. Rust); see also Dorland's at 488.

Kinsbourne's theory, cell death will occur. Id. at 697A-698. Dr. Wiznitzer stated that there is no evidence to support Dr. Kinsbourne's theory that a lower level of imbalance between excitation and inhibition disrupts the functioning of the brain rather than causing cell death. Id. at 696. He observed that in science, a hypothesis must be proven; the burden does not shift to another to disprove the hypothesis. See id.

Dr. Wiznitzer added that the proposed overexcitation model that contemplates excess glutamate, the excitatory neurotransmitter, and a decrease in GABA function, the inhibitory neurotransmitter, is not an accurate reflection of the complicated excitatory/inhibitory balancing process. Id. at 702A-703. Dr. Wiznitzer explained that the state of overexcitation in the brain is associated in the literature with seizure activity rather than autism. Id. at 706-708. Dr. Wiznitzer noted that "very simplistic" models have been proposed to explain how autism develops and "probably the prevailing model nowadays is the neuro network model that's been known for quite awhile. Id. at 720; see also Section III.A.3, above (discussing the architectural structure of the autistic brain).

The difficulty with petitioners' claim that vaccine-strain measles can cause neuroinflammation is twofold. First, the hypothesis lacks evidentiary support. Second, the hypothesis is unsupported by and is at variance with the known science. The balance between the excitatory and inhibitory neuronal circuitry in the brain is preserved by a complex series of compensatory mechanisms. That complex system of compensatory mechanisms makes the skewing to the excitatory extreme proposed by Dr. Kinsbourne much less likely. Additionally, the proposition that a chronic state of low level overexcitation in the brain causes cell dysfunction rather than cell death is unsupported speculation that does not militate in favor of a finding on petitioners' behalf. Finally, the petitioners' claim that vaccine-strain measles virus can cause neuroinflammation is based upon a finding of persisting measles virus in the body. But as discussed in Section III.C.4., above, the published reports of positive measles findings in the examined tissues of autistic children lack scientific validity. Absent reliable evidence to the contrary, the undersigned cannot find petitioners' claim that vaccine-strain measles virus can cause neuroinflammation to be a tenable one.

6. Legal Evaluation of Petitioners' Claim regarding the Role of MMR Vaccine in the Development of Autism Spectrum Disorders

The undersigned now evaluates the aspect of petitioners' claim that receipt of the MMR vaccine contributes to the development of autism spectrum disorder. The undersigned evaluates this aspect of petitioners' claim in accordance with 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.

a. The Proposed Medical Theory

Petitioners posit that the measles vaccine causes immunosuppression in certain

genetically predisposed children that permits the viral measles component of the vaccine to persist in the body and cause inflammation, first in the gut and then in the brain, that leads to the neurodevelopmental disorder of autism. Petitioners' theory, however, is premised upon a series of biological implausibilities.

The testimony offered by respondent's expert Dr. Griffin (an acknowledged expert on measles to whom petitioner's expert Dr. Kennedy was willing to defer) and by other respondent's witnesses with several decades of experience working with the measles virus (including Drs. Ward and Zweiman) as well as the filed documentary evidence establish that the scientific community has gained a good understanding of the infectious process associated with the wild-type measles virus, the proper immunological response to such infection, and the period of time during which the body clears itself of the virus and concomitantly is susceptible to other infections. In the rare circumstance when the wild-type measles virus persists in the body and causes disease, the resulting disease–either SSPE in an immunocompetent person or MIBE in an immunocompromised person–is characterized by neurological deterioration that leads to death. The neurological injuries that manifest as movement disorders with SSPE or respiratory problems with MIBE are distinguishable from the impairments in communication, social interaction and behavior that are distinctive features of autism.

The scientific community has also gained a good understanding about the measles vaccine. The measles vaccine is distinguishable from the wild-type measles virus in several key respects. First, the measles vaccine is much less virulent that the wild-type virus. Second, the measles vaccine has been designed specifically to provoke an immune response in the body but not to replicate well in the body. Third, the most significant complications associated with the measles virus simply do not occur with the measles vaccine. Measles vaccine generally does not cause disease, and there is no period of clinically significant immunosuppression that follows vaccination. The characteristics of the measles virus that inform petitioners' theory of causation are not the characteristics of the attenuated measles component of the MMR vaccine.

Petitioners' claim that the measles virus can persist in the gut of certain vaccinated children and cause inflammation is based on reported findings of persistent measles virus in the biopsied gut tissue taken from autistic children who have received the MMR vaccine and developed gastrointestinal symptoms. Petitioners' reliance, however, on the published reports of positive test results, the unpublished positive findings of the preliminary Walker study, and the positive lab results obtained by Unigenetics lab from biopsied gut tissue taken from children involved in the OAP litigation is unavailing. Strong evidence, including highly credible expert testimony, indicates there were numerous irregularities in the testing procedures. Those irregularities compromised the integrity of the conducted tests and have rendered the test results unreliable. Underscoring the unreliability of the test results is the inability of other laboratories (that is, accredited laboratories not affiliated with either Dr. Wakefield, his colleagues, or the Unigenetics lab) to replicate the reported findings in gastrointestinal tissues or blood cells.

Petitioners' theory is based on the characteristics of the wild-type measles virus rather than on the characteristics of the attenuated vaccine-strain measles virus. Petitioners' theory is further based on unreliable reports of positive measles findings. The bases for petitioners' theory that the measles component of the MMR vaccine can lead to the development of autism are unsound. Petitioners have failed to offer reliable support for the proposition that the MMR vaccine can cause autism and have failed to meet their burden of proof under the first prong of the Althen standard.

b. The Sequence of Cause and Effect

Petitioners' witnesses have relied on unreliable reports of positive measles findings as an important basis for their expressed opinions. Petitioners' witnesses have also relied on the characteristics of the wild-type measles virus rather than the vaccine-strain measles virus in their expressed opinions. The grounds for the expressed opinions of petitioners' witnesses are unsound and unsupported. Such grounds cannot inform a logical sequence of cause and effect as required under the second prong of the Althen standard. Because the reasoning underlying the expressed opinions is unsound, the testimony of petitioners' witnesses cannot stand. See Perreira, 33 F.3d at 1377 n.6; Burns, 3 F.3D at 417.

c. The Temporal Association

Following a measles infection, the wild-type measles virus can be detected by PCR techniques in the body for a period of up to five months after the clearance of the viral rash. See Cedillo Ex. V at 2 (Dr. Griffin's report). The measles vaccine, however, does not replicate well in the body even though it does trigger an immunological response sufficient to generate an immunity to measles infection. See Cedillo Tr. at 2776-2777 (Dr. Griffin). Petitioners have offered no reliable evidence that vaccine-strain measles virus persists in the following receipt of the MMR vaccine. See Section III.C.4, above.

Dr. Krigsman testified that the onset of gastrointestinal problems in autistic children within six months of the administration of the MMR vaccine are vaccine-related. See Cedillo Tr. at 536A-537A (Dr. Krigsman). Dr. Kinsbourne testified that he did not know what time period is required for a persisting measles virus to travel from the gastrointestinal system to the brain. Id. at 1143 (Dr. Kinsbourne). He stated that measles virus "can take months or years . . . to reach the brain from its source," but he did not identify that "source." Id. Neither expert, however, offered reliable support for his opinion concerning the timing required for a persisting measles virus to produce the various inflammatory effects that petitioners claim can lead of the development of autism. Without more than a showing that the injury occurred following the vaccination, petitioners fails to satisfy the third prong under the Althen standard.

IV. The Hazlehursts' Specific Allegations[261]

A. Factual Background: Yates' Medical History

1. The Medical Records

Petitioners' first child, William Yates Hazlehurst, was born on February 11, 2000. Hazlehurst Ps' Ex. 2 at 6. He weighed 9 pounds 2 ounces. Id.; Hazlehurst Ps' Ex. 1 at 14. His Apgar scores[262] were 8 and 9. Hazlehurst Ps' Ex. 1 at 14. At one day old, Yates received a newborn hearing screen. Hazlehurst Ps' Ex. 1 at 34. The results were normal. Id.

Five days after Yates' birth, on February 16, 2000, Dr. Carlton Hays of the Jackson Clinic Professional Association evaluated Yates as part of a well-infant pediatric check-up and noted that he may have "mild jaundice of his face and upper chest . . . ." Hazlehurst Ps' Ex. 2 at 5. In Dr. Hays' assessment, Yates was a "well infant with very reasonable weight loss to this point." Id. (omitting all capitals format).

Nearly one month after Yates' birth, on March 7, 2000, Dr. Hays examined Yates for symptoms associated with colic, gastroesophageal reflux, and thrush.[263] Hazlehurst Ps' Ex. 2 at 9-10. Dr. Hays treated Yates' yeast infection with an antifungal preparation, specifically an oral suspension of nystatin, and Dr. Hays provided a nystatin cream to Mrs. Hazlehurst for her to apply to her breasts. Id. At the time of this visit, Mrs. Hazlehurst was still breast-feeding.

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[261] Testimony taken during the Hazlehurst hearing is contained in its entirety in the Hazlehurst transcript to which the undersigned cites. For reasons undetermined, the transcription service recorded the final page number of Volume One of the transcript, which pertains to the proceedings conducted on October 15, 2007, as page 130/260. Volume Two of the transcript, which pertains to the proceedings conducted on October 16, 2007, then commences on page 261. What appears to be a gap of 130 pages in the transcript does not reflect a gap in the transcribed testimony, but rather a pagination mistake.

Additionally, in the Hazlehurst transcript at pages 262 and 556A, Joseph Lowe is erroneously identified as representing respondent in this litigation. Mr. Lowe did not participate in the proceedings as counsel for either party to the litigation. Mr. Lowe is a staff attorney with the Office of Special Masters, and he attended the proceedings in that capacity.

[262] 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.

[263] Thrush is an oral yeast infection. See Dorland's at 1908.

One month later, on April 7, 2000, Yates had his two-month checkup. Id. at 11. During that exam, he received the following vaccinations: diphtheria, tetanus, and acellular pertussis ("DTaP")[264], hemophilus influenzae type b ("Hib"),[265] and inactivated polio virus ("IPV")[266]. Id. at 11-12.

On June 6, 2000, Yates had his four-month well-baby examination. Id. at 14. At that exam, he received four vaccinations: DTaP, Hib, Prevnar,[267] and IPV. Id. at 12, 14.

On August 16, 2000, Yates had his six-month pediatric visit. Id. at 19. At that time, he received DTaP, Hepatitis B, Hib, and Prevnar vaccinations. Id. at 12, 19. At six months of age, Yates had received nine doses of vaccines that possibly contained thimerosol.[268] See id. at 11-12, 14, 19 (records of Yates' two-month, four-month, and six-month pediatric examinations).

On November 22, 2000, Dr. Hays examined Yates for his nine-month pediatric visit. Ps' Ex. 2 at 29-31. The medical records reflect that Yates was having "shaking episodes [that l]ast for a second or two[,] entire body trembles, acts normal afterwards[,] occurring less frequently[,] none in past two months." Id. at 29. At the nine-month visit, Yates received his second hepatitis B, third IPV and third Prevnar vaccination. Id. at 12, 32.

On January 17, 2001, Yates was examined by Dr. Hays for thrush and treated with the antifungal, Diflucan. Id. at 33. Yates was eleven months old at the time of the visit. Id.

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

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

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

[267] Prevnar is a brand name for "a preparation of pneumococcal heptavalent conjugate vaccine," which protects against infection by the Streptococcus pneumoniae bacteria. Dorland's at 1505; see id. at 1999.

[268] By this time, all of Yates' received vaccinations, with the exception of the inactivated polio vaccine (which contained attenuated polio virus), potentially contained thimerosal. See Cedillo Ex. II at 29 (vaccination chart contained in Institute of Medicine, Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders, K. Stratton et al., eds. (National Academy Press 2001)).

As reflected in the medical records, Yates saw his pediatrician not only for well-baby visits but also for seven sick visits during his first year. Two of the seven visits were for yeast infections. See Hazlehurst Ps' Ex. 2 at 9-10, 33 (visits on 3/7/00 and 1/17/01). Although Yates presented with ear-pulling more than three times during his first year of pediatric visits, Dr. Hays diagnosed Yates with ear infections and prescribed the antibiotic amoxicillin only three times: on September 27, 2000; on October 31, 2000; and on February 8, 2001. Hazlehurst Ps' Ex. 2 at 22-25, 36.[269]

On February 8, 2001, three days before Yates' first birthday, he received his third hepatitis B, fourth Hib, fourth Prevnar, and first measles, mumps, and rubella ("MMR") vaccination. Id. at 37. As recorded in the notes of this pediatric visit, Yates' parents expressed concern regarding an "ongoing cold for 2 weeks" and indicated that Yates was "starting to pull on [his] ears a little." Id. at 34. But, as noted in the medical notes, Yates did not have a fever. Id. Dr. Hays prescribed a 10-day course of Amoxil, an antibiotic, for Yates. Id. at 36.

The records pertaining to this one-year visit also indicate that Yates was walking without assistance and that he was using the words "mama" and "dada." Id. at 34. The records further reflect that Yates was a "[w]ell [c]hild" with "[n]ormal growth and development." Id. at 36. At almost one year of age, Yates had received 11 doses of vaccines that possibly contained thimerosal and the MMR vaccine.

In his second year of life, Yates saw his pediatrician six times for illnesses. He also saw his pediatrician for his regular well-child visits.

On February 23, 2001, nearly two weeks after his first birthday and his 12-month pediatric visit, Yates returned to see Dr. Hays for an evaluation of his persistent cough and a re-evaluation of his ears. Id. at 40. Dr. Hays speculated that Yates' persistent cough could be due to brochospasms. Id. He ordered a trial of Albuterol, an asthma medication. Id. Dr. Hays remarked that Yates "seemed to have thrush again [and that] he [had] restarted Diflucan." Id. Dr. Hays' notes indicate that Yates' previous ear infection had resolved after switching his prescription from Amoxil to Ceftin. It appears that the Amoxil had caused a rash. Id.

On April 24, 2001, when Yates was 14 and one-half months old, Yates returned to Dr. Hays after "cr[ying] all last night [and] tugging on his ears." Id. at 41. Dr. Hays evaluated Yates and determined that although there was "fussiness," there was no disease present. Id. Dr. Hays noted that there was "[n]o fever" and he was "drooling a little bit and possibly teething." Id. at 41. Dr. Hays opined that "it could be an early otitis . . . [that] just hasn't declared itself yet." Id. He recommended the treatment of Yates' symptoms and continued observation of Yates. Id.

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[269] Although Yates was pulling on his ears at both his September 5, 2000, and his October 26, 2000, visits, Dr. Hays' notes for those dates describe Yates' illness as an upper respiratory infection rather than an ear infection. See Hazlehurst Ps' Ex. 2 at 22, 24.

Yates saw Dr. Hays four months later, on August 17, 2001, for his 18-month physical. Id. at 43. Dr. Hays' records indicate that there were "[n]o parent[al] concerns regarding[] eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, musculoskeletal, integumentary, neurological, endocrine, hematologic, lymphatic, allergic, [or] immunology" symptoms based on the checked responses on the questionnaire completed by the Hazlehursts. Id. A copy of the completed questionnaire was included in Dr. Hays' notes. Yates' parents had indicated on the questionnaire that Yates had problems "sometimes" with his stomach and intestines. Id. at 42. But the filed pediatric records do not elaborate on what those specific problems were. The records from that office visit do reflect that Yates' stooling was "loose [and] soft." Id. at 43. However, Dr. Hays expressed no particular concern about Yates' stooling in his office visit notes. Id. He simply recorded the parents' observations. The Hazlehursts also indicated on the questionnaire completed in connection with this office visit that Yates had problems sometimes with his mouth, his breathing, and that his lymph nodes were "swollen in back of neck." Id. at 42. From the filed records, Dr. Hays does not appear to have expressed any particular concern about those parental complaints either. Again, he simply recorded the parents' observations.

On September 20, 2001, Yates saw Dr. William Stepp, another pediatrician at the Jackson Clinic, because "he ha[d] been [un]usually fussy the last day or two." Id. at 49. Other than Yates' restlessness, "there [was] no sign of illness." Id. The record reflects that Yates was pulling at his ears. Id. Dr. Stepp noted that Yates "has had some ear infections in the past but not in a long, long time. He has not been sick in a long time." Id. Dr. Stepp's assessment was "irritability with no disease found." Id. (omitting all capitals format). Dr. Stepp's plan was to reassure the parents and to advise them to continue to monitor Yates.

On October 23, 2001, Yates saw Dr. Jimmy Hoppers, another pediatrician with the Jackson Clinic. Id. at 50. Dr. Hoppers examined Yates and found that he had a bilateral ear infection. Dr. Hoppers prescribed the antibiotic Cefzil. Id. Because that particular antibiotic caused Yates to develop a rash, Yates' prescription was changed from Cefzil to Biaxin.[270] Id. at 52.

On January 7, 2002, Dr. Joe Ragon, another pediatrician with the Jackson Clinic, examined Yates for thrush. Id. at 53. His examination revealed that Yates had a right ear infection and an oral yeast infection. Id. Dr. Ragon prescribed Zithromax for the ear infection and Diflucan, an antifungal, for the yeast infection. Id.

Two weeks later, on January 18, 2002, Yates returned to see Dr. Hays for a follow-up visit. Dr. Hays noted the recently diagnosed right ear infection and thrush and stated that the "symptoms seem largely resolved." Hazlehurst Ps' Trial Ex. 2 at 1. Written in the

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[270] This is the second recorded instance of an allergic response to a prescribed antibiotic. Eight months earlier in February 2001, Yates developed a rash after taking the antibiotic Amoxil. See Hazlehurst Ps' Ex. 2 at 40.

history section of the medical record is Dr. Hays' note that "[m]om is worried about the fact that he is still having some yeast infections in his mouth. He also occasionally has diaper rash that often responds to Desitin[271] but occasionally needs antifungals. He has been growing well otherwise and has not had severe recurrent infections." Id. (footnote added). Dr. Hays noted that he had a discussion with Mrs. Hazlehurst concerning Yates' infections, and he stated "that recurrent thrush and yeast infections can be a sign of immunodeficiency, but [Yates'] good growth and lack of other serious illnesses makes me less concerned about this." Id. Dr. Hays' proposed course of action included continued observation of Yates. But, "[i]f he has additional unexplained fungal infections, we will consider [a] referral to immunology for evaluation." Id.

A month later, on February 14, 2002, Yates saw Dr. Jonathan Lentz, a pediatrician, for a croup-like illness. Hazlehurst Ps' Ex. 2 at 55. A week later, Yates was examined and treated at a Care Clinic for an acute upper respiratory infection and a bilateral ear infection. Id. at 56. He was also treated for thrush.[272] Id.

On March 21, 2002, Yates saw Dr. Hays for his two-year visit. He was 25 months old at the time of the appointment. On the pediatric questionnaire completed during that visit, Yates' parents indicated that they had concerns about his "learning, development or behavior." Id. at 58. In the medical records under the "other" section, Dr. Hays noted "[c]oncerns for possible PDD/Autism." Id. at 60. Dr. Hays further noted "[r]echeck in 3 months and consider Evaluation at Vanderbilt for development." Id. The medical records also indicate Yates' parents' concern about his recent episode of otitis media (ear infection) and thrush. Id. at 59. With respect to Yates' hearing, the medical records indicate that Yates "doesn't reliably respond to name, doesn't always respond to sounds by quieting or turning head toward source." Id. With respect to Yates' vision, the medical records reflect that "[Yates] focuses and follows with eyes." Id. In addition, the records reflect that Yates "[u]ses 4-10 words, does not say mama, makes sounds in sequence-sound like sentences, . . . [is] [h]appy to play alone[,] [i]mitates simple acts [such as] hugging/loving doll, [or] sweeping[,] . . . [d]oes not routinely ask for things." Id.

The particular record notation from Yates' two-year checkup that Yates "does not say mama" provides evidence of the loss of a previously acquired skill. Yates' medical records from his one-year checkup state that he was using the word "mama." Id. at 34.

Five days later, on March 26, 2002, Mr. Dunwel MacAllister, an audiologist, assessed Yates' hearing at the request of Dr. Hays, and in response to Yates' mother's concerns about possible hearing loss and delays in the development of Yates' speech. Mr. MacAllister wrote, "I did not observe a behavioral response (head turn, eye blink, startle) when I presented my voice through speakers up to 80 dB. I did observe a head turn for

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[271] Desitin is an over-the-counter ointment for diaper rash.

[272] The record states, in the bottom right corner, "oral candiasis." Hazlehurst Ps' Ex. 2 at 56. The undersigned construes the notation as a misspelling of "oral candidiasis," which is an oral candida infection (otherwise known as thrush). See Dorland's at 282, 1908.

warble tone testing at 80 dB . . . testing was discontinued because of excess fussiness and a crying behavior." Hazlehurst Ps' Ex. 2 at 63. The audiology records indicate that the tympanogram of the right ear suggested "normal middle ear compliance with significant negative middle ear pressure[,] which may be consistent with eustachian tube dysfunction." Id. The left ear test suggested reduced middle ear compliance values with possibly normal middle ear pressure valves." Id. The test not completed due to non-cooperation. Id. Recommendation was made for further middle ear testing and a referral to Dr. Ron Kirkland. Id.

Two days later, on March 28, 2002, Dr. Kirkland evaluated Yates and noted that "[e]ven though the likelihood of sensorineural hearing loss still exists, I think the more likely situation now is that this youngster will end up having normal or relatively normal hearing . . . but have some conductive loss from a history of recurrent otitis media." Hazlehurst Ps' Ex. 2 at 65. Dr. Kirkland scheduled Yates for "a hearing evaluation with auditory brainstem response on April 5." Id. at 66.

On April 5, 2002, Yates returned to the audiologist, Mr. MacAllister, who conducted a further hearing assessment while Yates was asleep. Mr. MacAllister concluded that the "screening results as well as the hearing evaluation . . . suggest[] that William's hearing falls within the normal range for each ear."[273] Hazlehurst Ps' Ex. 2 at 70.

Nearly two weeks later, on April 17, 2002, Dr. Hays evaluated Yates again. Dr. Hays had received the results of Yates' hearing tests, which were normal. Expressing concern about Yates' speech delay, Dr. Hays informed the Hazlehursts that "[w]e will go ahead and pursue getting an appointment with Vanderbilt for [a] developmental evaluation if he is not improving as we would expect in the next couple of months." Id. at 72.

The medical records reflect that less than one week later, Mrs. Hazlehurst gave a written authorization for Yates' medical records to be released to the Child Development Center, Intake Office, at Vanderbilt University Medical Center. See Hazlehurst Ps' Ex. 2 at 73.

On May 23, 2002, Dr. Karl Studtmann of the West Tennessee Ear Nose Throat (ENT) Clinic examined Yates. Hazlehurst Ps' Ex. 11 at 1. Yates was 27 months old. As stated on the patient information form for this visit, the purpose of the visit was to evaluate Yates' "speech defect." Hazlehurst Ps' Ex. 11 at 7. The medical records from that clinic visit provide:

> 2 year old child with a history of at least 8 episodes of otitis media over the past 8 months. He has been treated with multiple antibiotics including Biaxin, Zithromax, Surfatrim. Despite this he continues to have recurrences. The patient has had ABR [auditory brain-stem response, (a hearing test)] which was reportedly normal according to the parents. The patient is very interesting in that he had a period of time when his ears were clear. He had a

[273] William is Yates' first name.

> remarkable improvement in his language skills and was much more alert and interactive. Since that time he has had a marked regression in his language skills. The parents were somewhat concerned that he might have had some sort of processing disorder. However, he does seem to have normal interaction and seems normally affectionate with his family.

Hazlehurst Ps' Ex. 11 at 1. Dr. Studtmann's recommendation was to place tubes in Yates' ears at the next available date. Id.

On May 29, 2002, Yates was examined at The Children's Clinic, in Jackson, Tennessee. Hazlehurst Ps' Ex. 5 at 3. The medical records reflect that "[Yates h]as been followed at the Jackson Clinic but the [Hazlehursts'] insurance has switched so they are going to start coming here." Hazlehurst Ps' Ex. 5 at 1. Additionally, the records reflect that Yates [i]s "being evaluated at Vanderbilt this next month for possible autism or autism related disorders." Id. The following notations were also in the medical records from that Children's Clinic visit:

> [Yates a]lso has chronic otitis media, was due to have tubes put in tomorrow by Dr. Studtmann. Has had at least 8 confirmed episodes of otitis media, but last time they checked him, his ears were clear. He has speech delay. Had spoken very well until about a year ago when it seemed to be decreasing or less than a year ago. Has indistinct speech, flaps his hands when he gets excited. He does not make good eye contact. Seems to relate well to other children and to adults.

Id. At the time of his Children's Clinic visit, Mrs. Hazlehurst reported that "he runs a low grade fever all the time but just popped up to 102 today." Id. The impressions from the visit were:

> [1.] [h]erpangina [viral infection in mouth]
> 2. [p]ossible autistic child
> 3. [h]istory of chronic otitis media with speech and hearing delay/problems.

Id.

Two weeks later, on June 10, 2002, pressure equalization tubes were inserted in both of Yates' ears. See Hazlehurst Ps' Ex. 11 at 2.

Nearly one month later, on July 3, 2002,[274] Dr. Vanessa Elliott, a clinical psychologist, evaluated Yates for developmental delays at the Vanderbilt University

[274] Although the record is dated July 3, 2002, there is other evidence in the record suggesting that this evaluation actually took place on June 3, 2002, and the records were dated incorrectly.

Medical Center.[275] See Hazlehurst Ps' Ex. 6. Yates was nearly 27 months old when Dr. Elliott evaluated him. The Hazlehursts were referred to Dr. Elliott for an evaluation because Yates was "reported to have speech delays and trouble communicating his wants and needs. His parents also report[ed] that he appears deaf on occasion and has a fascination with letters and numbers. The parents are concerned that Yates may have some form of autism and are seeking a thorough evaluation to determine how best to help their son." Hazlehurst Ps' Ex. 6 at 1. Based on her evaluation of Yates, Dr. Elliott concluded that Yates was "demonstrating a significant number of behaviors consistent with a diagnosis of [a]utism." Id. at 4.

After Dr. Elliott's evaluation of Yates, Mr. Hazlehurst and his mother presented at the pediatric clinic in Jackson to question Dr. Hays regarding "immunization policies at the clinic." Hazlehurst Ps' Ex. 2 at 81. Mr. Hazlehurst explained to Dr. Hays that he was seeking information pertaining to "Yates' recent diagnosis at Vanderbilt of autism spectrum disorder." Id. Mr. Hazlehurst began a recorded interview of Dr. Hays with "general questions about autism and what it is." Id. Dr. Hays provided Mr. Hazlehurst with "a computer printout of immunizations that Yates had received, including manufacturer and lot numbers, with the exception of [Yates'] first three immunizations, which were not on the computer." Id.

Subsequently, Yates was evaluated by a registered occupational therapist on July 1, 2002. Hazlehurst Ps' Ex. 12 at 9. At the time of the evaluation, Yates was 29 months old. Hazlehurst Ps' Ex. 12 at 9. The occupational therapist noted the following:

> Mother reports normal development through age 18 months. Around his [second] birthday, Mr. and Mrs. Hazlehurst noticed that his speech had not been developing and had begun to regress. Yates was referred to Vanderbilt [for] a developmental evaluation. This was completed . . . by Dr. Elliott, a psychologist, with a diagnosis of autism. . . . His tubes were placed in early June of this year.

Id. at 9-14; Hazlehurst Ps' Ex. 15 at 1.

Yates' medical records indicate that he did receive an immunological evaluation when he was 32 months old. The records reflect that on October 28, 2002, Michael S. Blaiss, M.D., a pediatric immunologist, examined Yates and reported that "all the immune studies were normal on Yates."[276] Hazlehurst Ps' Ex. 16 at 14. Dr. Blaiss further reported

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[275] Dr. Elliott's evaluation is dated July 3, 2002. The records also include notes from an initial speech therapy evaluation, performed by Robin Garabedian, a speech language pathologist, at the Kiwanis Center for Child Development. These records indicate that this evaluation also took place on July 3, 2002, and reference Dr. Elliott's diagnosis of Yates' autism as taking place as well on June 3, 2002.

[276] Dr. Blaiss "is a Clinical Professor of Pediatrics and Medicine at University of Tennessee. He is also in private practice in allergy and clinical immunology in Memphis. (continued...)

that Yates had "IgG of 618; IgA 77; IgM 59. He had normal compl[e]ment studies and total complement levels.[277] His tetanus titer was normal[, and] [h]e had normal T and B cell numbers." Id. Dr. Blaiss concluded that Yates showed "no evidence of any type of immunological defect." Id.

Also included in the medical records for Yates and of interest to this litigation is a report by gastroenterologist Dr. Timothy Buie of Massachusetts General Hospital at the request of Yates' grandparents, Dr. Buie examined Yates on April 17, 2003. Hazlehurst Ps' Ex. 14 at 91-92; Hazlehurst Ps' Ex. 20 at 4-7; See Hazlehurst Tr. at 81A (Yates' grandmother describing her efforts and the efforts of her husband, who is also a gastroenterologist, to obtain an appointment with Dr. Buie for Yates.). During the examination, Dr. Buie performed a colonoscopy on Yates to evaluate his gastrointestinal problems. In his notes, Dr. Buie wrote: "The digital rectal exam was normal. Noted nodular lymphoid hyperplasia at the sigmoid colon and rectum. Biopsies were taken with a cold forceps for histology. The colon (entire examined) portion was normal. Impression: The colon . . . is normal." Hazlehurst Ps' Ex. 14 at 91-92; Hazlehurst Ps' Ex. 20 at 6-7. During a status conference with the undersigned in the course of this litigation, petitioners' counsel stated that Yates' biopsied gastrointestinal tissue was not submitted for PCR-testing to check for the presence of the measles virus. See Order dated 7/18/07 at 2.

2. The Testimony of Yates' Family

In addition to the filing of Yates' medical records, members of Yates' family offered testimony about their observations of Yates' development during the first years of his life. In short, the Hazlehursts contend that Yates developed normally during the first year of his life. Hazlehurst Brief at 6. His family asserts that after Yates received his MMR vaccination on February 8, 2001, three days before his first birthday, his behavior changed, and he lost many of his earlier social and communication skills. Compare Hazlehurst Brief at 2, 10 with Hazlehurst Brief at 6. Yates' family testified more specifically during the Hazlehurst hearing about the observed changes in Yates' behavior and when the family first noticed those changes. The undersigned found that the Hazlehurst family members testified sincerely and honestly.

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[276](...continued)
. . . He is the immediate past President of American College of Allergy, Asthma, and Immunology and a Fellow of American Academy of Allergy, Asthma, and Immunology. Dr. Blaiss has also served on the board of American Board of Allergy and Clinical Immunology and the Joint Council of Allergy, Asthma, and Immunology. He is on the editorial board of Annals of Allergy, Asthma, and Immunology and the Journal of Asthma. Dr. Blaiss has given numerous presentations throughout the world." See http://www.glgroup.com/Council-Member/Michael-Blaiss-7579.html (last visited on 2/1/09).

[277] "The complement system is composed of about twenty different proteins that work together to destroy invaders and to signal other immune system players that the attack is on." L. Sompayrac, How the Immune System Works at 15.

Members of Yates' family testified during the hearing that one month after Yates had received the MMR vaccination, he became "wild," "very hyperactive," and "out of control." Hazlehurst Tr. at 31A-38A (Angela Hazlehurst, petitioner, and Yates' mother), 57A-61 (Anne Gerard, Yates' paternal aunt), 74A-77A (Aud Hazlehurst, Yates' paternal grandmother), 98A-104A (Rolf Hazlehurst, petitioner, and Yates' father). Yates' mother testified that as of March of 2001, "you had to constantly watch Yates." Hazlehurst Tr. at 31A. She stated that at Christmas of 2001, Yates "jollily, gladly sat up for a beautiful Christmas photo. I could put him on my hip, I could hold him, or he could sit in my lap, and there wasn't a problem." Id. at 32A. But "[b]y Easter, we were concerned of even leaving Yates in the nursery just because he just didn't seem to be quite as consoled." Id. Mrs. Hazlehurst further stated that "[m]y little boy that once sat on my lap, he just wanted to run." Id. When asked if the way that Yates interacted with his parents also changed in March 2001, Mrs. Hazlehurst indicated that it had. She said that "[a]t some point in that spring[,] [I] felt [that]. . . Yates just doesn't seem to be into me, and I made a note of it, and I thought well, maybe it's because he's sickly." Id.

Mrs. Hazlehurst noted other changes in Yates' behavior and developmental skills in 2001. She stated that by the summer, "Yates had lost all meaningful speech. Bye-bye, mama, patty-cake, please, thank you, were gone, and they were replaced with unmeaningful speech such as an obsession with numbers and letters." Id. at 33A. "I can specifically pinpoint a trip to Norway [at] the end of June. . . . Yates was so wild and hyper that we had to purchase a harness to keep him with us, so on this trip there's photos, and Yates is always in a harness because he would run so wildly. During this time because we were on vacation and not home, I have specific memories of diarrhea. We could not purchase enough diapers in Norway. There were also a few screaming episodes in Norway where Yates was unconsolable." Id. at 34A.

Yates' paternal grandmother, Mrs. Aud Hazlehurst, testified that after his first birthday, February 11, 2001, "Yates seem[ed] to stay sick all the time." Hazlehurst Tr. at 82A (Mrs. Aud Hazlehurst). She further testified that his head and his lymph nodes felt hot to the touch, and he seemed to stay warm. Id. at 83A-84A. It was Yates' grandmother's recollection that some time around Easter, between March and April of 2001, Yates became particularly difficult to control. Id. at 73A-77A. Yates just wanted to run. Id. at 74A-76A. Yates' grandmother also recalled that Yates' symptoms began shortly after his first birthday, and to help pinpoint the period of time within which a noticeable change in Yates' behavior occurred, she compared Yates' behavior at Easter in 2001 with his behavior during the preceding Christmas in 2000. She explained that "at Christmastime, we had noticed how he played with his toys. Of course, he wasn't a year old then, but he was running around, getting into packages, unwrapping them but at a normal speed. After . . . his first birthday I can remember saying isn't it sad, he's sick. He doesn't interact with us like he did, but he had a runny nose and pulling on his ear and a slight fever . . . . [H]e never seemed to be the same Yates after his first birthday." Id. at 73A-74A. In addition, Yates' grandmother also remarked that Yates' speech changed after his first birthday with "probably the most noticeable change . . . in the fall." Id. at 77A. His grandmother also recalled that Yates became a particularly discriminating eater right around the time of the Norway trip. She said "[r]ight before we left for Norway in June is when I would say he became very picky because I had this conversation with Aunt Bert, and she packed him special foods that she knew he would eat [on the trip]." Id. at

79A.

Yates' father, Rolf Hazlehurst, succinctly described in his testimony the time line of Yates' decline: "he develops typically, hits that plateau at his first birthday. Then in the spring he's slowly going down spring and summer, and it wasn't until the fall that he just drops like a rock, and that's the point it becomes obvious. That's the point I started to get concerned." Id. at 120A.

Yates' mother testified that Yates' gastrointestinal problems first appeared during the family's trip to Norway, which was a memorable event, in part, due to the family's ongoing need to purchase diapers for Yates' diarrhea. See id. at 34A. When asked how long Yates' diarrhea lasted, Mrs. Hazlehurst indicated that in June of 2001, "we made some dietary changes, and those changes helped somewhat with the diarrhea. I would say the diarrhea continued up until we saw Dr. Buie, which is why we went to see Dr. Buie . . . . [W]e were concerned [about] . . . the distended gut and the diarrhea." Id. at 35A.

Yates' grandmother also talked about his gastrointestinal problems. It was her recollection that the problems began on the trip to Norway and lasted until he was diagnosed with autism: "Unfortunately, it lasted for a very long time. I believe Yates had been diagnosed with autism when I was getting very, very, very concerned that he was getting [to be] skin and bones. It really hurt me to put him in the bathtub. His belly was [so] large. . . ." Id. at 80A. Yates' grandmother acknowledged that her concern for her grandson and her hearing "about all the findings in England" led to her imploring her husband to "call Christopher Williams. . . a well-renowned gastroenterologist that came to the United States frequently, but . . . practice[s] in London. We called Dr. Williams, and he says well, let me get you in touch with Simon Murch, who is up on children with gastrointestinal problems. We called. We did not know Simon Murch, but I called and introduced myself and said I'm a desperate grandmother. I need help. I need the help bad because I can't stand to look at Yates being so thin. He said [his] . . . recommendation would be to get in touch with Dr. Buie at Harvard, and he also mentioned Dr. Krigsman . . . I believe at the time. He said personally he knew Dr. Buie, so I called Harvard." Id. at 81A.

Yates' father provided additional information regarding Yates' gastrointestinal problems. Mr. Hazlehurst stated that during the family trip to Norway, which lasted from June 23 through July 7, 2001, was "the first time I can recall [Yates'] . . . gastrointestinal [symptoms]. First . . . the loose stools, and then diarrhea, and it may be that I'm remembering it because we were in pretty tight quarters. We were on a ship. . . . [in] a small cabin, and it tends to be more noticeable when there's three of you piled into this small room, and then he's frequently having bowel movements." Id. at 106A. Mr. Hazlehurst indicated that Yates' gastrointestinal problems "got better when we put him on the casein and gluten-free diet, but it really did not clear up until we took him to see Dr. Buie." Id. at 108A. According to Mr. Hazlehurst, Yates saw Dr. Buie in April 2003. Id. Mr. Hazlehurst explained: "I wouldn't say [the diarrhea was] constant in the beginning. In the spring or summer, it's less frequently, spring of 2001. By the fall 2001, it is more intense in both number of times and the severity, and there's some constipation mixed in there as well. Id.

Mr. Hazlehurst stated that his concerns with Yates' development began in 2001, more particularly in "late fall, early winter of 2001, but I kept that to myself. I had difficulty admitting there's something wrong with my child." Id. When asked about the first change in Yates' behavior that he had noticed, Mr. Hazlehurst stated that although he saw changes in Yates' behavior after February 8, 2001, "the changes did not occur overnight. He didn't become autistic like he got the shots, and he was autistic. It didn't happen that way. It was a slow downward spiral. It's kind of like watching grass grow. It's happening, but you don't really notice it. [One] . . . of the changes that I can remember after he was vaccinated, and shortly before he turned one, [was that] he seemed to have less interaction with us." Id. at 98A-99A.

Mr. Hazlehurst reiterated earlier testimony from his wife, his sister, and his mother that Yates started running wild in the spring and summer of 2001. See id. at 99A-102A. During this time, "Yates . . . . didn't want to be still." Id. Mr. Hazlehurst further elaborated that "[Yates] would not sit still. You'd put him down and he's running around the room and [exhibiting] destructive behavior. Just wanting to push everything off the tables. Starting in that time period he became obsessed with flushing the toilet." Id. at 102A.

Although none of the Hazlehurst family's testimony specifically addressed how the family first causally linked Yates' vaccinations to the development of his autism, the testimony made clear that the family believed that the vaccinations that Yates received prior to and on February 8, 2001 were responsible for the development of Yates' autism. On March 26, 2003, the Hazlehursts filed this petition on behalf of their son, Yates, seeking compensation under the Vaccine Program.

B. Petitioners' Claim after the Hearing in this Case Limited to the Impact of the MMR Vaccine Only

Petitioners in this case assert that Yates received thimerosal-containing vaccines, Amended Petition ¶ 3, and petitioners filed medical records reflecting Yates' immunization history. Petitioners' Exhibit 2 at 12. However, petitioners have not supplied specific evidence that the vaccines that Yates received actually contained thimerosal.[278]

Moreover, after the hearing in this case, the Hazlehursts stated in their post-hearing brief that "[a]t the hearing, it became apparent (to Rolf and Angela Hazlehurst) that the evidence that the MMR vaccination caused Yates' regressive autism was stronger than that implicating thimerosal vaccines." Hazlehurst Petitioners' Post-Hearing Brief (Hazlehurst

[278] Whether Yates' vaccines contained thimerosal is of interest because vaccine manufacturers discontinued the use of thimerosal as a preservative in most childhood vaccines after the issuance of the Joint Public Health Statement in September 1999 by the American Academy of Pediatrics and the United States Public Health Service recommending the removal of the thimerosal from childhood vaccines. See Section III.B.3., supra.

Brief) at 1. Although "[i]t was not clear [to the Hazlehursts] that the available evidence on thimerosal-containing vaccines would satisfy the third Althen criteria[, which requires a proximate temporal relationship between the received vaccine and the injury], for establishing causation in fact," petitioners assert that their case "remains an appropriate test case for the thimerosal and MMR theory because the focus of their case, MMR vaccine causation, is an essential element of any case alleging that thimerosal and MMR caused a child to develop autism." Id. at 1-2. As reflected in their post-hearing brief, the Hazlehursts limited "the focus of their case [solely to] MMR vaccine causation." Accordingly, the undersigned considers only the arguments and the evidence pertaining to the MMR vaccine in deciding the Hazlehursts' case.

In support of their specific claim, the Hazlehursts argue that the persistence of the measles virus in Yates' body caused neurological damage that resulted in his autistic condition. Petitioners contend that Yates' was developmentally normal prior to the receipt of his MMR vaccine, and that he suffered a regressive form of autism after that vaccination. See Hazlehurst Brief at 15-16. Petitioners assert that Yates' autistic condition is complicated by gastrointestinal problems that were also caused by the persistence of the measles virus in Yates' gastrointestinal tract. Id.

In considering this case as one of the three test cases on the first general causation theory, the undersigned addressed in Section III.B, above, the general causation evidence developed in the Cedillo and Snyder cases as well as the general causation evidence developed in this case on the causal link, if any, between the development of autism and the receipt of thimerosal-containing vaccines in combination with the MMR vaccine. The undersigned found that petitioners' offered no reliable scientific evidence supporting their claim that mercury exposure through thimerosal-containing vaccines causes immunosuppression in vaccinees, facilitating the development of autism. This aspect of petitioners' general causation theory fails.

The undersigned decides Yates' case on the singular ground proposed by the Hazlehursts and therefore, limits the following specific causation discussion to the causal contribution, if any, of Yates' MMR vaccine to the development of his regressive autism.

C. Dr. Corbier's Theory of Causation

In support of their claim, the Hazlehursts offered the testimony of Jean Corbier, M.D., Yates' treating neurologist. See Hazlehurst Tr. at 266A. Dr. Corbier testified as petitioners' only expert witness during the hearing in Hazlehurst.

Dr. Corbier opined that autism is a neurodevelopmental condition that presents with core areas of deficits: (1) problems with communication and language; (2) impaired social interaction; and (3) behavioral abnormalities that include very restricted interests and self-stimulatory behaviors such as handflapping. Hazlehurst Tr. at 267A. Dr. Corbier testified that the timing of the appearance of the first symptoms of autism is "highly variable." Id. at 267A. Some children present with symptoms at a year or less, and others start showing signs between the ages of 15 months and two years. Id.

Dr. Corbier stated that the differences in the timing of the first appearance of the

symptoms of autism suggest that there are differences in the underlying causes of autism. Id. at 269A. The earlier the onset of the symptoms, the more likely that the cause of the autism is genetic, prenatal, or metabolic. Id. But if the child develops regressive autism (the onset of which is later, is characterized by withdrawal and a loss of interest, and is preceded by normal development), the causal factors are "very likely . . . [to be] genetic influences and external environmental factors." Id. at 269A-271A.

Dr. Corbier testified that studies have implicated the MMR vaccine as an environmental factor that can contribute to the development of regressive autism in a subset of children fitting within a particular "clinical profile." Id. at 271A. The clinical profile that he stated would implicate the MMR vaccine as a cause of a child's regressive autism is: (1) normal development before receiving the MMR vaccine; (2) evidence of immunological problems that result from a genetic vulnerability; (3) the presentation of gastrointestinal problems; and (4) the development of regressive autism between one to nine months after MMR vaccination.[279] Id. at 271A-272A, 277A, 306, 313A-315A, 325A-326A, 336A, 360A-364A; see also Hazlehurst Brief at 15-16.

As the basis for his opinion that a causal relationship exists between the MMR vaccine, autism and gastrointestinal symptoms, Dr. Corbier explained, as a threshold matter, "several studies have implicated the measles virus itself as a contributing factor to both gastrointestinal problems and neurological problems, including autism and developmental delay." Hazlehurst Tr. at 272A (emphasis added). Dr. Corbier added that other studies have reported finding the measles virus in tissue taken from the gut of developmentally delayed children with gastrointestinal problems (referring to the 2002 Uhlmann article) or reported finding persistent vaccine-strain measles virus in tested tissues taken from the gut of children with autism (referring to the 2000 Kawashima article). Id. at 272A-273A. He observed that because wild-type measles virus "is very virulent and very immunosuppressive," the existence of a causal relationship between the MMR vaccine, autism, and gastrointestinal symptoms "would make a lot of sense, based on a biological framework." Id. at 274A. Additionally, because wild-type measles has been associated with the conditions of SSPE and MIBE that produce serious neurological consequences in the affected persons, see Section III.C.2.d, above, Dr. Corbier stated that the wild-type measles virus provides a "perfect model for looking at" the neurological effects of the attenuated MMR vaccine. See id. at 275A-276A.

Dr. Corbier posited that the 2002 Uhlmann study, upon which he relies for the proposition that measles virus is found in the gut of children with autism, is a reliable study because the investigator "used a lot of controls and up-to-date techniques to try to verify the persistence of measles virus in the group of children that he studied: namely, children with developmental delays." Id. at 279A. In Dr. Corbier's opinion, the 2002 Uhlmann study "was a well-done, valid study." Id. Of the labs that have tried to replicate the Uhlmann findings, Dr. Corbier thinks that Dr. Walker's lab "has done a better job at

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[279] Dr. Corbier based his opinion regarding the time period within which the onset of regressive autism would occur after the MMR vaccination on the time period within which encephalitis has been reported to occur after the MMR vaccination. Hazlehurst Tr. at 306, 336A.

replicating the [Uhlmann] findings than [have] other molecular biologists." Id. at 279A-280A. Dr. Corbier stated that the preliminary findings of the Walker study about which Dr. Hepner and Dr. Krigsman testified during the Cedillo hearing "validate[d] the findings of Dr. Uhlmann and others." Id. at 280A, 434A (acknowledging that the results of that study have yet to be published).

Dr. Corbier opined that the MMR vaccine can cause autism by first impairing the immune system of the vaccinee. Id. at 327A. The impaired immune system allows the measles virus to persist and affect the brain directly. See id. But, he added, a persistent measles virus is not required to cause central nervous system injuries. Id. at 280A. Rather, Dr. Corbier explained, after the clearance of the viral infection, an overreactive immune system can create in some circumstances an autoimmune disorder that causes central nervous system injuries. Id. at 280A-281A, 327A. Autism is the resultant injury in a "very specific subset of children" who have the particular clinical profile that Dr. Corbier described. See id. at 271A. Dr. Corbier does not think that the MMR vaccine causes autism in general, only in a certain population. Id.

The undersigned turns now to examine the components of Hazlehursts' claim based on the causation theory articulated by Dr. Corbier and informed by the opinions of the other experts who testified during the hearings in the first three test cases.

D. Examining the Components of the Hazlehursts' Claim

1. The Claim that Yates has Regressive Autism that Followed First a Normal Course of Development and Then the MMR Vaccine

Dr. Corbier first saw Yates for neurological treatment in September 2002, Yates was approximately 19 months old and had been diagnosed with autism two months earlier. See Hazlehurst Tr. at 334A At the time that Dr. Corbier examined Yates, he took a history of Yates that suggested that the onset of Yates' regressive condition occurred at the age of 18 months. Id. But a subsequent review of videotapes of Yates and the opportunity to hear the testimony of Yates' family members during the Hazlehurst hearing informed Dr. Corbier's opinion that key changes in Yates' behavior first occurred several months after Yates received the MMR vaccine. Id. at 288A-299A. Dr. Corbier testified that Yates had developed normally during his first year of life. Hazlehurst Tr. at 288A.

Dr. Corbier described certain changes in Yates' behavior after his receipt of the MMR vaccine–specifically, running wild, losing some words "that he had mastered before," losing interest in others and in toys that he used to enjoy, and becoming a picky eater–that Dr. Corbier viewed as the first symptoms or signs of Yates' regressive autism. See id. at 288A-290A, 292-293A. Yates received a diagnosis of autism in July 2002. See Hazlehurst Ps' Ex. 6 at 4.

Respondent does not dispute petitioners' claim that Yates exhibited a normal course of development prior to the onset of his autism or that Yates developed the regressive form of autism. The evidence supports a finding that Yates' autism is more likely than not the regressive form.

The evidence also supports a finding that the onset of Yates' autism began within the six month time period following the receipt of his vaccination. Yates received a diagnosis of autism nearly five months after he had received the MMR vaccine. Although a temporal association does exist between the two events because the injury did occur after the vaccination, that showing alone is not sufficient for petitioners to prevail on their claim. The Federal Circuit requires a proximate temporal relationship between the vaccination and the injury, see Althen, 418 F.3d at 1278 (the third prong of the three-prong test) (emphasis added), and "some evidence of a temporal linkage," see Pafford, 451 F.3d at 1358. Petitioners must present evidence that supports a finding that the onset of the injury occurred within a medically acceptable time frame. See Pafford, 451 F.3d at 1358.

Here, Dr. Corbier described timing as a "paramount" consideration in his diagnostic opinion pertaining to Yates. Hazlehurst Tr. at 336A. His opinion on the time within which an autistic injury must follow the MMR vaccine to be causally-related is based on articles discussing biological possibility and known reports of post-MMR encephalitis. He determined that the autistic injury must follow the MMR vaccine within a one to nine month period of time to be causally-related and medically appropriate. Petitioners were not assisted, however, by Dr. Kinsbourne's testimony that he did not know how long it would take for measles virus, after a MMR vaccine, to reach the brain. See Cedillo Tr. at 1156-1157 (Dr. Kinsbourne). But when questioned further at hearing, he stated that based on his review of the medical records of children with regressive autism in connection with the U.K. litigation, he found the onset of autism occurred within a week to three months after the MMR vaccine. See id. at 1177-1178A. After three months, the onset of autism "sort of tailed off" and his confidence that the onset was vaccine related "might decrease" as well. Id. The opinions of the experts differ, and do not persuade the undersigned that the timing of the onset of Yates' autistic condition was more likely than not causally-related to his received MMR vaccine particularly when considered in connection with the other prongs of the Althen standard.

2. The Claim that Yates has a Compromised Immune System

Dr. Corbier pointed to Yates' "recurrent" viral and yeast infections, swollen lymph nodes, and prolonged fever as evidence of a compromised immune system. Hazlehurst Ps' Ex. 26 at 3-6, 8, 12, 16-17; Hazlehurst Tr. at 299, 305A, 315A-319A, 362A-364A, 427A-431A. He explained that

> [S]omeone who is sick all the time, you can infer that there's something [wrong] with their immune system; their immune system is impaired. . . . So I think that the fact that he was sickly, sick all the time, means–and even the lymphadenopathy that several [family] members have pointed out. Lymphadenopathy is just swollen lymph nodes that [are] . . . usually a reactive sign that there's an infection going on.[280]

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[280] Lymphadenopathy is defined as "disease of the lymph nodes." Dorland's at 1074. It is further defined as: "1. Any disease process affecting a lymph node or lymph (continued...)

> If the lymph nodes are swollen all the time or for a long period of time, it means that the body is still reacting to viruses. In fact, it would actually make me think of a persistence of some type of virus. And of course, we talked of persistence of measles virus.

Hazlehurst Tr. at 316 (footnote added). Dr. Corbier acknowledged, however, that he is a specialist in child neurology and not in child immunology. Hazlehurst Tr. at 415A. He added that on issues related to immunology, he would defer to a board-certified pediatric immunologist. Id. at 416A.

Two of the filed records in this case reflect a mention by Yates' family of concern about his lymph nodes. During an office visit on September 5, 2000, when Yates was nearly seven months old, Yates' mother reported to the pediatrician Dr. Hays her concern about a few little lymph nodes she had felt behind Yates' left ear and she asked whether he might have an ear infection. Hazlehurst Ps' Ex. 2 at 22. Additionally, at two years of age (and one month prior to the assessment indicating that Yates had a speech/language developmental disorder), Yates presented to his pediatrician with enlarged tonsils, lymph nodes, and a runny nose for treatment of an acute bilateral ear infection and an upper respiratory infection. See Hazlehurst Ps' Ex. 2 at 56, 60. Yates' father and his paternal grandmother stated in their filed affidavits that Yates frequently had swollen lymph nodes. Hazlehurst Ps' Ex. 29, ¶ 28 (Rolf Hazlehurst's affidavit stating that Yates' had chronically swollen lymph nodes between the spring of 2001 and the fall of 2004); Hazlehurst Ps' Ex. 30, ¶ 11 (Aud Hazlehurst's affidavit stating that she would "always . . . check his swollen lymph nodes").

Yates' father and paternal grandmother also testified that Yates felt "warm" for a protracted period of time. See Hazlehurst Tr. at 83A-84A, 87A, 126A-127A; see also Hazlehurst Ps' Ex. 30, ¶ 11 (Aud Hazlehurst's affidavit stating that after Yates turned one year old, "his head was always hot"). Although his family expressed concern about his temperature, Yates' father and his paternal grandmother acknowledged that they had not obtained reliable measures of Yates' temperature during that time. See Hazlehurst Tr. at 87A, 126A-127A.

Yates' family's concerns may have prompted the evaluation of Yates' immune system by pediatric immunologist Dr. Blaiss In October 2002. The results of Yates' immunological examination were normal.

Aware of the results of Yates' immunological testing but struck by Yates' clinical picture, Dr. Corbier described Yates as having an immunological impairment. Hazlehurst Tr. at 319A. He conceded, however, that Yates was "[n]ot necessarily immunodeficient" which "[m]ost physicians" recognize as an immune system with "severe abnormalities that you can document with lab[] [work]." Id.

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[280](...continued)
nodes. 2. The appearance of enlarged lymph nodes found on a radiologic examination of any kind." Stedman's at 1126.

Respondent's expert witness Christine McCusker, M.D., a board-certified pediatric immunologist, testified during the Hazlehurst hearing that she concurred with the conclusion reached by Yates' treating immunologist, which was documented in Yates' medical records, that Yates had no immunological defect. His immunoglobulin levels were within the normal limits for his age, an indication that his body was able to make and maintain a level of antibodies. Hazlehurst Tr. at 578A-579A His complement levels were also normal and showed normal function. Id. at 581A; see also L. Sompayrac, How the Immune System Works at 15 (stating that the complement system is composed of twenty different proteins that work together to destroy invading agents).

Dr. McCusker testified that Yates' immune system was normal and that his vaccinations neither caused nor contributed to his autistic disorder. Hazlehurst Tr. at 565A-566A. Dr. McCusker stated that there is no reliable medical evidence in the peer-reviewed medical literature that implicates immune system mechanisms in autistic disorders. Nor is there any evidence of which she is aware based her own experience as a pediatric immunologist, that a causal association exists between autism and compromised immune system mechanisms. Id. at 585A-586A. She has tested the immune profiles of nearly 100 children with autism over an eight-year period and has found that only one had an immunodeficiency. Id.

Dr. McCusker looked at the frequency of Yates' infections to evaluate whether he experienced more frequent infections than expected for his peer group. Hazlehurst Tr. at 566A. She explained that during the first four months of life, children are partly protected immunologically by maternal antibodies. Id. at 567A. The first infections usually occur in children between four and six months of age. Id. at 568A. The frequency of infection increases as the maternal antibodies begin to wane. Id. at 567A. Between six months and two or three years of age, a child can be expected to have six to 10 infections per year, more or less. Id. at 568A. That number of infections is generally considered by pediatricians to be the normal range. Id. Dr. McCusker stated that Yates' infection history of "four physician[-]diagnosed upper respiratory infections and seven ear infections, five of which were associated with documented viral illnesses . . . [was] entirely within . . . a normal frequency of infection in a child of his age." Id. at 566A-567A.

Dr. McCusker addressed the condition of Yates' lymph nodes. Dr. McCusker pointed out that no abnormality was reported in the one record notation pertaining to Yates' swollen lymph nodes. See id. at 572A; see also Hazlehurst Ps' Ex. 2 at 22. Dr. McCusker stated that swollen or palpable lymph nodes are normal in small children. Hazlehurst Tr. at 572A. The palpable lymph nodes (or lymphadenopathy) reflect a normal immune response to the "onslaught of infectious agents" that Yates experienced. Id.

Dr. McCusker also addressed Yates' body temperature. Id. at 573A. Dr. McCusker explained that children have a temperature range between 97 to 101.3 degrees Farenheit (or 36 to 38.5 Celsius) that is considered normal. Id. at 573A-574A. That temperature range reflects normal variances in metabolic rate and is not considered clinically significant. Id. at 574A. Dr. McCusker stated that fever is usually accompanied by behavior changes, and in the absence of a fever, a child that "feel[s] hot" raises no concern. Id.

Dr. McCusker discussed Yates' episodes of thrush. Id. at 575A. She stated that "in the case of a child who required a lot of antibiotic use" or a child who engages in mouthing behaviors (such as thumb sucking or blanket sucking), episodes of thrush would not necessarily cause concern. Id. at 575A-576A, 591A. Yates was prescribed a number of courses of antibiotic use in connection with his ear infections. See generally id.

Dr. McCusker testified that Yates' immunological evaluation showed no evidence of an immunodeficiency. Nor was his medical history through the first seven years of his life consistent with the expected clinical course of an immunodeficient patient. See Hazlehurst Tr. at 583A-585A. Children with primary immunodeficiency, a condition present at birth, "become sicker and sicker and sicker with recurrent infections." Id. at 584. Dr. McCusker observed that "if [Yates] ha[d] an important primary immunodeficiency, he would [have] continue[d] to have infections at a frequency that would [have] increased . . . and the severity would [have] worsen[ed] as well." Id. at 602. Notably, "[his] infection history markedly decreased." Id.

A compromised immune system is potentially one of the clinical profile factors that Dr. Corbier would consider when evaluating whether the MMR vaccine could be implicated in the development of the vaccinated child's regressive autism. See Hazlehurst Tr. at 271A-272A, 277A, 314A, 362A. The testimony by petitioners' expert Dr. Corbier, who is not an immunologist, that Yates' immune system is compromised, however, conflicts with the normal results of Yates' immunological testing or with the testimony of Dr. McCusker, a pediatric immunologist with considerable clinical experience. The weight of the evidence does not support petitioners' claim that Yates has a compromised immune system. And as discussed in Section III.C.3., above, the undersigned finds that petitioners have failed to prove that the administration of the measles virus can cause immunosuppression in a vaccinee. Petitioners have failed to demonstrate that the MMR vaccine can or did cause any immune dysfunction in Yates. This aspect of petitioners' claim cannot stand.

3. The Claim that Yates has Gastrointestinal Problems

Petitioners' expert Dr. Corbier stated that the onset of Yates' gastrointestinal problems was marked initially by a diarrheal condition and later by the appearance of "a protuberant belly." Id. at 292, 320A. Yates' family testified that Yates' diarrhea began in June 2001, approximately four months after his first birthday and his receipt of the MMR vaccine. See Hazlehurst Tr. at 34A-35A, 80A, 106A-108A; see also Hazlehurst Ps' Ex. 2 at 43 (pediatric records dated 8/17/01 indicating that Yates' stooling was "loose [and] soft"). He subsequently developed a distended stomach and began to experience constipation intermittently with the diarrhea. See Hazlehurst Tr. at 35A, 80A-80B, 108A.

Concerned about Yates' gastrointestinal problems, Yates' family sought a gastrointestinal evaluation of Yates from Dr. Buie in April 2003. See Hazlehurst Tr. at 81A; Hazlehurst Ps' Ex. 14 at 91-92; Hazlehurst Ps' Ex. 20 at 4-7. Based on Yates' colonoscopy and digital exam, Dr. Buie concluded that Yates' colon was normal. Hazlehurst Ps' Ex. 14 at 91-92; Hazlehurst Ps' Ex. 20 at 4-7. Although Dr. Buie biopsied tissue from Yates' colon, that tissue was not sent for PCR testing. See Hazlehurst Tr. at 303.

During Dr. Corbier's testimony, he repeatedly referred to Yates' gastrointestinal "problems" or "symptoms." See Hazlehurst Tr. at 293A, 302A, 305A, 307-308. The gastrointestinal problems that were important to Dr. Corbier's theory of vaccine-related causation were Yates' diarrhea and the detected presence of eosinophilia and lymphoid hyperplasia in his gut. Id. at 308-309A, 320A. He did not assert that Yates suffered from gastrointestinal disease.

Respondent's expert Dr. MacDonald concurred. He testified that based on his review of Yates' medical records, Yates had gastrointestinal problems but did not suffer from inflammatory bowel disease. Hazlehurst Tr. at 613A. The testimony from Yates' family indicates that he had chronic diarrhea and a swollen abdomen. Dr. MacDonald stated that many of the children examined at the Royal Free Hospital and involved in the Wakefield studies had similar complaints. See Hazlehurst Tr. at 673A. These complaints are indicative of an overflow diarrheal condition. See id. at 673A-674A. Overflow diarrhea occurs when fluid that accumulates around impacted fecal matter begins to leak out through the anus. Id. at 674A. Although overflow diarrhea appears to be classic diarrhea, it is a diarrhea associated with constipation. Id. It is not the type of diarrhea that is seen in patients with inflammatory disease. Id. As respondent's expert Dr. Hanauer explained during the Cedillo hearing, inflammatory bowel disease produces "persistent diarrhea with inflammation in the stool." Cedillo Tr. at 2105. Stool that contains white blood cells or "pus cells," not mere mucous, is evidence of inflammation. Id. at 2142-2143.

Dr. MacDonald addressed the gastroenterological findings of Dr. Buie documented in Yates' medical records. Dr. Buie found no inflammation of Yates' ileum. See Hazlehurst Tr. at 664 (Dr. MacDonald); Hazlehurst Ps' Ex. 20 at 4-6. Yates did have, however, nodular lymphoid hyperplasia at the sigmoid colon and rectum. Hazlehurst Ps' Ex. 14 at 91-92; Hazlehurst Ps' Ex. 20 at 4-7.

Dr. MacDonald stated that "[l]ymphoid nodular hyperplasia is . . . an enlargement of the lymph nodes in the small intestine and the colon." Hazlehurst Tr. at 616A. It is well-documented "as part of the normal situation," that there are more lymph nodes and larger lymph nodes in the intestines of children than in the intestines of adults. Id. Moreover, Dr. MacDonald testified, the lymphoglandular complexes, which include lymphoid nodular hyperplasia, that appear in autistic subjects are "identical to" the lymphoglandular complexes that appear in "healthy individuals" and are considered a normal component of the gastrointestinal tract. Id. at 617A-618 (citing Hazlehurst Ex. H at 978-979 (the Levine article[281])). Dr. MacDonald acknowledged, however, that there is some evidence that the presence of lymphoid tissue masses (or lymphoid hyperplasia) in the lining of the gastrointestinal system could be associated with constipation or with food allergies. See Hazlehurst Tr. at 667A-668A, 670A (Dr. MacDonald); Hazlehurst Ex. A19

[281] D. Levine and R. Haggitt, Normal histology of the colon, Am. J. Surg. Pathology 13(11): 966-984 (1989).

at 45 (2002 Kokkonen article[282]) (discussing study results that support the view that lymphoid nodular hyperplasia "is related to enhanced immunologic activity, [food allergies] being the most common underlying state"); Hazlehurst Ex. A25 at 609, 611 (2004 Turunen article[283]) (in study of chronically constipated children, found lymphoid nodular hyperplasia in 74% of subjects and found an association between chronic constipation and milk hypersensitivity). Because lymphoglandular complexes appear without distinction in autistic patients and in healthy controls, the likelihood that a finding of lymphonodular hyperplasia in the gastrointestinal tract is related to the development of autism is remote.

Dr. MacDonald explained that, based on his review of "hundreds and thousands of colonoscopies," the finding of lymphoid nodular hyperplasia in Yates' sigmoid colon and rectum was not diagnostic of a disease. See Hazlehurst Tr. at 616A-617A (indicating that the presence of lymphoid nodular hyperplasia offers "[n]o" pathological diagnosis). Dr. MacDonald further explained that a finding of lymphoid nodular hyperplasia, without more, was not indicative of inflammatory bowel disease. Id. at 618.

Dr. MacDonald also addressed the pathological finding of eosinophils in Yates' biopsied tissues. See Hazlehurst Tr. at 620A-621A; Hazlehurst Ps' Ex. 50 at 1 (letter from Dr. Buie). Dr. MacDonald explained that eosinophils are "a type of [non-specific] inflammatory cell." Hazlehurst Tr. at 621A. Eosinophils are normally found at "low levels" in the blood, but during an allergic response, they move into tissues. Id. Eosinophils have been found in the lamina propria (the membrane within the lining of the gut) of developmentally normal children who have severe, chronic constipation but no inflammatory bowel disease. Id. at 622A-623A; see also Hazlehurst R's Trial Ex. 2 at 1 (Dr. MacDonald's trial slides) (referencing Hazlehurst Ex. A15 at 368 (2001 Furlano article[284])). Because eosinophils are found in both constipated autistic patients and constipated healthy controls, the likelihood that a finding of eosinophils within the lining of the gastrointestinal tract is related specifically to the development of autism is considerably diminished.

Petitioners have argued that gastrointestinal complaints of abdominal pain and diarrhea, similar to Yates', and gastrointestinal findings of lymphoid nodular hyperplasia and eosinophils, similar to Yates', are indicative of the autistic enterocolitis condition described in the literature by Dr. Wakefield, Dr. Uhlmann, and others. See Hazlehurst Tr. at 302A, 304, 307-30 (Dr. Corbier). Although petitioners have asserted that the condition

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[282] J. Kokkonen and T. J. Karttunen, Lymphonodular hyperplasia on the mucosa of the lower gastrointestinal tract in children: an indication of enhanced immune response? J. Pediatr. Gastroenterol Nutr. 34(1): 42-6 (Jan. 2002).

[283] S. Turunen et al., Lymphoid nodular hyperplasia and cow's milk hypersensitivity in children with chronic constipation, J. Pediatr. 145(5): 606-11 (Nov. 2004).

[284] R. Furlano et al., Colonic CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism, J. Pediatr. 138: 366–372 (Mar. 2001).

is a form of inflammatory bowel disease caused by a persisting measles virus in the gut, the condition is not a recognized condition in authoritative gastroenterological textbooks. See Cedillo Tr. at 523-525A (Dr Krigsman); accord id. at 2090-2091 (Dr. Hanauer).

In support of their position that autistic enterocolitis is a type of inflammatory bowel disease occurring in autistic children, petitioners have relied primarily on the series of Wakefield studies. See Cedillo Tr. at 420-422, 519, 524A (Dr. Krigsman); see also Hazlehurst Tr. at 414A-415 (Dr. Corbier) (defining autistic enterocolitis as a "new entity" describing the "subset of children . . . that ha[ve] gastrointestinal problems, lymphonodular hyperplasia, and autism"). But as discussed in Section III.C.1.a, above, that body of work has been discredited scientifically. See also Hazlehurst Tr. at 660-661A (Dr. MacDonald).

Petitioners have offered no reliable evidence rebutting either Dr. MacDonald's testimony that a finding of lymphoid nodular hyperplasia during Yates' colonoscopy is not indicative of inflammatory bowel disease or Dr. MacDonald's testimony that the finding of eosinophils in Yates' lamina propria is not indicative of inflammatory bowel disease. As established by Yates' own medical records and as informed by the testimony of the witnesses, the undersigned finds that Yates developed gastrointestinal problems but not inflammatory bowel disease. As discussed in Section III.C.5.a, above, petitioners have failed to prove that vaccine strain measles can cause gastrointestinal inflammation or inflammatory bowel disease. Additionally, petitioners have failed to prove either that vaccine strain measles can cause gastrointestinal problems of the type that Yates experienced or that the gastrointestinal problems of which Yates complained are specific to autistic subjects. This aspect of petitioners' causal chain lacks the requisite support.

4. The Claim that Yates' Autistic Condition and His Gastrointestinal Problems are Vaccine-Related

Dr. Corbier set forth in his testimony the basis for his opinion that the MMR vaccine was causally related to Yates' autism and his gastrointestinal symptoms. Dr. Corbier stated that Yates has had an "extensive genetic workup" and "a variety of metabolic testing." Id. at 301A. The known genetic causes of autism were ruled out, id., and Yates' metabolic testing was normal, see id. at 302A. Imaging of his brain did not reveal any of the structural abnormalities that cause an autistic-like presentation. See id. Dr. Corbier testified as Yates' treating neurologist that having ruled out the factors that are known to cause autism, he could find no "better explanation" than the MMR vaccine as the cause of Yates' "neurological deterioration" and "gastrointestinal problems following the vaccine." Id. He opined that the vaccine "played a significant role in Yates' case" due, in part, to a persistent measles virus in Yates' gut. Id. at 302A, 311A, 414A. He further opined that Yates would not have developed autism if he had not received the MMR vaccine. Id. at 304.

Dr. Corbier stated that he could not prove that Yates has persisting measles virus but asserted that it was more likely than not. Id. at 414A. Although Dr. Buie biopsied tissue from Yates' colon during a gastroenterological examination at Massachusetts General Hospital in April 2003, none of Yates' biopsied tissue was ever sent to a laboratory for PCR testing to determine whether Yates had persistent measles virus present in his gastrointestinal system. See Hazlehurst Ps' Ex. 20 at 4-7. Absent specific test

results for Yates reporting a positive finding of persistent measles virus in his gastrointestinal tissues, petitioners rely on a number of published articles reporting findings of persistent measles virus in other autistic children with similar gastrointestinal symptoms and findings to Yates' described problems and detected lymphonodular hyperplasia. See Hazlehurst Tr. at 304 (Dr. Corbier). Petitioners also rely on the unpublished preliminary findings of the Walker study. See id. at 280A.

The published articles on which petitioners rely most particularly are the Wakefield series of articles and the 2002 Uhlmann article. These articles were addressed in Section III.C.1 and Section III.C.4.e, above, and were determined to be scientifically unreliable. Dr. MacDonald testified about the problems identified by the scientific community with each of the articles in the series of publications by Dr. Wakefield and his colleagues. See Hazlehurst Tr. at 629A-638. Dr. Bustin, Dr. Chadwick, Dr. Griffin, and Dr. Ward also testified about the published findings and the practices at the Unigenetics lab where similar findings were made; they addressed in detail the questionable test results reported, the irregularities in laboratory test procedures, and the inability of accredited laboratories to replicate the positive measles findings. See Section III.C.4.g and Section III.C.4.e, above.

Dr. Corbier's opinion regarding the role that vaccines play in causing autism is premised, in part, on studies that have reported a finding of measles virus in the tissues taken from the gut of autistic children. See id. at 327A. Dr. Corbier admitted during his testimony that if there were no evidence of persistent measles virus, his current position of vaccine-related causation would be "lessen[ed]." Id. at 416A

Because the linchpin of petitioners' theory, the finding of persistent measles virus in the biopsied tissue taken from the gastrointestinal lining of autistic children, is glaringly unreliable, the basis for Dr. Corbier's opinion that the MMR vaccine was causally related to Yates' autism and his gastrointestinal symptoms is critically flawed and scientifically untenable. Petitioners have failed to prove that their theory of vaccine-related causation is biologically plausible as required by the first prong of Althen. Nor have petitioners demonstrated that the unsupported links of their proposed causal chain cohere to establish a logical sequence of cause and effect as required by the second prong of Althen. Having failed to satisfy their evidentiary burden, petitioners cannot prevail on their vaccine claim. Accordingly, the undersigned need not reach or consider any alternative theories of causation.

V. Conclusion

The Hazlehursts' experience as parents of an autistic child, as described during the evidentiary hearing in this case, has been a very difficult one. The undersigned is moved as a person and as a parent by the Hazlehursts' account and again extends to the Hazlehursts very sincere sympathy for the challenges they face with Yates. The undersigned's charge, however, does not permit decision making on the basis of sentiment but rather requires a careful legal analysis of the evidence.

The parties have submitted a wealth of evidence and have presented the testimony of a number of experts, the most persuasive of whom have extensive clinical and research

experience in the particular areas of interest in this case, and whose opinions were well-supported by reliable and scientifically sound literature. Having carefully and fully considered the evidence, the undersigned concludes that the combination of the thimerosal-containing vaccines and the MMR vaccine are not causal factors in the development of autism and therefore, could not have contributed to the development of Yates' autism. The weight of the presented evidence that is scientifically reliable and methodologically sound does not support petitioners' claim. Petitioners have failed to establish entitlement to compensation under the Vaccine Act. Absent the filing of a timely motion for review, the Clerk of the Court shall enter judgment accordingly.

IT IS SO ORDERED.

s/ Patricia E. Campbell-Smith
Patricia E. Campbell-Smith
Special Master

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