IN THE UNITED STATES COURT OF FEDERAL CLAIMS
OFFICE OF THE SPECIAL MASTERS
No. 03-1202V
Filed: March 12, 2010

TIMOTHY and MARIA DWYER, parents of COLIN R. DWYER, a minor,	*	Omnibus Autism Proceeding; Theory 2 Test Case; Thimerosal-Containing Vaccines; Ethylmercury; Causation; "Clearly Regressive" Autism; Oxidative Stress; Sulfur Metabolism Disruption; Excitotoxicity; Expert Qualifications; Weight of the Evidence
Petitioners,	*	
v.	*	
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

DECISION[1]

James Collins Ferrell, Esq., Houston, TX; Thomas B. Powers, Esq. and Michael L. Williams, Esq., Portland, OR; for petitioners.

Lynn Elizabeth Ricciardella, Esq. and Voris Johnson, Esq., U.S. Department of Justice, Washington, DC, for respondent.

VOWELL, Special Master:

On May 14, 2003, Timothy and Maria Dwyer ["petitioners"] filed a "short form" petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, *et seq*.[2] [the "Vaccine Act" or "Program"], on behalf of their minor

[1] Vaccine Rule 18(b) provides the parties 14 days to request redaction of any material "(i) which is trade secret or commercial or financial information which is privileged and confidential, or (ii) which are medical files and similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." 42 U.S.C § 300aa12(d)(4)(B). Both parties have waived their right to request such redaction. *See* Petitioners' Notice to Waive the 14-Day Waiting Period, filed February 1, 2010; Respondent's Consent to Disclosure, filed January 13, 2010. Accordingly, this decision will be publically available upon filing.

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2006).

son, Colin Dwyer ["Colin"].[3] Subsequently-filed documents have clarified the injury claimed as a pervasive developmental disorder ["PDD"],[4] substantially caused by Colin's exposure to mercury in thimerosal-containing vaccines ["TCVs"]. *See* Petitioners' Post-Hearing Brief ["Pet. Post-Hearing Br."] at 1.

To be eligible for compensation under the Vaccine Act, a petitioner must either demonstrate a Vaccine Table[5] injury, to which a statutory presumption of causation attaches, or prove by a preponderance of the evidence that a vaccine listed on the Vaccine Table caused or significantly aggravated an injury. *Althen v. Sec'y, HHS*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Grant v. Sec'y, HHS*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). The petitioners in this case do not contend that Colin suffered a "Table" injury. Therefore, in order to prevail, they must demonstrate by preponderant evidence: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Althen,* 418 F.3d at 1278. *See also Hines v. Sec'y, HHS*, 940 F.2d 1518, 1525 (Fed. Cir. 1991).

Colin's case was heard as part of the largest omnibus proceeding in the history of the Vaccine Act. It was one of three test cases on the second of two theories[6] of

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[3] *See* Autism General Order #1, dated July 3, 2002, Ex. A, *available at* http://www.uscfc.uscourts.gov/sites/default/files/autism/Autism+General+Order1.pdf ["Autism Gen. Order #1"], 2002 WL 31696785 (Fed. Cl. Spec. Mstr. July 3, 2002). By filing such a petition, the filers averred that: (1) the vaccinee suffered from an autism spectrum disorder ["ASD"], or an autism-like disorder, that had persisted for longer than six months; (2) the petition was filed within three years of onset of that disorder; and (3) a vaccine listed on the Vaccine Injury Table, 42 C.F.R. § 100.3, was the cause of the condition.

[4] Pervasive developmental disorders is the umbrella term used in the DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS (American Psychiatric Association, 4th ed. text revision 2000) ["DSM-IV-TR"] at 69 to identify what are often referred to as ASDs. The terms "pervasive developmental disorder" and "autism spectrum disorder" are used interchangeably. Section IV, below, explains these disorders in greater detail.

[5] A "Table" injury is an injury listed on the Vaccine Injury Table, 42 C.F.R. § 100.3, corresponding to the vaccine received within the time frame specified.

[6] At one time, the Petitioners' Steering Committee ["PSC"] advanced three theories of causation, but subsequently reduced that to two after determining that the evidence in support of the third theory, that the measles component of the measles, mumps, rubella ["MMR"] vaccine causes some ASDs, was encompassed in the evidence adduced in the first theory of causation ["Theory 1"]. The Theory 1 cases posited that a combination of TCVs and the measles component of the MMR vaccine causes ASDs. Decisions in the Theory 1 cases may be found at *Cedillo v. Sec'y, HHS*, No. 98-916V, 2009 WL 331968 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff'd*, 89 Fed. Cl. 158 (2009), *appeal docketed*, No. 10-5004 (Fed. Cir. Oct. 7, 2009); *Hazlehurst v. Sec'y, HHS*, No. 03-654V, 2009 WL 332306 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff'd*, 88 Fed. Cl. 473 (2009), *appeal docketed*, No. 09-5128 (Fed. Cir. Sept. 21, 2009); *Snyder v. Sec'y, HHS*, No. 01-162V, 2009 WL 332044 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff'd*, 88 Fed. Cl. 706

causation ["Theory 2"] advanced by petitioners in the Omnibus Autism Proceeding ["OAP"]. Theory 2 is that the mercury in TCVs can cause at least some forms of ASD, and that it did so in the three Theory 2 test cases,[7] including Colin's.

After considering the record as a whole, I find that petitioners have failed to establish by preponderant evidence that Colin's condition was caused or significantly aggravated by TCVs. They failed to demonstrate either that the mercury component of TCVs can cause ASD or that it did so in Colin's case. None of the causation hypotheses advanced were reliable as medical or scientific theories.

In essence, petitioners propose effects from mercury in TCVs that do not resemble mercury's known effects on the brain, either behaviorally or at the cellular level. To prevail, they must show that the exquisitely small amounts of mercury in TCVs that reach the brain can produce devastating effects that far larger amounts experienced prenatally or postnatally from other sources do not. In order to account for this dichotomy, they posit a group of children hypersensitive to mercury's effects, but the only evidence that these children are unusually sensitive is the fact of their ASD itself. In an effort to render irrelevant the numerous epidemiological studies of ASD and TCVs that show no connection between the two, they contend that their children have a form of ASD involving regression that differs from all other forms biologically and behaviorally. World-class experts in the field testified that the distinctions they drew between forms of ASD were artificial, and that they had never heard of the "clearly regressive" form of autism about which petitioners' epidemiologist testified. Finally, the causal mechanism petitioners proposed would produce, not ASD, but neuronal death, and eventually patient death as well. The witnesses setting forth this improbable sequence of cause and effect were outclassed in every respect by the impressive assembly of true experts in their respective fields who testified on behalf of respondent. Therefore, I hold that petitioners have failed to establish their entitlement to compensation, and their petition is denied.

A brief history of omnibus proceedings under the Vaccine Act is necessary to explain what constitutes the "record as a whole"[8] upon which this case was decided. That history is set forth in Section I, below.

(2009).

[7] The other Theory 2 cases are *King v. Sec'y, HHS*, 03-584V, and *Mead v. Sec'y, HHS*, 03-215V.

[8] *See* § 13(a): "Compensation shall be awarded...if the special master or court finds on the record as a whole...." *See also* § 13(b)(1) (indicating that the court or special master shall consider the entire record in determining if petitioner is entitled to compensation).

Section I. Omnibus Proceedings in Vaccine Act Cases.

A. Historical Use of Omnibus Proceedings under the Vaccine Act.

The Vaccine Act contains no provision for class action suits or omnibus proceedings.[9] However, the Act does permit the consideration of evidence without regard to formal rules of evidence and encourages flexibility in procedures. *See* § 12(d)(2)(A)-(E). Certain provisions of the Vaccine Act and its legislative history indicate that Congress contemplated that the special masters would develop expertise in the complex medical and scientific issues involved in actual causation claims and would then apply this expertise to the resolution of other cases.[10] Vaccine Rule 8(a) provides: "The special master will determine the format for taking evidence and hearing argument based on the specific circumstances of each case and after consultation with the parties." *See also Lampe v. Sec'y, HHS*, 219 F.3d 1357, 1362 (Fed. Cir. 2000) (quoting *Hodges v. Sec'y, HHS*, 9 F.3d 958, 961 (Fed. Cir. 1993)). The Court of Federal Claims has noted that "instead of being passive recipients of information, such as jurors, special masters are given an active role in determining the facts relevant to Vaccine Act petitions," and that "the special masters have the expertise and experience to know the type of information that is most probative of a claim." *Doe v. Sec'y, HHS*, 76 Fed. Cl. 328, 338-39 (2007). The Federal Circuit has commented on the "virtually unlimited" scope of the special master's authority to inquire into matters relevant to causation (*Whitecotton v. Sec'y, HHS*, 81 F.3d 1099, 1108 (Fed. Cir. 1996)), and the deference properly accorded to their fact-finding (*Munn v. Sec'y, HHS*, 970 F.2d 863, 871 (Fed. Cir. 1992)). *See also* J. Weinstein, *Improving Expert Testimony*, 20 U. RICH. L. REV.

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[9] Omnibus proceedings bear some resemblance to multi-district litigation in federal district courts. *See* 28 U.S.C. § 1407 (2006). However, unlike multi-district litigation, the parties in an omnibus proceeding are not bound by the outcome of the test cases. *See, e.g.*, Autism Gen. Order #1at 6-7 (permitting petitioners to opt in or out of the OAP and to introduce their own evidence to prove their individual case).

[10] *See, e.g.*, H.R. Rep. No. 101-386, at 516 (1989) (Conf. Rep.) (Report on the 1989 amendments stated that "[t]he system is intended to allow the proceedings to be conducted in what has come to be known as an 'inquisitorial' format, with the master conducting discovery (as needed), cross-examination (as needed), and investigation."). For example, medical acronyms need not be explained anew to a special master who has heard such acronyms in numerous cases. Basic scientific evidence is often cursorily addressed by the experts, with the expectation that the special master will ask questions concerning any matters not completely clear. However, special masters are not doctors; thus they do not "diagnose" petitioners. Although due process concerns preclude the wholesale importation of evidence adduced in one proceeding to another proceeding without the consent of the parties, in omnibus proceedings the parties consent to import evidence from the "test case" into other individual cases. Absent such consent, special masters advise the parties when they intend to consider evidence derived from their own efforts, usually in the form of medical journal articles, and permit the parties to comment on such evidence. Institute of Medicine ["IOM"] Reports, learned treatises, medical textbooks, medical dictionaries, or handbooks explicating medical abbreviations or tests are often consulted and referenced in the body of an opinion without formal notice to the parties. *See, e.g.*, *Stroud v. Sec'y, HHS*, 113 F.3d 1258 (Fed. Cir. 1997) (special masters may rely upon an IOM report that neither party filed as evidence).

473, 494-95 (1986) (encouraging judges presiding over non-jury trials "to become familiar with the scientific background by reading about the issues and discussing them with the experts" and noting that "[t]he court owes an obligation to the parties, to society, and to itself to assist in obtaining the best possible answers to the scientific questions before it.").

Because cases involving the same vaccine and injury often involve the same body of medical expertise, the Office of Special Masters ["OSM"] developed omnibus proceedings to answer the common question of whether a particular vaccine can cause the injury in question–the general causation question. The issue of whether it did so in a specific case can then be resolved more expeditiously, based on a ruling in an omnibus test case.[11]

The proceedings in the OAP test cases have followed the "test case" format developed for conducting omnibus proceedings under the Vaccine Act. This format involves hearing evidence and issuing an opinion in the context of a specific case or cases, then applying the evidence developed to other cases involving the same vaccine and the same or a similar injury. *See, e.g.*, *Capizzano v. Sec'y, HHS*, No. 00-759V, 2004 WL 1399178 (Fed. Cl. Spec. Mstr. June 8, 2004), *rev'd on other grounds*, 440 F.3d 1317 (Fed. Cir. 2006) (hepatitis B vaccine and rheumatoid arthritis). By the agreement of the parties, the evidence adduced in the omnibus proceeding is applied to other cases, along with any additional evidence adduced in those particular cases. The parties are thus not bound by the results in the test case, only agreeing that the expert opinions and evidence forming the basis for those opinions may be considered in additional cases presenting the same theory of causation. This method has proven efficient in resolving similar cases by settlement or dismissal, based on the special master's analysis of the scientific evidence in the test case.

B. The Omnibus Autism Proceeding.

1. Creation of the OAP.

On July 3, 2002, Chief Special Master Golkiewicz issued Autism Gen. Order #1 to address issues arising from the unprecedented filing of more than 300 petitions for compensation in a six-month period, all alleging that vaccines caused a

[11] For example, the common issue of whether Vaccine A can cause Disease X might be heard in the context of an individual case. If the special master determines that Disease X could, indeed, be caused by Vaccine A, the special master would also attempt to determine under what circumstances causation could be established, what specific symptoms would be required, and when those symptoms must manifest in order to attribute the disease or injury to the vaccine. The findings, issued in the context of deciding an individual case, would then provide guidance to the parties in other cases involving that vaccine and injury. Such findings might result in settlement or withdrawal of many pending cases without the necessity of additional hearings.

neurodevelopmental disorder known as autism or an ASD.[12] Autism Gen. Order # 1 established the OAP to process efficiently and expeditiously the current ASD petitions as well as the large number of anticipated petitions presenting the same claims.[13]

Autism Gen. Order #1 and the OAP grew out of meetings with an informal advisory committee comprised of members of the petitioners' bar and legal and medical representatives of the respondent in Vaccine Act cases, the Secretary of Health and Human Services. Autism Gen. Order #1 noted that the large number of petitions already filed, and the even larger number of anticipated petitions,[14] would stretch both the court's resources and those of the bar. Petitioners acknowledged that their cases were not yet ready for adjudication, as they were seeking discovery and additional time for the completion of scientific studies to bolster their claims. Conducting such discovery in the context of an omnibus proceeding, rather than in individual cases, was clearly a more efficient use of resources of both the bar and the court.

Autism Gen. Order # 1 established the PSC to represent the interests of petitioners. Membership on the PSC was determined by the petitioners' bar, with two attorneys selected by the PSC to serve as "lead counsel." The PSC has represented the general interests of autism petitioners continuously since the inception of the OAP. However, counsel of record retained responsibility for all other aspects of their own individual cases, including keeping clients informed about the process, and obtaining medical records and other pertinent documents.[15]

Those petitioners with ASD petitions pending in the Program at the time Autism Gen. Order # 1 was issued were permitted to "opt in" to the OAP, while retaining the right to "opt out" at any time and return their cases to active status for resolution on an individual basis. Relatively few petitioners have availed themselves of this opportunity.

New petitions filed after the issuance of Gen. Order #1 used a "short form"

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[12] Autism and ASDs are discussed in some depth in Section IV.

[13] The publicly accessible website, www.uscfc.uscourts.gov/omnibus-autism-proceeding, contains the OAP Master File (under the "docket" link), which includes orders, decisions, and periodic updates issued by the special masters assigned to the autism docket. Most of petitioners' and respondent's filings, including general causation evidence, are posted on this website. Beginning in June 2007, audio files and transcripts of the Theory 1 hearings were also posted on this website. The Theory 2 hearing transcripts and audio files are also posted, along with the expert reports.

[14] Well over 5,000 such petitions have been filed, approximately 4,800 of which remain pending. *See* Autism Update, OAP Master File, filed October 9, 2009. Since the OAP was established, over 500 petitions have been resolved by decisions, voluntary dismissals, or involuntary dismissals of petitions filed outside the statute of limitations.

[15] A few law firms represent substantial numbers of OAP petitioners, with three firms each representing more than 400 petitioners. Other attorneys represent only a few petitioners or even a single petitioner.

petition format set forth in the order, as petitioners did in this case. Autism Gen. Order #1 at 7. In a subsequent order, filed into the OAP Master File on July 8, 2002, Chief Special Master Golkiewicz acknowledged respondent's concerns[16] that the short form petitions would not permit evaluation of cases for the statutorily-required documentation,[17] but found that the OAP procedures represented the most efficient method for handling the overwhelming number of cases.[18]

2. The OAP Discovery Process.

The discovery process in the OAP was initially handled by Special Master George Hastings, to whom all the cases were once assigned. Based on a draft proposed by petitioners' representatives, Autism Gen. Order # 1 established a master schedule for resolving the ASD cases, which included a discovery period, followed by a hearing on the general issue of causation, within two years of the OAP's inception.

However, delays ensued. Although the master schedule anticipated completion of discovery and designation of petitioners' experts by August 2003, followed by petitioners' experts' reports in November, 2003, those deadlines were subsumed by disputes arising in the discovery process. Most of the discovery issues were amicably resolved, but some remained contentious. Rulings were issued in some matters that could not be resolved by the parties. *See, e.g.*, Autism Update and Order, OAP Master File, filed September 24, 2003.

3. Preparations for Hearing the Test Cases.

Autism Gen. Order #1 was written in contemplation of a "general causation hearing" in March, 2004. At the request of the petitioners, this hearing date was postponed. In a lengthy Ruling issued on August 11, 2005, Special Master Hastings summarized reasons for the delay in the original timetable and addressed a government

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[16] In the Vaccine Rule 4 reports filed in response to short form petitions, respondent continued to object to the short form procedure.

[17] Section 11(c) of the Vaccine Act requires the petition to be accompanied by certain documentary evidence, including records pertaining to the vaccination and subsequent treatment. *See also* Vaccine Rule 2(c), RCFC, Appendix B.

[18] The PSC, counsel for respondent, and the OSM have developed and implemented a plan to supplement the short form petitions and to resolve expeditiously those cases with jurisdictional or other defects. Approximately 200 cases per month are added to the process, which entails the filing of sufficient medical records to make a determination whether the case was timely filed and whether the vaccinee has an ASD or similar condition. Further filings then ensue in those cases filed within the statute of limitations and properly assigned to the OAP. Once all the statutorily-mandated documents are filed, the remaining cases will be resolved, at least in part, by the causation evidence filed in the three Theory 1 test cases and the *King, Mead,* and *Dwyer* Theory 2 test cases. Of course, in accordance with Autism Gen. Order # 1, petitioners may withdraw from the OAP at any time, and may present evidence of causation on their own.

argument that he lacked the authority to delay the proceedings longer than 420 days. Although he declined to force petitioners to try their cases before they were ready to do so, he set a January 31, 2006 deadline for identification of expert witnesses. After requesting and receiving an enlargement of this deadline, petitioners filed a list of 16 experts on February 14, 2006, and filed a curriculum vitae ["CV"] for each of those experts on March 22, 2006. On April 21, 2006, Special Master Hastings deferred the filing of expert reports until December 31, 2006.

On July 18, 2006, the PSC filed a proposal for conduct of the general causation proceedings. The PSC proposed a new hearing date in June, 2007, with the hearing conducted over a two-to-three-week period in which petitioners would present evidence regarding all theories of causation. The PSC opposed consideration of any specific case. In September, 2006, Special Master Hastings adopted the PSC proposal for a three-week general causation hearing. He ordered petitioners to file expert reports by February 16, 2007, with respondent's expert reports to be filed 60 days later.[19] At this point, it was still unclear whether the general causation issues would be considered alone or in the context of a test case.

The plan to consider all theories of causation at a single hearing was later modified. As early as May, 2006, it appeared that the petitioners might request to bifurcate the general causation issue into two proceedings, one addressing whether the MMR vaccine could cause autism and the other addressing whether TCVs do so. *See* Autism Update, OAP Master File, filed May 16, 2006. On January 9, 2007, the PSC proposed hearing a single actual case to test the theory that a combination of the MMR vaccine and TCVs caused ASDs. Subsequent hearings to address two other theories, one in which TCVs alone were causal (Theory 2), and the other in which the MMR vaccine alone was causal (Theory 3) were planned.[20]

The January 9, 2007 PSC filing also addressed an informal proposal by the court that involved detailing two additional special masters to hear the general causation question. The PSC opposed the proposal. Nevertheless, on January 11, 2007, Chief Special Master Golkiewicz assigned two additional special masters to the OAP docket. Special Master Campbell-Smith and I were the two additional special masters assigned. *See* Notice Regarding Assignment of Autism Cases to Additional Special Masters, OAP

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[19] The many delays requested by petitioners to file their expert reports resulted in a highly compressed schedule in the final four months before the *Cedillo* hearing began. Until the petitioners' expert reports were actually filed on February 20, 2007, respondent did not know precisely what petitioners' theory (or theories) of MMR-TCV causation entailed. Thus, respondent's experts had a very tight time schedule in which to review petitioners' expert reports and the scientific and technical literature upon which they were based, and to prepare their own reports and supporting materials.

[20] The PSC later determined that test cases involving Theory 3 would not be necessary because the evidence pertaining to this theory had been presented during the Theory 1 cases. *See* PSC Notice Re: Theory 3, OAP Master File, filed August 7, 2008; Autism Update, OAP Master File, filed September 29, 2008.

Master File, filed January 11, 2007 (setting forth the reasons for detailing two additional special masters).

a. The Theory 1 Cases.

The procedural history of the Theory 1 test cases was addressed in some detail in my decision in *Snyder v. Sec'y, HHS*, No. 01-162V, 2009 WL 332044 (Fed. Cl. Spec. Mstr. Feb. 12, 2009),[21] and only matters subsequent to the decision denying compensation will be addressed here. Motions for review in all three Theory 1 test cases were filed with the Court of Federal Claims in March, 2009. In published orders, all three motions were denied. On July 24, 2009, Judge Wiese denied the motion for review in *Hazlehurst* and affirmed the special master's decision. 88 Fed. Cl. 473 (2009). On August 6, 2009, Judge Wheeler denied the motion for review in *Cedillo* and affirmed the special master's decision. 89 Fed. Cl. 158 (2009). In both of these cases (*Cedillo* and *Hazlehurst)*, appeals were filed with the Court of Appeals for the Federal Circuit. Those appeals remain pending. On August 11, 2009, Judge Sweeney denied the motion for review in *Snyder* and affirmed my decision. 88 Fed. Cl. 706 (2009). Petitioners in the *Snyder* case did not appeal Judge Sweeney's decision.

b. The Theory 2 Cases.

Once it became clear that the PSC desired a separate evidentiary hearing on the theory that TCVs cause ASDs, the special masters instructed the PSC to identify and present three cases by September 30, 2008. Autism Update, OAP Master File, filed March 14, 2007, at 5-6. On June 25, 2007, the PSC submitted a scheduling proposal that outlined a process for identifying potential Theory 2 test cases, submitting expert reports, and holding evidentiary hearings in January, 2008. The deadline for identifying the test cases and submitting expert reports was initially set for August 31, 2007. Petitioners submitted three general causation expert reports by September 4, 2007, and requested and received an enlargement of time to identify their test cases and file their case-specific expert reports, with a due date of November 19, 2007. Order Concerning Schedule for PSC's "Second Theory" of Causation, OAP Master File, filed September 27, 2007. The hearing date was postponed to May, 2008. *Id.*

After further requests for delay, the PSC identified three Theory 2 test cases and filed case-specific expert reports in January, 2008. Autism Update, OAP Master File, filed January 17, 2008, at 2. Respondent filed expert reports on February 25, 2008, and March 14, 2008.

In early April, 2008, the PSC informed the court that petitioners wished to add Dr.

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[21] Decisions in the other two Theory 1 test cases, *Cedillo* and *Hazlehurst* were issued simultaneously with *Snyder*. In each case, the special master found that the petitioners had failed to establish by a preponderance of the evidence that the MMR vaccine, in combination with TCVs, can cause ASDs.

Marcel Kinsbourne as an expert witness.[22] Respondent did not object, and Dr. Kinsbourne's expert report was filed on April 22, 2008–one month before the general causation hearing commenced. *See* Transcript ["Tr."][23] at 2041-42.

The hearing and the weeks preceding it contained a number of additional surprises in terms of late-breaking events. On April 3, 2008, the three special masters were informed that the petitioners in one of the three Theory 2 test cases wished to withdraw from the OAP and proceed on a different theory of causation. Order Concerning Case Processing, OAP Master File, filed April 16, 2008, at 2. Special Master Hastings, Special Master Campbell-Smith, and I ordered the PSC to designate a replacement test case prior to the commencement of the Theory 2 general causation hearing on May 12, 2008. *Id.* The undetermined third test case was to be assigned to me.

On May 5, 2008 (the week prior to the start of the general causation hearing), petitioners filed more than 200 medical journal articles in the *King* and *Mead* cases. Tr. at 242. Additionally, at the hearing itself, one of petitioners' experts, Dr. Deth, presented considerable testimony about matters not contained in his expert report, including a substantial amount of evidence concerning unpublished research conducted at his laboratory.[24]

Because the change in the third test case occurred so close to the commencement of the general causation hearing in May, 2008, the new case could not be identified in time for specific causation evidence concerning it to be presented at the May, 2008 hearing. Thus, in addition to the general causation evidence applicable to all Theory 2 cases, only the specific causation evidence pertaining to the *Mead* and *King* cases was presented at the May 12-30, 2008 hearing. Autism Update, OAP Master File, April 23, 2008, at 4. *See also* Autism Update, OAP Master File, filed July 8, 2008, at 2. The PSC finally designated the *Dwyer* case as the third test case during an OAP status conference held on June 12, 2008. Autism Update, OAP Master File, filed September 29, 2008, at 2.

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[22] During the status conference in which the addition of Dr. Kinsbourne to petitioners' witness list was discussed, petitioners' counsel represented that Dr. Kinsbourne had approached the PSC, indicating that he could proffer an opinion on causation. *See* Tr. at 2041, 2044-45 (respondent's counsel discussing this status conference). At the hearing, Dr. Kinsbourne testified that petitioners' counsel approached him about testifying in the Theory 2 cases, and that he became involved in the cases around March, 2008, shortly before he wrote his expert report. Tr. at 846.

[23] The general causation testimony was almost exclusively presented during the May, 2008 general causation hearing. For that reason, references to this general causation testimony are identified using the abbreviation "Tr." References to testimony in the *Dwyer* hearing use the same designation, prefaced by the case name [*i.e.*, "Dwyer Tr. at __"].

[24] This evidence is discussed in much greater detail in Section VII below.

Respondent filed expert reports on general causation prepared by Drs. Clarkson and Magos, but neither was available to testify at the May, 2008 general causation proceeding. Initially, respondent intended to call Dr. Clarkson and Dr. Magos to testify at the July, 2008 hearing, and petitioners intended to recall Dr. Aposhian (and possibly, Dr. Kinsbourne) at that time to offer rebuttal testimony. Tr. at 2039-41, 2150-52 (bench ruling indicating that petitioners could recall witnesses at the July hearing, but their testimony would be strictly limited to rebuttal of Drs. Clarkson and Magos).

On June 12, 2008, respondent's counsel informed the court and petitioners that Drs. Magos and Clarkson would not be called to testify at the July hearing. *See* Order Modifying Schedule for PSC's "Second Theory of Causation" Cases, OAP Master File, filed June 17, 2008, at 1. Petitioners maintained that they should still have an opportunity to recall Dr. Aposhian at the July hearing to rebut the doctors' expert reports, as they were still part of the record. *Id.* Respondent subsequently sought and received permission to withdraw Drs. Clarkson's and Magos' expert reports from the record. Order Concerning Theory 2 General Causation Rebuttal, OAP Master File, filed July 3, 2008, at 2.

The *Dwyer* case was heard on July 21-22, 2008. Petitioners submitted a supplemental expert report by Dr. Aposhian on April 2, 2009. Respondent filed a responsive supplemental expert report by Dr. Brent on May 8, 2009. The evidentiary record in *Dwyer* was closed on August 27, 2009.[25]

C. Evidence Constituting the Record as a Whole.

The evidence before me thus includes all of the evidence, less the medical records of the other children, introduced before, during, and after the *King/Mead* hearing, as well as all of the evidence filed in the *Dwye*r case itself. By orders filed November 16, 2009 and March 1, 2010, I filed compact discs containing certain evidence adduced in *King* and *Mead* into the record of this case.

To avoid the confusion the multiple exhibit numbers for the same scientific or technical journal occasionally engendered in the Theory 1 cases, the parties in the Theory 2 cases were ordered to maintain respective "Master Lists" of medical and

[25] I delayed closing the evidentiary record in this case for several months after receiving Dr. Brent's supplemental report because petitioners had indicated at the conclusion of the *Dwyer* hearing that they anticipated filing several soon-to-be-published studies that were expected to enhance their causation claim. Dwyer Tr. at 298-99, 332. No additional studies were filed after July 6, 2009, when petitioners filed an updated version of their master list of scientific articles. *See* Order, dated March 1, 2010 (crossfiling these additional studies into this case). As of the date of this decision, petitioners have not requested that the evidentiary record be reopened to consider any additional studies.

scientific literature.[26] Although some articles appeared on both petitioners' master reference list ["PML"] and respondent's master reference list ["RML"], this process generally worked well, avoiding the repetitive filing of documents in each case.[27] A similar process was employed with regard to exhibits used at trial, with each party's exhibits being identified as "trial exhibits."[28] For example, Petitioners' Trial Exhibit ["Pet. Tr. Ex."] 2, the slides accompanying Dr. Aposhian's testimony, have the same trial exhibit number in each of the three test cases.[29]

The expert reports were assigned different exhibit numbers or letters in each case.[30] Throughout this opinion, I will use the exhibit numbers and letters assigned expert reports in Colin Dwyer's case,[31] even if a witness referred to it by one of the exhibit designations from the *Mead* or *King* cases.

Accuracy problems with the original transcripts filed resulted in numerous changes. The parties filed a joint stipulation agreeing on corrections, and more

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[26] In citing to these articles, I used the page number in the article itself, rather than page numbers assigned at the time of filing. I note that it appears respondent's latest master list chronicled 522 articles (filed July 11, 2008), but an article labeled RML 523 was subsequently filed on October 7, 2008. Respondent also filed medical literature with exhibit letters after the institution of the master list practice (*see* Res. Exs. FF-II, filed May 27, 2009) that were not listed on her master list.

[27] The fact that a particular medical journal article was filed by a particular party or by both parties does not constitute a party's endorsement of the article's premise or conclusions. Special masters customarily require that a copy of any articles discussed (favorably or unfavorably) in an expert's report be filed with the report. A special master is not required to accept an expert report at face value (*see* § 13(b)(1) (indicating that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court")) and may thus explore the basis for the expert's conclusions by reading and evaluating materials cited in the report. *See also Perreira v. Sec'y, HHS*, 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994); *Burns v. Sec'y, HHS*, 3 F.3d 415, 417 (Fed. Cir. 1993).

[28] At each hearing, some expert witnesses used slide presentations to aid the court in following key points of their testimony. Other documents were used in cross-examination or in rebuttal testimony. These exhibits were designated as trial exhibits and assigned consecutive exhibit numbers, preceded by the designation of the party offering the exhibit.

[29] In *Dwyer*, counsel refiled the trial exhibits using master reference list numbers. To correspond more closely to the transcript, which included frequent references to the trial exhibit number and page of the slides, I will continue to identify petitioners' trial exhibits by the numbers assigned during the hearings.

[30] For example, Doctor Deth's expert report was Petitioners' Exhibit 23 in the *King* case, Petitioner's Exhibit 17 in the *Mead* case, and PML 713 in the instant case. During the general causation hearing, testimony concerning his report might have referred to either the *King* or the *Mead* exhibit number.

[31] Petitioners also filed their general causation expert reports using master reference list numbers, rather than assigning the exhibits the next-in-order exhibit number in the *Dwyer* case. I will use the master reference number for the expert reports and CVs, as no other exhibit numbers were assigned to them in this case.

accurate transcripts were subsequently filed. All transcript references are to these corrected and revised transcripts.

The evidentiary record[32] in this case thus encompasses, *inter alia*, the transcripts of more than three weeks of testimony and accompanying trial exhibits, including that offered in the general causation hearing; over 1200 medical and scientific journal articles; 20 expert reports;[33] supplemental expert reports filed by both parties post-hearing; the testimony of fact witnesses on behalf of Colin; and Colin's medical and educational records.

D. Expert Witnesses and Their Qualifications.

In addition to presiding over and hearing all of the testimony in Colin's own case, I was present for all of the expert testimony in the general causation hearing, and thus had the opportunity to see and hear all of the witnesses whose testimony pertains to Colin Dwyer's case.

My evaluation of the testimony and the qualifications of the witnesses offering that testimony is based, in part, on the factors the Supreme Court set forth in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993) and *Kuhmo Tire Co. v. Carmichael*, 526 U.S. 137 (1999). Although the Federal Rules of Evidence, upon which *Daubert* and *Kuhmo Tire* are based, do not apply in Vaccine Act cases, the Federal Circuit has approved the use of the *Daubert* factors as a framework for evaluating the reliability of expert testimony in Vaccine Act proceedings. *Terran v. Sec'y, HHS*, 41 Fed. Cl. 330, 336 (1998), *aff'd*, 195 F.3d 1302, 1316 (Fed. Cir. 1999).

The relative disparity in qualifications is not determinative on the issue of causation. A qualified expert with lesser qualifications may offer an opinion that, for a variety of reasons, is more persuasive than that of a more qualified expert testifying on behalf of an opposing party. It is, however, a factor to be considered in determining the weight to be given to an expert witness' opinion.

Nevertheless, witness qualifications are an important, and a largely objective,

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[32] The Vaccine Act requires the special master to consider the record as a whole. *See* § 300aa–13(a): "Compensation shall be awarded...if the special master or court finds on the record as a whole...." *See also* § 300aa–13(b)(1) (indicating that the court or special master shall consider the entire record in determining if petitioner is entitled to compensation).

[33] I reviewed the case-specific report filed by Dr. Rust in the *Mead* case, as well as the case-specific reports filed by Dr. Mumper in the *King* and *Mead* cases for information relating to general causation, but such general causation evidence was otherwise included in their testimony, in Dr. Mumper's case-specific report in Colin's case, or in the evidence from other witnesses. I have thus not considered their reports in the other cases in arriving at my decision in this case. Likewise, I have not considered the withdrawn reports from Drs. Magos and Clarkson, or evidence that relied upon their reports.

basis upon which to assess and weigh expert opinions. In virtually every area of specialization in science and medicine about which testimony was offered, respondent's experts were far more qualified to opine than those of petitioners. Speaking generally, the qualifications of the experts proffered by respondent, the relationship of those qualifications to the subject matter of their testimony, and the quality of their testimony far exceeded those of petitioners' experts.

In terms of research, clinical experience, and publications in the subject matter of the testimony proffered, respondent's witnesses were truly experts, and some were world-class experts, in their fields. In contrast, most of petitioners' experts had few publications relating to the subject matter of their testimony and far less experience in the subject matter of their proffered opinions. Respondent's experts were practicing physicians or research scientists (and sometimes both) who have taught and written extensively on the specific subject matter about which they testified. Although most of petitioners' witnesses had adequate, and occasionally excellent, qualifications as physicians and scientists, most were either not engaged in research and treatment, or were engaged in research that was, at best, tangential to the subject matter of their testimony. One of petitioners' expert witnesses had testified very frequently in Vaccine Act cases, and thus appeared to derive substantial income from expert witness fees.

In terms of clinical experience in diagnosing and treating children with ASD, every one of respondent's experts who treated children with ASD had more academic training and clinical and research experience than petitioners' experts. None of Colin's own treating physicians testified in this case, and to the extent that any of his medical records reflect any opinions on causation, they focused on a temporal connection between onset of his symptoms and a purported second MMR vaccination.[34] Thus, there are no opinions of treating physicians to be considered on the causation issue. Of the three witnesses who specifically opined on the cause of Colin's condition, two were engaged in treating children with ASD, but respondent's expert had far more years of experience in such treatment, more advanced training, and a record of research and publication in the field not possessed by petitioners' expert. The third expert filed a very generic expert report, and did not testify.

The responses of witnesses to questions, whether from opposing counsel or from the special masters themselves, was also a factor in weighing and evaluating testimony. In general, respondent's experts provided more responsive answers to such questions. Respondent's experts were generally more careful and nuanced in their expert reports and testimony. In contrast, petitioners' experts were more likely to offer opinions that exceeded their areas of expertise, to "cherry-pick" data from articles that were otherwise unsupportive of their position, or to draw conclusions unsupported by the data cited. When an expert relied on a specific medical or scientific journal article in testimony or referenced it in his or her report, I carefully compared the testimony or report to the

[34] Colin's medical records, vaccinations, and treatment are discussed in more detail in Section X, below.

article cited. Doctors Kinsbourne and Aposhian, in particular, on several occasions cited articles for propositions not contained in the publication. Several of these instances are set forth in greater detail in the sections dealing with their testimony.

The expert witnesses included, *inter alia*, neurologists, toxicologists, pharmacologists, epidemiologists, psychiatrists, and pediatricians. For purposes of comparison of qualifications, I have grouped the experts in subsections below by their primary field of expertise or the primary focus of their testimony; however, some experts offered opinions in more than one scientific discipline.[35]

1. Epidemiologists.

Epidemiology is the science that studies the patterns or distributions of diseases in human populations, and attempts to identify risk factors for those diseases. Tr. at 3088-89, 3625. All three epidemiologists who testified, Drs. Greenland, Goodman, and Fombonne, had superb qualifications as expert witnesses. Of the three, Dr. Fombonne had the most experience in conducting studies and writing about autism's epidemiology. Additionally, Dr. Rutter, who performed some of the earliest epidemiological studies of ASD, was well qualified by his experience and publications to proffer opinions on epidemiology, but I have listed his qualifications below in the section pertaining to the psychiatrists and psychologists, because that area was the primary focus of his testimony.

a. Doctor (Ph.D.) Sander Greenland.[36]

Doctor Greenland is currently a professor of epidemiology and statistics at the University of California, Los Angeles. He has served on the faculty there since 1979. Tr. at 73. He has a Ph.D. in public health. Tr. at 73.

He co-authored a textbook used in numerous public health and medical schools, and has authored more than 300 peer reviewed[37] articles. Tr. at 43-44, 73. Doctor

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[35] For example, one of respondent's witnesses, Dr. Rutter, offered opinions in psychiatry, genetics, and epidemiology, all areas in which he was extraordinarily well qualified.

[36] Doctor Greenland's CV was filed as PML 714; his expert report was filed as PML 715. The slides he used during his testimony were Pet. Tr. Ex. 1. Although the table of contents for the transcript in the general causation hearing identified Dr. Greenland (and every other witness, including two of the petitioners), as "MD," (Tr. Index at 3) neither his testimony nor his CV reflected a medical degree.

[37] In the peer review process, after a manuscript is submitted to a medical journal, an editor sends the manuscript out to experts in the field. The experts review the submission to determine if it is worthy of publication and whether there are any problems involving methodology, techniques, or conclusion. The peer reviewer's comments are presented to the editor in a report. After receiving comments from two or three peer reviewers, the editor then determines if the article should be published, revised, or rejected. Tr. at 1786-87. As Dr. Brent added, the process is not perfect, but it is the best system available. Tr. at 1786. All good publications are peer reviewed. Tr. at 1786.

Greenland lectures worldwide on epidemiological methods and statistics and is a reviewer and an associate editor for epidemiology journals. Tr. at 73, 75.

During his career, Dr. Greenland has served as a consultant on epidemiology and statistics for governmental agencies and private corporations, and as an investigator on more than 30 grants and contracts from agencies such as the National Institutes of Health and the Rockefeller Foundation. Tr. at 74.

b. Doctor Eric Fombonne.[38]

Doctor Fombonne is currently the head of the division of child psychiatry for the McGill University system in Montreal, Quebec, and heads the Department of Psychiatry and Director of the Autism Clinic at Montreal Children's Hospital.[39] Tr. at 3614. He holds a federal appointment as a Canada Research Chair, and is a tenured professor of medicine at McGill, where he teaches medical students and residents. Tr. at 3614.

Doctor Fombonne's medical degree is from the University of Paris. Tr. at 3607. He completed residencies in general psychiatry and child and adolescent psychiatry, and has the French equivalent of board certification in child and adolescent psychiatry. Tr. at 3608-09. He also holds a master's certificate in biostatistics and human physiology and has advanced training and experience in the epidemiology of psychiatric disorders, including autism. Tr. at 3608, 3610.

Doctor Fombonne has been working in the field of autism spectrum disorders since 1986.[40] Tr. at 3609. His clinical practice[41] includes the diagnosis of new cases of autism and a caseload of children he follows on a long-term basis. Tr. at 3619. He was

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[38] Doctor Fombonne's CV was filed as Res. Ex. F, and his expert report was filed as Res. Ex. E. The slides he used during his testimony were Res. Tr. Ex. 12.

[39] Within the hospital, he teaches pediatricians and family practice physicians about autism, as well as providing lectures to community, research, and clinical practice groups. Tr. at 3615. He lectures at conferences worldwide in the areas of autism, epidemiology, and vaccines, and assists in organizing such conferences. Tr. at 3615-16. In addition to teaching physicians about the early signs of autism, he also teaches about the psychopharmacological management of children with autism. Tr. at 3617.

[40] After work in France on the epidemiology of child psychiatric disorders, he moved to London to work with Sir Michael Rutter at the Maudsley Hospital and Institute of Psychiatry, one of the premier psychiatric research facilities in the world, to run that facility's autism program and head the section on affective disorder research. He was also heavily involved with the autism section in the same research unit. Tr. at 3610-12. He was appointed to the position of reader, similar to a professorship, in epidemiological child psychiatry at King's College, University of London, in 1997. Tr. at 3612-13.

[41] During 2007 and 2008 he saw approximately 250-300 new patients. Tr. at 3619. He also runs a psychopharmacology clinic for school-aged children, adolescents, and young adults with ASD diagnoses, who have severe behavioral problems that have been unresponsive to behavioral interventions and for whom medication is appropriate. Tr. at 3619-20.

involved in developing the diagnostic criteria for the ICD-10[42] and the DSM-IV. Tr. at 3617-18.

His epidemiological work in autism has involved conducting approximately 10 studies. He has published more than 160 peer reviewed articles on childhood developmental and behavioral disorders as well as 34 book chapters pertaining to such disorders and the epidemiology of autism. He serves on the editorial board of four journals, serves as a reviewer for many journals, and was a reviewer for the National Institutes of Health. Tr. at 3621-23. Doctor Fombonne is currently involved in writing an autism textbook chapter on the epidemiology of autism for the American Psychiatric Association. Tr. at 3624.

He appeared as an expert witness on autism and epidemiology in the Theory 1 cases,[43] and testified for the defendant at a *Daubert* hearing in a case against a thimerosal manufacturer in the Eastern District of Texas.[44] Tr. at 3624-25.

c. Doctor Steven Goodman.[45]

Doctor Goodman is currently a professor of oncology, epidemiology, biostatistics, and pediatrics at the Johns Hopkins School of Medicine, where he has held a faculty appointment since 1989.[46] Tr. at 3065-66.

He received his medical degree from New York University and then trained in pediatrics at Washington University in St. Louis. After becoming board certified in pediatrics, he received a master's degree in biostatistics and a Ph.D. in epidemiology from the Johns Hopkins School of Public Health. Tr. at 3065-66. Doctor Goodman no longer practices clinical medicine, but instead works primarily in epidemiology. Tr. at 3066. He is on the executive board of the Society for Clinical Trials.[47] Tr. at 3066,

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[42] INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES AND RELATED HEALTH PROBLEMS (World Health Organization, 10th revision) ["ICD-10"].

[43] *Snyder*, No. 01-162V, 2009 WL 332044, at *12.

[44] *Easter v. Aventis Pasteur, Inc.*, 358 F. Supp. 2d 574 (E.D. Tex. 2005) (*Daubert* ruling). The case was dismissed without prejudice. No. 5:03-141 (E.D. Tex. Mar. 29, 2005).

[45] Doctor Goodman's CV was filed as Res. Ex. H. His expert report is Res. Ex. G.

[46] Doctor Goodman teaches a required seminar for doctoral candidates in advanced principles of epidemiology, and courses on meta-analysis, clinical research methods, and ethics in clinical research. Tr. at 3067-68. He lectures on issues of inference and evidence synthesis (drawing conclusions from data) to professional groups and organizations, such as the FDA. Tr. at 3068.

[47] The annual meeting of this society is sponsored by both academic institutions and corporate sponsors, including two vaccine manufacturers. Doctor Goodman is not paid for his work for the society or for his travel on its behalf. He edits the society's journal. Tr. at 3120-21.

3120.

His publications include more than 100 peer reviewed scientific articles, with cancer research the primary focus. He has authored six book chapters and wrote the lead chapter in the 2004 Surgeon General's report on smoking. Tr. at 3069-70. He served as the senior statistical editor for one of the world's leading medical journals and has performed editorial and reviewer roles for other medical and scientific journals. Tr. at 3071. Doctor Goodman has been a member of various IOM committees, including the IOM's Immunization Safety Review Committee.[48] Tr. at 3072, 3076.

2. Toxicologists, Medical Toxicologists, and Teratologists.

Toxicology is the science that explores the adverse effects of chemical substances on living systems. Tr. at 1796; Res. Tr. Ex. 4, slide 2. Those who study these effects can be considered toxicologists. Tr. at 1796-97. The title of "medical toxicologist" has a specific meaning, because it is a subspecialty of medicine recognized by the American Board of Medical Specialties. To qualify as a medical toxicologist, a person must be a licensed physician who is board certified, has completed a two-year post-residency fellowship, and has passed a certifying examination, with periodic recertification. Tr. at 1797. Petitioners' testifying expert, Dr. Aposhian, is a toxicologist.[49] Tr. at 246. In contrast, respondent's expert, Dr. Brent, is a medical

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[48] The IOM committees are comprised of individuals who are regarded as experts in a field relevant to the report being prepared. Committee members read through published reports, listen to public testimony and other evidence, and develop conclusions regarding the subject being studied. Tr. at 3074-75. Before being published, IOM reports are peer reviewed by a panel of scientists who comment on the committee's work. The committee responds to the review panel's comments, and must explain why any change recommended was or was not made. Tr. at 3075. At the time of the review, the identity of the reviewers is not known to the committee members. Tr. at 3075-76. The Immunization Safety Review Committee was formed because of concern by Congress and the Centers for Disease Control and Prevention ["CDC"] about a variety of hypotheses concerning vaccine safety and the desire for a fair and unbiased review of these hypotheses. Tr. at 3076. The committee has issued a series of reports involving various vaccines and autism and other developmental disorders. Tr. at 3077-78.

[49] Doctor Aposhian debated the significance of this terminology. He claimed that "the board" uses the term "clinical toxicologist" rather than "medical toxicologist." Tr. at 245. The American Board of Medical Specialities uses the term "medical toxicologist," (*see* www.abms.org), but perhaps Dr. Aposhian meant another organization, such as The American Academy of Clinical Toxicology, which uses "clinical toxicologist" (*see* www.clintox.org), but does not define the term and does not certify specialists. When challenged on this point during cross-examination, he testified that the terminology must have "changed then...[b]ecause two of the members at the University of Colorado spent time in my laboratory, and one of them took time off to study for her board exams in clinical toxicology." Tr. at 245. In response to a question about whether he was a medical toxicologist, Dr. Aposhian responded: "It depends on how you define the term medical toxicologist." Tr. at 245. He then discussed several overseas consultations that involved his supervision of a team dealing with human toxicology issues. Tr. at 246. The Institute of Medicine draws a distinction between these terms: "The term *clinical toxicologist* implies a more clinical orientation, but [like toxicologist] has no specific definition or implications. *Medical toxicologists* are physicians with specific training and board certification in the subspecialty of medical toxicology, which focuses on the care of poisoned patients." IOM, FORGING A POISON PREVENTION AND CONTROL SYSTEM 1

toxicologist,[50] one of 350 medical toxicologists in the United States. Tr. at 1797.

Teratology is a type of toxicology focused on the effects of toxins on the developing human or animal. Tr. at 2911. Teratologists are experts on birth defects. Tr. at 2912. Doctor Rodier was the only teratologist who testified.

a. Doctor (Ph.D.) Vas Aposhian.[51]

Doctor Aposhian is professor emeritus of molecular and cellular biology and of pharmacology in the College of Medicine at the University of Arizona. Tr. at 137; CV of Dr. Aposhian, PML 710, at 1. He retired in January, 2008. Tr. at 243. His lab remains active, and he currently holds grants for research from both private foundations and the federal government. Tr. at 137, 243.

He holds a Ph.D. in physiological chemistry from the University of Rochester and spent three years doing research as an NIH senior postdoctoral fellow. Tr. at 139; Pet. Tr. Ex. 2, slide 3. He has published more than 200 articles, served as associate editor of a number of journals, and has reviewed many papers for peer reviewed journals. Tr. at 139. Much of his published work has dealt with heavy metal toxicology. Tr. at 140. He cited developments in chelation as his major contribution to science since 1979. Tr. at 250.

He described himself as "a basic science bench investigator." He has not published any peer reviewed article on autism, mercury in the immune system, thimerosal toxicity, or ethylmercury toxicity. Tr. at 247-48. Nevertheless, he also described himself as an expert on the relationship of mercury to autism.[52] Tr. at 248.

b. Doctor Jeffrey Brent.[53]

Doctor Brent is a clinical professor of pediatrics and medicine at the University of Colorado Health Sciences Center. He is a board certified medical toxicologist, and

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n.1 (2004). I resolve this debate against Dr. Aposhian. Although highly qualified in the general area of toxicology, he is not a medical toxicologist.

[50] Doctor Haynes is also a medical toxicologist, but he did not testify. His qualifications are discussed, with those of the other non-testifying expert, below.

[51] Doctor Aposhian's CV was filed as PML 710. His original expert report was filed as PML 711, and his supplemental report as Pet. Ex. 21. The slides he used during testimony were Pet. Tr. Ex. 2.

[52] He testified that he acquired his expertise on mercury and autism in response to a request to testify before a Congressional committee on mercury toxicity. Tr. at 249-50.

[53] Doctor Brent's CV was filed as Res. Ex. B. His expert report was Res. Ex. A, and his supplemental expert report was Res. Ex. EE. The slides he used to illustrate his testimony were Res. Tr. Ex. 4.

maintains a private clinical practice in addition to his clinical duties at the Health Sciences Center.[54] Tr. at 1781.

He holds a master's degree in molecular biology, a Ph.D. in biochemistry, and a medical degree. He completed a residency in emergency medicine, and a two-year subspecialty fellowship in medical toxicology. Tr. at 1782. He remained on the faculty at the University of Colorado after completing his fellowship there, and he is now a full professor.[55] Tr. at 1782-83.

He is the recipient of the Louis Roche award, given annually by the European Association of Poison Control Centers and Clinical Toxicologists to one person who has contributed greatly to the field of toxicology. Tr. at 1783. He has served as a consultant to many government agencies, including the United States Department of Justice and the CDC. Tr. at 1783-84. He frequently lectures on toxicology throughout the U.S. and internationally. Tr. at 1784-85.

He is a reviewer for a number of medical journals and has published more than 200 articles in peer reviewed journals, as well as abstracts and book chapters on toxicology. Tr. at 1786-87.

Although he received money from a pharmaceutical company for speaking engagements early in his career, he has not done so in the last 15 years. He has received some funding from pharmaceutical companies for research, including research on a newer class of antidepressants to determine their safety. Tr. at 1787-88. More recently, he received a grant from the FDA for clinical trials of a new antidote, which has now been introduced into clinical use. Tr. at 1789.

He has appeared as an expert witness several dozen times in the last 18 years, including providing testimony on behalf of a pharmaceutical company. Tr. at 1789-90. He provided a deposition in the *Easter* case[56] on behalf of defendant GlaxoSmithKline. Tr. at 1790-91. He was also an expert witness in the Theory 1 OAP cases.[57]

In his private practice, Dr. Brent sees and treats patients with heavy metal

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[54] His private practice, Toxicology Associates, is a single specialty group practice devoted to medical toxicology. The practice involves patient care, research, and teaching. Tr. at 1792.

[55] His clinical professorial duties involve serving as an attending physician, where he sees patients suffering adverse effects of drugs or chemicals. In this regard, he supervises the residents and fellows who provide the direct patient care. He lectures in training programs at the university and is expected to publish and conduct research. Tr. at 1791-92.

[56] This is the same civil litigation in which Dr. Fombonne provided expert testimony. *See supra* note 44; *see also* Tr. at 1791.

[57] *See Snyder*, No. 01-162V, 2009 WL 332044, at *19-20.

toxicity, including mercury toxicity. Tr. at 1792-95. He has treated children with autism for lead toxicity related to pica. He also receives patients on referral from their primary care physicians who are seeking information on chelation therapy. Tr. at 1795-96.

c. Doctor (Ph.D.) Patricia Rodier.[58]

Doctor Rodier is a teratologist. She currently works at the University of Rochester Medical Center as a professor of obstetrics and gynecology. Tr. at 2910-11.

She received a Ph.D. from the University of Virginia in experimental psychology, completed post-doctoral work at the University of Virginia Medical School in embryology and teratology, and remained there on the medical school faculty. Tr. at 2911. In connection with her Ph.D., Dr. Rodier was selected to be a Woodrow Wilson fellow. Tr. at 3007.

Although a medical school professor, Dr. Rodier has few teaching or administrative duties. Tr. at 2912. For the last 20 years, she has been almost completely supported by research grants. Doctor Rodier has studied autism since the early 1980s. Tr. at 2917. She currently holds two NIH grants for work on autism totaling approximately $2.5 million per year.[59] Tr. at 3007. She has published more than 50 peer reviewed articles on brain damage. Report of Dr. Rodier, Res. Ex. U, at 1-2; Tr. at 2913.

Doctor Rodier is the director of the NIH Collaborative Program of Excellence in Autism, and of the NIH Autism Research Center of Excellence located at the University of Rochester. Res. Ex. U at 1. Doctor Rodier has served as the president of the editorial board of one journal and as a reviewer for several others. Tr. at 2914.

Her testimony in the Theory 2 cases was her first court appearance as an expert, although she had previously submitted expert reports or affidavits in two other cases, including the *Redfoot* case.[60] Tr. at 3008. She did not testify because the cases were dismissed before trial. Tr. at 3008.

Doctor Rodier limited her expert opinions to two areas: (1) the relationship between mercury and autism; and (2) the time in human development when autism

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[58] Doctor Rodier's CV was filed as Res. Ex. V, and her expert report as Res. Ex. U. The slides she used during her testimony were Res. Tr. Ex. 11.

[59] These grants fund 30-40 researchers at the Ph.D. or M.D. level, with Dr. Rodier supervising the research. Tr. at 3008.

[60] The plaintiff in *Redfoot v. B.F. Ascher & Co.* alleged that defendant's nasal spray product, which contained thimerosal, caused her son's autism. Defendants prevailed on summary judgment. No. 05-2045, 2007 WL 1593239 (N.D. Cal. June 1, 2007). Doctor Rodier also testified that she prepared an expert report for "the Canadian Omnibus which was on the same subject as this one." Tr. at 3008.

begins. Tr. at 3009.

3. Pharmacologists, Neuropharmacologists, and Neurotoxicologists.

Pharmacology is "the science that deals with the origin, nature, chemistry, effects, and uses of drugs." DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (30th ed. 2003) ["DORLAND'S"] at 1415. Neuropharmacology is "that branch of pharmacology dealing especially with the action of drugs upon various parts and elements of the nervous system." DORLAND'S at 1258. Neurotoxicology is the scientific study of poisons and their effects on nerve tissue. *See* DORLAND'S at 1260, 1926 (defining neurotoxic and toxicology).

Particularly in this area, the relative disparity in the qualifications of the parties' experts was most apparent, with the qualifications of respondent's experts overwhelmingly greater than those of petitioners' expert, Dr. Deth. Doctor Deth testified about oxidative stress, sulfur metabolism, and dopamine receptors, with relatively sparse and recently acquired qualifications in each of those areas.[61] Respondent's experts had superb and long-standing expertise, each in defined areas. To illustrate: Dr. Deth had one publication on oxidative stress, a review article. In contrast, Dr. Roberts, one of respondent's experts, has written approximately 180 publications on oxidative stress and holds several patents related to oxidative stress. Much of Dr. Deth's testimony concerned dopamine receptors (discussed in some detail in Section VII), but he had relatively little in the way of publications or research credentials on these receptors. In contrast, Dr. Mailman had more than 100 peer reviewed publications on dopamine receptors. There were similar disparities between Dr. Deth's qualifications and those of respondent's other experts in these fields.

a. Doctor (Ph.D.) Richard Deth.[62]

Doctor Deth is currently a professor of pharmacology in Northeastern University's Department of Pharmaceutical Sciences in Boston, where he has held a faculty appointment for nearly 32 years. Tr. at 493-94. He holds a Ph.D. in pharmacology from the University of Miami, and completed a post-doctoral fellowship at the University of Leuven in Belgium. Tr. at 495; CV of Dr. Deth, PML 712, at 1.

In conjunction with his faculty appointment, he maintains a laboratory where he has performed research, first in cardiovascular studies relating to hypertension, and more recently in receptors, the molecules that respond to neurotransmitters. His

[61] Each of these terms (oxidative stress, sulfur metabolism, and dopamine receptors) are defined and discussed in Section VII below.

[62] Doctor Deth's CV was filed as PML 712, and his report was filed as PML 713. His slide presentation, used during his testimony, was Pet. Tr. Ex. 3.

research has been supported by NIH[63] and American Heart Association grants, as well as by autism advocacy groups.[64] Tr. at 494-95. His research budget in 2008 was about $90,000. Tr. at 594-95.

He trains doctoral students as well as undergraduates, and has approximately 70 peer reviewed publications. He has some work in press regarding autism. Tr. at 495-96. He asserted that one of his books was closely related to his autism research. Tr. at 496. His discovery of a dopamine receptor signaling activity in 1998 prompted him to leave cardiovascular research and move into neuroscience and neuropharmacology. Tr. at 496-97. His research pertinent to the causation hypothesis he advanced is discussed in detail in Section VII below.

b. Doctor (Ph.D.) Richard Mailman.[65]

Doctor Mailman is currently a professor of psychiatry, pharmacology, neurology, and medicinal chemistry at the University of North Carolina School of Medicine, where he did postdoctoral training in drug metabolism and neuropharmacology. Tr. at 1975. He earned his Ph.D. in physiology with a minor in toxicology from North Carolina State University. His position primarily involves research, but spends approximately 25% of his time teaching graduate students, medical students, and residents. Tr. at 1975-76.

He has published more than 170 peer reviewed articles and about 85 book chapters. At least two-thirds of his publications involve work on dopamine receptors. Tr. at 1976-77. He sits on the editorial boards of three journals, and reviews papers for between 15 and 20 journals per year. Tr. at 1977.

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[63] These NIH grants apparently pertained to Dr. Deth's cardiovascular research. He testified that the two "grants pending" on his CV were never approved, including a grant proposal submitted to the NIH for funding for autism research. Tr. at 586-87; CV, PML 712, at 4. He testified that his NIH proposal was rejected because the reviewer felt "it was inappropriate to study thimerosal, because [the reviewer had already made up his mind that] it doesn't cause autism," based on the FDA's public position on the thimerosal-autism theory. Tr. at 588. Further information regarding the NIH approval process for grants is provided in Section VII below.

[64] Over the last five years, his funding has largely come from organizations composed of parents of children with autism, such as Autism Speaks, SafeMinds, the National Autism Association, and the Autism Research Institute ["ARI"]. Tr. at 595. SafeMinds contributed roughly one quarter of his budget for research in 2007 and 2008. Tr. at 596. I note that SafeMinds was formed by a group of parents who believed that mercury was responsible for their children's ASD. *See* J. Baker, *Mercury, Vaccines, and Autism*, AM. J. PUBLIC HEALTH, 98(2): 244-53, 251 (2008) ["Baker"], filed as PML 599. Doctor Deth had two separate grants from ARI during the calendar year prior to his testimony, one involving the importance of methylcobalamin in methionine synthase activity and another to investigate methods to measure homocysteine thiolactone. Tr. at 596. The latter study grant was for $35,000, and the former was similar in size. Tr. at 597. Doctor Mumper, one of petitioners' other experts, is a director of ARI. Dwyer Tr. at 97.

[65] Doctor Mailman's CV is Res. Ex. R, and his report is Res. Ex. Q. The slides he used to illustrate his testimony are Res. Tr. Ex. 5.

Between 2001 and 2004, Dr. Mailman founded and owned a small pharmaceutical company, DarPharma, Inc. Tr. at 2018. The company was sold in 2005. Tr. at 2019. One of the company's research interests was developing drugs to treat Parkinson's disease and other conditions, including ADHD. Tr. at 2021-22. He is currently involved with a new, privately held company. Tr. at 2025-26. He also currently receives federal research funding in the form of two grants. Tr. at 2028.

c. Doctor L. Jackson Roberts, II.[66]

Doctor Roberts has been a full professor at Vanderbilt University since 1986. Tr. at 2155. In 2006, he was appointed to an endowed chair as the T. Edwin Rogers Professor of Pharmacology. Tr. at 2155. He has a laboratory at Vanderbilt, where he supervises and mentors four research assistants and a Ph.D. student. Tr. at 2159-60.

Doctor Roberts received his medical degree from the University of Iowa. He is board certified in internal medicine. Tr. at 2154. He moved to Vanderbilt University for a fellowship in clinical pharmacology and remained there after completing it. Tr. at 2154-55.

Doctor Roberts has been elected to two prestigious medical societies, the American Society for Clinical Investigation and the Association of American Physicians. He has received a merit award from NIH, which is a 10-year funding grant given only to scientists with a long record of accomplishments. Tr. at 2156-57. In 2006, he received an award from the Society for Free Radical Biology in Medicine and the Earl Sutherland prize for achievement in research from Vanderbilt University. Tr. at 2157.

He is the associate editor of a medical journal and has published more than 340 peer reviewed articles, abstracts, and book chapters, with approximately 180 on oxidative stress. Nearly all of his papers published since 1990 have been in the area of oxidative stress. He also lectures about oxidative stress and oxidative injury at international meetings and at professional societies. Tr. at 2157-58, 2160-61. He has a long list of current grants, including two on oxidative injury or damage. Tr. at 2158-59. He holds several patents specifically relating to oxidative stress, granted between 1997 and 2003. Tr. at 2160; Res. Tr. Ex. 6, slide 3.

Doctor Roberts limited his field of expertise to oxidative stress and oxidative damage as it relates to various diseases. Tr. at 2165-66.

[66] Doctor Roberts' CV was filed as Res. Ex. T and his expert report as Res. Ex. S. The slide presentation accompanying his testimony was Res. Tr. Ex. 6.

d. Doctor (Ph.D.) Jeff Johnson.[67]

Doctor Johnson is a professor in the School of Pharmacy at the University of Wisconsin. He received a master's degree in pharmacology from the University of Minnesota and a Ph.D. from the University of Wisconsin in environmental toxicology. Tr. at 2198. He completed a postdoctoral fellowship at the University of Washington in neuroscience. Tr. at 2199. He described himself as a neurotoxicologist. Tr. at 2203.

His teaching responsibilities at the University of Wisconsin include both undergraduates and professional students in the pharmacology doctoral program. In addition to teaching, he has a research laboratory where the primary focus of his work is on neurodegenerative diseases, including Alzheimer's, Parkinson's, ALS,[68] and Huntington's disease. His specific research focus is on ways to prevent cell loss and neuronal death in these diseases. Tr. at 2199.

He has published extensively in this field of research, serves as a reviewer for 20-30 different journals, and has garnered several awards. Tr. at 2200-01; CV of Dr. Johnson, Res. Ex. R, at 2. He served on a study section at NIH for five years, reviewing grant applications in the area of neurotoxicology and alcohol. Tr. at 2202-03.

e. Doctor (Ph.D.) Dean Jones.[69]

Doctor Jones joined the faculty at Emory University in 1979, where he currently holds a faculty appointment in the Department of Medicine.[70] Tr. at 2692-93. Doctor Jones earned a Ph.D. in medical biochemistry from the University of Oregon and did a postdoctoral fellowship in nutritional biochemistry at Cornell University. Tr. at 2692. He was a visiting scientist in molecular toxicology at the Karolinska Institute in Stockholm for two years.

He has received Emory University's Albert E. Levy Research Award, the premier research award given by the university. He received a Nobel Fellowship for research in molecular toxicology approximately 10 years before his testimony. Tr. at 2693.

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[67] Doctor Johnson's CV was filed as Res. Ex. J, and his expert report as Res. Ex. I. The slides he used during testimony were Res. Tr. Ex. 7.

[68] "ALS" stands for amyotrophic lateral sclerosis. It is a motor neuron disease marked by progressive degeneration of the neurons and motor cells in particular areas of the brain and spinal cord. It is sometimes called "Lou Gehrig disease." DORLAND'S at 1668.

[69] Doctor Jones' CV was filed as Res. Ex. L and his expert report as Res. Ex. K. His slide presentation from the trial was Res. Tr. Ex. 9.

[70] He teaches nutritional biochemistry, gastroenterology, pharmacology, toxicology, and metabolism. Tr. at 2696.

He is a regular reviewer for journals and served for several years on two of NIH's toxicology study sections. He chaired the NIH's Alcohol and Toxicology study section. The chair oversees the peer review process for grant applications. Tr. at 2694.

One of his current major grants is on oxidative stress mechanisms, examining protective mechanisms against oxidative stress in cellular nuclei and cytoplasm. He is also one of the assistant program directors on a $22 million award from NIH to a consortium of three universities. He directs two Emory laboratories. One focuses on clinical biomarkers, including oxidative stress markers, cytokine measurements, inflammatory markers, and analytical services for researchers throughout Emory University. Tr. at 2695. The other, his own research laboratory, is focused on oxidative biochemistry. Tr. at 2695-96.

He has written more than 325 peer reviewed articles, reviews, and book chapters. Tr. at 2696. About two-thirds of his peer reviewed articles are in the field of sulfur metabolism. Tr. at 2696-97. More than 100 of his original research articles address the issue of oxidative stress, a topic about which he lectures nationally and internationally.[71] Tr. at 2697.

Doctor Jones limited his expert testimony to sulfur metabolism and oxidative stress. Tr. at 2698.

4. Neurologists, Neuropathologists, Psychiatrists, and Clinical Psychologists.

a. Doctor Marcel Kinsbourne.[72]

Doctor Kinsbourne currently teaches methodology and statistics. Tr. at 776. It appears from his CV that this is at the undergraduate level at New School University in New York. *See* PML 716 at 2. He is a pediatric neurologist who focused on mental development disorders in children, including dyslexia, early in his career. Tr. at 770. His clinical practice involving children ended about 18 years prior to his testimony. He now focuses on research and writing. Tr. at 775-76, 910.

During an associate professorship at Duke, he was chief of the division of Pediatric Neurology and head of the Developmental Evaluation Clinic, where he had the opportunity to see children with autism and ASD. Tr. at 770-71. He co-authored one article on care of children with autism while at Duke in 1971. CV, PML 716, at 8. He also began a research program concerning attention deficit disorder, which resulted in seeing children who may have had either attention-deficit/hyperactivity disorder

[71] He was an invited speaker at a meeting in Korea on oxidative biochemistry in 2007 and in Japan in 2008 on biomarkers of oxidative stress, health, and disease. Tr. at 2697. Shortly after the hearing in this case, he was scheduled to attend a free radical research meeting in Berlin. Tr. at 2697-98.

[72] Doctor Kinsbourne's CV was filed as PML 716, and his expert report was PML 717.

["ADHD"] or a high-functioning level of autism. Tr. at 771-73.

Thereafter, he moved to Toronto to be a professor of child neurology, where he saw children with developmental disorders, including autism, at the university clinic, and published a number of articles on various issues in developmental disabilities. Tr. at 773. Upon leaving the University of Toronto, he returned to the U.S. to become the chief of the Division of Behavioral Neurology at the Eunice Kennedy Shriver Center for roughly 11 years. During that period, his clinical work and research was entirely in the area of developmental disabilities, and he saw hundreds of children. He also consulted with a state facility for children with mental retardation and developmental disabilities. Tr. at 773.

He has reviewed articles for medical and scientific journals. Since the early 1970s, he has written and updated a chapter on developmental disabilities, including autism, in a textbook on child neurology. Tr. at 773-74. During the 1980s, he published two articles on autism. The 1980s articles, the book chapter, and one article,[73] a study of certain autistic behaviors related to his hypothesis in this case and in the Theory 1 cases, are the extent of his writing on autism in the last 30 years. Tr. at 910. He has also written two articles on "overfocusing," which he now believes to represent high functioning autism, but which also appears to be present in normal children and in children with more severe forms of autism. Tr. at 774-75.

Doctor Kinsbourne acknowledged appearing on behalf of petitioners in about 130 cases in the Vaccine Program and indicated that he was currently retained in 20-30 cases.[74] Tr. at 918-19. He has opined that vaccines caused, among other disorders, encephalopathies, seizure disorders, Guillain-Barré syndrome, transverse myelitis, acute disseminated encephalomyelitis, and septicemia, in addition to autism. Tr. at 919.

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[73] M. Liss, et al., *Sensory and attention abnormalities in autistic spectrum disorders*, AUTISM 10(2): 155-72 (2006) ["Liss"], filed as PML 373.

[74] Doctor Kinsbourne's participation in the Vaccine Program has been more extensive than the transcript describes. As I chronicled in *Snyder*, "In the 20 years of the Vaccine Program's existence, Dr. Kinsbourne has appeared as an expert witness in at least 185 cases. This figure does not include his opinions in the many unpublished cases adopting stipulations of settlement, nor does it reflect pending cases in which he has filed an expert opinion." 2009 WL 332044, at *12. Although income from expert opinions and testimony is more difficult to estimate, I note that Dr. Kinsbourne has been awarded $500 per hour in recent Vaccine Act cases. *See, e.g.*, *Hall v. Sec'y, HHS*, No. 02-1052V, 2009 WL 3423036, at *30 (Fed. Cl. Spec. Mstr. Oct. 6, 2009); *Walmsley v. Sec'y, HHS*, No. 06-0270V, at *14 (Fed. Cl. Spec. Mstr. Nov. 6, 2009). Based on my experience in awarding expert fees, it would not be uncommon for an expert with Dr. Kinsbourne's qualifications to have received well in excess of $1000 for writing an expert report, and substantially more for testimony, in a single case.

b. Doctor Robert Rust.[75]

Doctor Rust currently holds the Worrell Chair in Neurology, Child Neurology, and Epileptology at the University of Virginia.[76] He is the director of child neurology and the co-director of the epilepsy and child neurology clinics there. Tr. at 2351.

Doctor Rust received a medical degree from the University of Virginia. He completed a residency in pediatrics at Yale University, followed by training in neurology, child neurology, developmental neurochemistry, and neonatal neurology at Washington University in St. Louis. Tr. at 2352. CV of Dr. Rust, Res. Ex. Y, at 2-3. He is board certified in pediatrics and neurology, with a subspecialty in child neurology. Tr. at 2352.

He has served on the editorial boards of medical journals, and currently serves as a reviewer for 16-18 journals. He has authored about 50 papers published in major neurology journals. Tr. at 2352-53. He has also authored more than 50 book chapters and reviews. Tr. at 2353.

His research interests are broad, and include autism, headache, behavioral disturbances in children, epilepsy, ataxia, and degenerative conditions of children. He is involved in research in the EEG aspects of both neonatal neurology and autism. Tr. at 2354. Doctor Rust has diagnosed "many hundreds" of children with autism over the course of his career. Tr. at 2355. He currently treats between 80 and 100 children with the condition. Tr at 2355.

Doctor Rust testified for respondent in *Hazlehurst*, a Theory 1 OAP case. Tr. at 2517; 2009 WL 332306, at *8. He has testified in two other Vaccine Act cases on behalf of petitioners. *See Snyder*, 2009 WL 332044, at *14.

c. Doctor Michael Rutter.[77]

Doctor Rutter is currently a professor of developmental psychopathology at the Institute of Psychiatry, Kings College, London.[78] Tr. at 3236. He received his medical

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[75] Doctor Rust's CV was filed as Res. Ex. Y. His expert report was filed as Res. Ex. X. Dr. Rust's slides from his trial testimony were Res. Tr. Ex. 8.

[76] He teaches neurology, pediatrics, developmental pediatrics, and psychiatry. Tr. at 2354. He has his own medical practice at the University of Virginia, and runs clinics for the residents in neurology, pediatrics, developmental pediatrics, and psychiatry, as well as outreach clinics run by the university for patients living in southwest Virginia. Tr. at 2355.

[77] Doctor Rutter's CV is filed as Res. Ex. AA, and his expert report is Res. Ex. Z.

[78] His current teaching responsibilities are all at the post-graduate level. Tr. at 3246. He teaches a course for Ph.D. students on social development, which deals, in part, with gene-environmental interactions and the use of natural experiments to test causal inferences about environmental causes of

degree in 1955 and the British equivalent of a Ph.D. in 1962. Tr. at 3236. He initially trained in general internal medicine, but also trained in both neurology and pediatrics before training in psychiatry and then in child psychiatry. Tr. at 3236. He has the British equivalent of a board certification in both psychiatry and internal medicine. Tr. at 3237.

Doctor Rutter began working in child psychiatry in 1959 or 1960. Tr. at 3238. He became a senior lecturer at the Institute of Psychiatry at Maudsley Hospital in 1966 and became a full professor there in 1973.[79] Tr. at 3239. He began treating children with autism in the early 1960s, and continues to do so, albeit in smaller numbers. Tr. at 3243. He has diagnosed hundreds of children with autism, and has followed many of them into adolescence, both clinically and as part of two major systematic follow-up studies. Tr. at 3243.

Since 1998, he has held a research chair, although he continues to teach and he maintains a clinical practice. Tr. at 3239. His current research involves quantitative genetic studies of twins and adoptees, and molecular genetic studies of autism. Tr. at 3244. He is particularly involved in examining gene-environment interactions. Tr. at 3245.

He is the clinical vice president of the Academy of Medical Science, and sits on research advisory committees around the world. Tr. at 3240. He has performed research in a variety of areas, including the first systematic epidemiological study in England examining mental disorders in children, the first co-morbidity study, quantitative genetic studies, and now molecular genetics studies, in addition to his work on autism. Tr. at 3240-41. He performed a study demonstrating the higher incidence of epilepsy in autistic adolescents and young adults, which was the first evidence that autism was a neurodevelopmental, rather than a psychiatric, disorder. Tr. at 3241-42. He also worked on twin and family studies of autism. Tr. at 3242. He was a co-author of the Autism Diagnostic Interview, Revised ["ADI-R"] and the Autism Diagnostic Observation Schedule ["ADOS"], which are tools used in research and diagnosis of autism. He worked on the development of the ICD-10 and DSM-IV diagnostic criteria, and the effort to bring the two diagnostic criteria closer. Tr. at 3242.

He has written more than 400 peer reviewed scientific articles, 200 book chapters, and 40 books pertaining to child psychiatry, development, and genetics. Tr. at 3245. Many of these pertain to ASD. Tr. at 3245-46. He has served on the editorial boards of a number of scientific journals related to psychiatry and development. Tr. at

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disease. Tr. at 3247. He lectures nationally and internationally on such topics as ADHD, gene-environment interaction, and autism. Tr. at 3247.

[79] He has held a consultant appointment in the National Health Service, the United Kingdom's medical system, since 1966. He set up the Medical Research Council's ["MRC"] child psychiatry unit in 1984 and served as its honorary director until 1998. He set up the MRC's Social, Genetic, and Developmental Psychiatry Center in 1994 and served as its honorary director until 1998.

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His honors, awards, and recognitions include election to the British Royal Society (the British equivalent of the National Academy of Sciences), election to the Institute of Medicine, and receipt of the Helmut Horten prize for his work on autism. In 1992 he was honored as a Knight Baronet for his work in child psychiatry. Tr. at 3248-49.

He previously agreed to serve as an expert witness in civil litigation in the U.S. regarding thimerosal, but during his preparation of his expert report, the litigation was either "put on hold" or abandoned, and the report was never completed. Tr. at 3249. He also agreed to serve as an expert witness in the United Kingdom MMR litigation, but the litigation was abandoned, and his report was never completed or filed. Tr. at 3249-50.

Doctor Rutter indicated that he followed the British tradition in preparing his expert report, explaining that it was his "duty as a scientist not to speak for or against any particular hypothesis, but to look at the evidence as a whole and to note the limitations, to note the strengths and then put it all together as a whole." Tr. at 3300.

d. Doctor Thomas Kemper.[80]

Doctor Kemper is a professor in three departments at the Boston University School of Medicine: Anatomy and Neurobiology, Pathology, and Neurology, but, having reached mandatory retirement age, he no longer actively teaches. Tr. at 2793-94. He formerly taught neuropathology and brain development in the medical school at Boston University. Tr. at 2794. He holds no board certifications, as they were not required in academic promotions. Tr. at 2794-95.

He graduated from the University of Illinois School of Medicine. Tr. at 2792. He did residency training in internal medicine and neurology, followed by a fellowship in neuropathology.[81] After completing his fellowship, he worked actively as a neuropathologist for more than 25 years at Boston University School of Medicine. Tr. at 2793.

He is now primarily a research scientist, but had a clinical practice for a considerable period. Tr. at 2794. He currently studies tissue received from brain

[80] Doctor Kemper's CV was filed as Res. Ex. N, and his expert report as Res. Ex. M. The slides he used to illustrate his testimony were Res. Tr. Ex. 10.

[81] Doctor Kemper defined neuropathology as the study of diseased brains, nerves, and muscles. The primary goal of neuropathology is to diagnose a condition so that treatment can be determined. Thus, neuropathology is relevant to both the diagnosis and the cause of disease. Tr. at 2796-97.

banks[82] to determine the nature of brain disease, and has devoted much of his professional life to investigating autism's neuropathogenesis. Tr. at 2796-97, 2799.

Doctor Kemper has written about 170 publications, with about 30 relating to autism. Tr. at 2795. He is a reviewer for numerous medical journals. Tr. at 2795.

e. Doctor (Ph.D.) Catherine Lord.[83]

Doctor Lord is the director of the University of Michigan's Autism and Communication Disorders Clinic[84] and a professor at the University of Michigan. Tr. at 3535, 3539. Her teaching responsibilities are at the graduate level and include assessments, workshops in diagnosis, and research design in developmental psychopathology. She has been teaching for 32 years.[85] Tr. at 3540.

She holds a Ph.D. from Harvard in psychology and social relations. Res. Ex. P, at 1. She did a post-doctoral internship at the University of North Carolina and is board certified in clinical psychology. Tr. at 3536.

Doctor Lord also has a research practice, which presently includes two early intervention projects.[86] Tr. at 3544-45. She is involved in a longitudinal study[87] of children referred at two years of age who have been followed for 14-17 years. Tr. at

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[82] Brain banks, as government sponsored entities, receive brains from donors, process them in a uniform manner, and make them available to investigators. Tr. at 2796-97.

[83] Doctor Lord's CV was filed as Res. Ex. P, and her report as Res. Ex. O.

[84] Her current clinical practice involves seeing one new child a week for diagnosis. This involves an assessment and a school visit (Tr. at 3541-42), but she also sees other new patients who are assessed by others on her team. Tr. at 3542. Over the course of her career, she has diagnosed approximately 4,000 children with autism. Tr. at 3542. Doctor Lord also supervises a clinic with five other Ph.D. workers, a speech pathologist, and a social worker, all of whom see new patients. Tr. at 3542. The goal of her clinic is to follow the child into adulthood. She still sees adults whom she met as children. Tr. at 3543. Her patients range from toddlers to those in middle age. Tr. at 3543. Her practice requires her to meet frequently with parents, both during the diagnostic process and in forming and executing treatment plans. Tr. at 3543-44.

[85] She worked at the University of Minnesota as an assistant professor of child development, moving from there to the University of Alberta School of Medicine. Tr. at 3536. After eight years there, she returned to the United States and set up a clinic at the University of North Carolina. She moved to the University of Chicago, and from there to her current position. Tr. at 3536-37; CV, Res. Ex. P, at 1-2.

[86] One involves training parents and the other involves in-home visits of about 20 hours per week. These are both randomized, controlled trials. Tr. at 3545.

[87] Doctor Lord explained that a longitudinal study is one that follows the same individuals over time. Tr. at 3556. Such studies are difficult to do because government grants are usually only for five year periods. Tr. at 3556. Her study is probably the longest-running one on autism. Tr. at 3557.

3545. She is also involved in developing a diagnostic test that will measure spontaneous communication. Tr. at 3545-46. She works with geneticists to help them quantify the severity of autistic deficits. Tr. at 3546. Her team is working on a method to diagnose autism in children as young as 12-18 months of age. Tr. at 3546-47. Her autism research has spanned nearly 40 years. Tr. at 3547.

She is one of the authors of the ADI-R and the ADOS. Tr. at 3548-50. She has published more than 125 peer reviewed articles in the areas of child development and psychology, with the majority of them pertaining to ASD. Tr. at 3552. She has written a number of papers about regression in ASD since her first publication on the topic in 1991 or 1992. Tr. at 3553. She has published nine books and 61 book chapters, and she currently serves on the editorial boards of six journals focused on child psychology and autism. Tr. at 3553.

Doctor Lord lectures approximately 20 times a year, nationally and internationally, at medical schools, conferences, parents' groups, and professional groups about diagnosis and longitudinal studies in autism. Tr. at 3540-41.

Her awards in the field of autism include one from the Royal Academy of Psychiatry in the United Kingdom, and one from California. She chaired a National Academy of Sciences committee examining the effectiveness of early intervention in autism. Tr. at 3537. She is one of four scientists on the strategic planning committee for autism research at NIH.[88] Tr. at 3537-38. She also serves as one of 12 members on the planning committee for autism and related diagnoses for the DSM-V, which is the diagnostic and statistical manual under preparation.[89] Tr. at 3538-39.

Prior to her appearance in the Theory 2 cases, she testified in three court cases, two of which involved parents accused of abusing their children and one in which the parents were suing the state over access to services. Tr. at 3554-55.

5. Specific Causation Experts.

a. Doctor Elizabeth Mumper.[90]

Doctor Mumper is a general pediatrician who opined on specific causation in

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[88] The committee was created in response to the Combating Autism Act, to plan how governmental agencies would set priorities for research and funding. Tr. at 3537-38.

[89] She was a member of the committee that formulated the DSM-IV. This involved the testing of the proposed criteria for diagnosis. Tr. at 3539.

[90] Doctor Mumper's CV was filed as Pet. Ex. 14, and her report regarding Colin Dwyer was filed as Pet. Ex. 13. Her rebuttal slides in the *King/Mead* hearing were Pet. Tr. Ex. 14.

Colin Dwyer's case, as well as in the other two Theory 2 cases.[91] Dwyer Tr. at 96. She earned her medical degree from the Medical College of Virginia, interned at the University of Massachusetts, and completed a residency at the University of Virginia. Dwyer Tr. at 97.

She then moved to private practice in Lynchburg, Virginia. After five years in private practice, Dr. Mumper began teaching in a residency program, where she stayed for 11 years. Tr. at 1188. She then returned to private practice in 2000. She is currently the medical director of ARI,[92] the clinician in charge of physicians' training programs for Defeat Autism Now ["DAN"], and director of the Rimland Center, a private medical practice. Dwyer Tr. at 97-98.

She sees about 1750 children per year in her practice, approximately 500 of whom have an ASD or other neurodevelopmental disabilities. CV of Dr. Mumper, Pet. Ex. 4, at 2; Tr. at 1205. About half her time is spent on children with ASD because their care is more time intensive. Dwyer Tr. at 101-02.

She lectures both nationally and internationally about her clinical experiences with autistic individuals. *See* Dwyer Tr. at 100-01. While she does some research, she has few publications, and her research is focused primarily on treatments for her patients. Tr. at 1344-54.

b. Doctor Bennett Leventhal.[93]

Doctor Leventhal is currently a tenured full professor of psychiatry at the University of Illinois College of Medicine in Chicago. Dwyer Tr. at 206, 209. He has been teaching medicine for more than 30 years.[94] Most of his teaching is devoted to developmental disorders and atypical child development. Dwyer Tr. at 208-09.

He obtained his medical degree from Louisiana State University in New Orleans, and then completed a residency in general psychiatry and child and adolescent

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[91] Doctor Mumper also testified about the thimerosal-autism theory in *Blackwell v. Wyeth*, a civil lawsuit brought in Maryland state court. The trial judge found she failed to qualify as an expert under the *Frye-Reed* test, and that decision was affirmed on appeal. 971 A.2d 235, 265-66, 268 (Md. 2009).

[92] ARI, the Autism Research Institute, funds some of Dr. Deth's research. *See supra* note 64. Doctor Mumper described ARI as the "parent organization of . . . Defeat Autism Now. " Tr. at 1192.

[93] Doctor Leventhal's CV was filed as Res. Ex. DD, and his expert report as Res. Ex. CC.

[94] Doctor Leventhal joined the clinical faculty at Duke Medical School and then later moved to the faculty at Eastern Virginia Medical School. Dwyer Tr. at 207. He moved to the University of Chicago in 1978, remained there until 2005, and then took a position at the University of Illinois. Dwyer Tr. at 207. He teaches residents, fellows, medical students, nursing and social work students, and Ph.D. candidates. Dwyer Tr. at 208-09. He also teaches internationally in Europe, the Middle East, Asia, and Australia. Dwyer Tr. at 210.

psychiatry at Duke University. Dwyer Tr. at 206. He is board certified in child and adolescent psychiatry. Dwyer Tr. at 206-07.

He has been honored by the American Academy of Child and Adolescent Psychiatry for lifetime achievement in working with the developmentally disabled. Dwyer Tr. at 208. He sits on the advisory boards of two autism advocacy organizations, including the Autism Society of America. Dwyer Tr. at 211, 218-19.

He sees patients through a university based practice about 20 hours per week. About three-quarters of these patients are developmentally disabled. Dwyer Tr. at 211-12. Over the course of his career, he has diagnosed thousands of children with ASD and, at the time of the hearing, he was seeing between 50 and 200 new cases per year. Dwyer Tr. at 212-13. He follows his autistic patients into adulthood. Dwyer Tr. at 213.

In his research practice, Dr. Leventhal is part of one of five NIH-designated Autism Centers of Excellence; each center is the recipient of a $5 million NIH grant to study autism. Dwyer Tr. at 216, CV of Dr. Leventhal, Res. Ex. DD, at 11. Doctor Leventhal is responsible for all the evaluations and all the patients in the studies at this center. Dwyer Tr. at 216. The research projects range from MRI and brain imaging studies to pharmacogenetic studies.[95]

Doctor Leventhal was one of the authors of the ADOS. Dwyer Tr. at 217. He is also the author of more than 120 peer reviewed child psychiatry articles, including some related to autism, as well as 20 books and book chapters. Dwyer Tr. at 218. He is a reviewer for several psychiatry journals. Dwyer Tr. at 220.

He has testified about 15-20 times, primarily in cases related to child abuse and divorce. His testimony in the *Dwyer* case was his first Vaccine Act court appearance. Dwyer Tr. at 220. He has consulted for pharmaceutical companies, most recently with Johnson and Johnson to help bring Risperdal, the first FDA approved drug to treat autism, to the marketplace. Dwyer Tr. at 221. He has spoken at conferences for drug companies in the past, but not presently. His university receives funding from drug companies, but he does not receive any financial support from such companies. Dwyer Tr. at 252-54.

6. Non-Testifying Experts.

Both parties retained experts who submitted reports but did not testify. Their qualifications are discussed below. A CV was also submitted in this case for Dr. Jean-Ronel Corbier as Pet. Ex. 1. No expert report was filed, and Dr. Corbier did not testify. Accordingly, I need not comment on his qualifications as an expert.

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[95] These studies examine how genes may predict responses to certain medications, leading to a better understanding of the disorder. Dwyer Tr. at 217.

In evaluating matters contained in expert reports filed by the two non-testifying witnesses, I have considered the experts' qualifications, as reflected in their filed CVs, the extent to which their opinions were supported by other evidence or testimony, the bases for their opinions, and the nature of the opinions offered in determining how much weight to accord the proffered opinions. I have also considered that these witnesses were not available for cross-examination or to answer questions posed by me or another of the special masters, recognizing that there is no right to a hearing nor any right of cross-examination in Vaccine Act cases. § 300aa-12(d)(2)(D); § 330aa-12(d)(3)(B).

a. Doctor John F. Haynes, Jr [96]

Doctor Haynes has held various academic appointments, and is currently an associate professor of emergency medicine and medical toxicology and Chief of the Division of Toxicology at Texas Tech University in El Paso. He is also an Adjunct Clinical Assistant Professor of Medicine at the University of Texas Medical Branch-Galveston. CV of Dr. Haynes, Pet. Ex. 16, at 4. Doctor Haynes is the medical director of the West Texas Regional Poison Center, and he is the chief of toxicology services at R.E. Thomason General Hospital in El Paso. He also teaches emergency medicine and toxicology there. CV, Pet. Ex. 16, at 5.

Doctor Haynes received his medical degree from the University of Texas and completed residencies in emergency medicine at the University of Southern California Medical Center in Los Angeles and Brooke Army Medical Center in San Antonio. CV, Pet. Ex. 16, at 1-2. He completed a part-time fellowship in medical toxicology at the University of Texas medical branch. He is board certified in emergency medicine and medical toxicology. CV, Pet. Ex. 16, at 2.

Doctor Haynes has various publications, but, based on their titles, none appears related to autism or mercury toxicity. CV, Pet. Ex. 16, at 6-7. He has lectured nationally and internationally, but these engagements have not, based on their titles, concerned autism or mercury. CV, Pet. Ex. 16, at 8-13. The only reference on his CV to autism or mercury is one "research activity," in the "exploratory stages," concerned with the "epidemiological study of the relationship of Thimerosal containing vaccines and the development of autism." CV, Pet. Ex. 16, at 13.

Doctor Haynes' three page report concerned whether thimerosal caused injury to Colin Dwyer. It contains no citations to research to support his assertions. Pet. Ex. 15. This lack of support, taken together with his lack of experience with mercury or autism, leaves me skeptical of his ability to opine reliably on the causation issues in this case. Accordingly, I have placed little weight on Dr. Haynes' report. I note that most of Dr. Haynes' opinions were contradicted by those of Dr. Brent, who was not only better

[96] Doctor Haynes' CV was filed as Pet. Ex. 16, and his expert report as Pet. Ex. 15.

qualified to opine, but provided evidence to support his opinions.

b. Doctor Manuel F. Casanova.[97]

Doctor Casanova holds the Kolb Endowed Chair in psychiatry at the University of Louisville. CV, Res. Ex. D, at 4.

Doctor Casanova received his medical degree from the University of Puerto Rico School of Medicine. CV, Res. Ex. D, at 1. He did a residency in neurology at University District Hospital in Rio Piedras, Puerto Rico, and clinical and research fellowships in neuropathology at The Johns Hopkins University School of Medicine. CV, Res. Ex. D, at 1-2. He is board certified in neurology. Report of Dr. Casanova, Res. Ex. C, at 2.

He is the recipient of various awards, is a reviewer for numerous medical journals, and has more than 140 peer reviewed publications. CV, Res. Ex. D, at 6-8, 20-33. He has lectured nationally and internationally on autism. CV, Res. Ex. D, at 10-17.

Doctor Casanova's report summarized research in the neuropathology of autism, including much of his own published research on brain pathophysiology in autism. Res. Ex. C.

Section II. The Legal Standards to be Applied.

This section addresses the legal standards to be applied in "off-Table" Vaccine Act cases. The legal arguments concerning the application of these standards to Colin's specific case are addressed in Section X, below.

When a petitioner alleges an "off-Table" injury, eligibility for compensation is established when, by a preponderance of the evidence, petitioner demonstrates that: he received, in the United States, a vaccine set forth on the Vaccine Injury Table and sustained an illness, disability, injury, or condition caused by the vaccine or experienced a significant aggravation of a preexisting condition. He must also demonstrate that the condition has persisted for more than six months.[98] Vaccine litigation rarely concerns whether the vaccine appears on the Table, the situs for administration, or whether the symptoms have persisted for the requisite time. In most Vaccine Act litigation, the issue to be resolved by the special master is whether the injury alleged was caused by the vaccine. This holds true for Colin's case as well.

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[97] Doctor Casanova's CV was filed as Res. Ex. D, and his expert report as Res. Ex. C.

[98] Section 300aa–13(a)(1)(A). This section provides that petitioner must demonstrate "by a preponderance of the evidence the matters required in the petition by section 300aa–11(c)(1)...." Section 300aa–11(c)(1) contains the factors listed above, along with others not relevant to this case.

To establish legal cause in an "off-Table" case, Vaccine Act petitioners must establish each of the three *Althen* factors: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a proximate temporal relationship between vaccination and injury. 418 F.3d 1274, 1278 (Fed. Cir. 2005). The applicable level of proof is the "traditional tort standard of 'preponderant evidence.'" *Moberly v. Sec'y, HHS*, 592 F.3d 1315, 1322(Fed. Cir. 2010) (citing *de Bazan v. Sec'y, HHS*, 539 F.3d 1347, 1351 (Fed. Cir. 2008); *Pafford v. Sec'y, HHS*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Capizzano v. Sec'y, HHS*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *Althen,* 418 F.3d at 1278). The preponderance standard "requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence." *In re Winship*, 397 U.S. 358, 371-72 (1970) (Harlan, J., concurring) (internal quotation and citation omitted).

Althen's medical theory factor does not require petitioners to establish identification and proof of specific biological mechanisms, as "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." *Althen*, 418 F.3d at 1280. The petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the injury or condition; showing that the vaccination was a "substantial factor"[99] in causing the condition and was a "but for" cause are sufficient for recovery. *Shyface v. Sec'y, HHS*, 165 F.3d 1344, 1352 (Fed. Cir. 1999); *see also Pafford,* 451 F.3d at 1355 (petitioner must establish that a vaccination was a substantial factor and that harm would not have occurred in the absence of vaccination). Petitioners cannot be required to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect...." *Capizzano*, 440 F.3d at 1325. Causation is determined on a case by case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y*, *HHS,* 35 F.3d 543, 548 (Fed. Cir. 1994). Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280. *But see Knudsen*, 35 F.3d at 550 (when evidence is in equipoise, the party with the burden of proof failed to meet that burden).

The medical theory must be a reputable one, although it need only be "legally probable, not medically or scientifically certain." *Knudsen,* 35 F.3d at 548-49. The Supreme Court's opinion in *Daubert* likewise requires that courts determine expert opinions to be reliable before they may be considered as evidence. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a

[99] The recently approved Restatement (Third) of Torts has eliminated "substantial factor" in the factual cause analysis. Section 26 cmt j. (2010) Because the Federal Circuit has held that the causation analysis in Restatement (Second) of Torts applies to off-Table Vaccine Act cases (*see Shyface v. Sec'y, HHS,* 165 F.3d 1344, 1352 (Fed. Cir. 1999); *Walther v. Sec'y, HHS*, 485 F.3d 1146, 1151 (Fed. Cir. 2007)), this change does not affect the determination of legal cause in Vaccine Act cases: whether the vaccination is a "substantial factor" is still a consideration in determining whether it is the legal cause of an injury.

standard of evidentiary reliability." 509 U.S. 579, 590 (1993) (footnote omitted). The Federal Circuit has stated that a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly,*592 F.3d at 1324.

Circumstantial evidence and medical opinions may be sufficient to satisfy *Althen'*s second prong. *Capizzano*, 440 F.3d at 1325-26. Opinions of treating physicians may provide the logical connection. *See Capizzano*, 440 F.3d at 1326; *Andreu v. Sec'y, HHS*, 569 F.3d 1367, 1376 (Fed. Cir. 2009); *Moberly,* 592 F.3d at 1323.

The requirement of temporal connection necessitates a showing that the injury occurred in a medically or scientifically reasonable period after the vaccination, not too soon (*see de Bazan*, 539 F.3d at 1352) and not too late (*see Pafford*, 451 F.3d at 1358). Merely showing a proximate temporal connection between a vaccination and an injury is insufficient, standing alone, to establish causation. *Grant*, 956 F.2d at 1148. A proximate temporal relationship, even when coupled with the absence of any other identified cause for the injury, is not enough to demonstrate probable cause under the Vaccine Act's preponderance standard. *See Moberly*, 592 F.3d at 1323 (citing *Althen*, 418 F.3d at 1278).

In Vaccine Act cases, special masters are frequently confronted by witnesses with diametrically opposed positions on causation. When experts disagree, many factors influence a fact-finder to accept some testimony and reject other contrary testimony. As the Federal Circuit noted, "[a]ssessments as to the reliability of expert testimony often turn on credibility determinations, particularly in cases ... where there is little supporting evidence for the expert's opinion." *Moberly*, 592 F.3d at 1325-26. Objective factors, including the qualifications, training, and experience of the expert witnesses; the extent to which their proffered opinions are supported by reliable medical research and other testimony; and the factual basis for their opinions are all significant factors in determining what testimony to credit and what to reject.

The Vaccine Act itself contemplates that the special masters will weigh the merits of the evidence presented in making entitlement decisions. Special masters are not bound by any particular "diagnosis, conclusion, judgment, test result, report, or summary," and in determining the weight to be afforded to these matters, "shall consider the entire record...." § 300aa–13(b)(1).

A trial court is not required to accept the *ipse dixit* of any expert's medical or scientific opinion. *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) (noting that *Daubert* does not require a court to admit opinions connected to data only by the *ipse dixit* of the expert); *Perreira*, 33 F.3d at 1377 n.6 ("An expert opinion is no better than the soundness of the reasons supporting it.").

The special master determines the reliability and plausibility of the expert medical opinions offered and the credibility of the experts offering them. Not all evidence carries

equal weight with a trier of fact. A medical opinion on causation may be based on factually incorrect medical histories or it may be offered by someone without the necessary training, education, or experience to offer a reliable opinion. An expert's opinion may be unpersuasive for a variety of reasons. Courts, whether they deal with vaccine injuries, medical malpractice claims, toxic torts, or accident reconstruction, must base their decisions on reliable evidence. *See Daubert*, 509 U.S. at 594-96.

Although *Daubert* interpreted Federal Rule of Evidence 702, an evidentiary rule not applicable to Vaccine Act cases, it, nevertheless, provides a useful framework for evaluating scientific evidence in such cases. *Terran*, 41 Fed. Cl. at 336; *see also Ryman v. Sec'y, HHS*, 65 Fed. Cl. 35, 40-41 (2005) (special master performs gatekeeping function when he "determines whether a particular petitioner's expert medical testimony supporting biological probability may be admitted or credited or otherwise relied upon" and as a "trier-of-fact...may properly consider the credibility and applicability of medical theories"). The special master's use of *Daubert*'s factors to evaluate the reliability of expert opinions in Vaccine Act cases has been cited with approval by the Federal Circuit more recently in *Andreu*, 569 F.3d at 1379 and *Moberly,* 592 F.3d at 1324

Special masters weigh the evidence found in the medical records (*see, e.g., Ryman*, 65 Fed. Cl. at 41-42); consider evidence of bias or prejudice on the part of a witness, affiant, or expert (*see, e.g.*, *Baker v. Sec'y, HHS*, No. 99-653V, 2003 WL 22416622, at *36 (Fed. Cl. Spec. Mstr. Sept. 26, 2003)); weigh opposing medical opinions and the relative qualifications of experts (*see, e.g.*, *Epstein v. Sec'y, HHS*, 35 Fed. Cl. 467, 477 (1996); *Lankford v. Sec'y, HHS*, 37 Fed. Cl. 723, 726-27 (1996)); examine medical literature, studies, reports, and tests submitted by either party (*see, e.g.*, *Sharpnack v. Sec'y, HHS*, 27 Fed. Cl. 457, 461 (1993), *aff'd*, 17 F.3d 1442 (Fed. Cir. 1994)); and may consider a myriad of other factors in determining the facts of the case and the mixed questions of law and fact that arise in causation determinations. Special masters decide questions of credibility, plausibility, reliability, and ultimately determine to which side the balance of the evidence is tipped. *See Pafford*, 451 F.3d at 1359.

In an off-Table case, petitioners do not automatically shift the burden to respondent to prove an alternate cause merely by offering an opinion of a medical expert. Respondent may challenge the factual underpinnings of a causation opinion, the opinion itself, or both. *See de Bazan*, 539 F.3d at 1353-54. If the special master concludes that petitioner's evidence of causation is lacking, then the burden never shifts to respondent to demonstrate the "factors unrelated" as an alternative cause for petitioner's injury. *See Bradley v. Sec'y, HHS*, 991 F.2d 1570, 1575 (Fed. Cir. 1993) (when petitioner has failed to demonstrate causation by a preponderance, alternative theories of causation need not be addressed); *Johnson v. Sec'y, HHS*, 33 Fed. Cl. 712, 721-22 (1995), *aff'd*, 99 F.3d 1160 (Fed. Cir. 1996) (even in idiopathic disease claims, the special master may conclude petitioner has failed to establish a *prima facie* case). In *de Bazan*, the Federal Circuit explicitly stated that the special master may consider all

of the evidence presented, including that of respondent, in determining whether petitioners have met their burden of proof. 539 F.3d at 1353-54.

If merely an opinion supporting vaccine causation, without more, is all that is necessary to meet petitioners' burden of proof, Congress would have said so. Congress could have said that any injury temporally connected to a vaccine is compensable. It did not. By specifying petitioners' burden of proof in off-Table cases as the preponderance of the evidence, directing special masters to consider the evidence as a whole, and stating that special masters are not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record (*see* § 300aa-13(b)(1)), Congress contemplated that special masters should weigh and evaluate opposing expert opinions in determining whether petitioners have met their burden of proof.[100] In weighing and evaluating expert opinions in Vaccine Act cases, the same factors the Supreme Court considered important in determining their admissibility provide the weights and counterweights. *See Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 149-50 (1999); *Terran*, 195 F.3d at 1316.

As the Court of Federal Claims noted:

> As fact-finders, Special Masters, like juries, are often faced with the "battle of the experts" when it comes to interpreting facts. And as fact-finders, they may find that truth lies somewhere in between the opposing, uncompromising views of the partisan experts. Expert opinion testimony is just opinion, and the fact-finder may weigh and assess that opinion in coming to her own conclusions.... A fact-finder, especially one with specialized experience such as a Special Master, can accept or reject opinion testimony, in whole or in part. When the evidence is in, and it is time to apply the facts to the law, the expert's role is over. Partisan testimony then gives way as the Special Master evaluates the testimony in light of the entire record, based on reasonable inferences born of common experience or the product of special expertise."

Sword v. United States, 44 Fed. Cl. 183, 188-89 (1999) (citations omitted); *see also Moberly*, 592 F.3d at 1325 ("Weighing the persuasiveness of particular evidence often requires a finder of fact to assess the reliability of testimony, including expert testimony, and we have made clear that the special masters have that responsibility in Vaccine Act cases.") (citations omitted).

Bearing all these legal standards in mind, I turn to the evidence presented on the issue of general causation: whether the vaccine component in question, thimerosal, can

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[100] *See* §§ 300aa–13(a)(1)(A) (preponderance standard); § 13(a)(1) ("Compensation shall be awarded...if the special master or court finds on the record as a whole..."); § 13(b)(1) (indicating that the court or special master shall consider the entire record in determining if petitioner is entitled to compensation and special master is not bound by any particular piece of evidence).

cause ASD. *Cf. Pafford*, 451 F.3d at 1355-56 (equating the "can it cause?" question to *Althen*'s first factor).

Section III. The General Causation Hypotheses.

The evidence supporting the proposition that TCVs can cause ASD was presented in the Theory 2 test cases in three different yet interrelated expert opinions on causation, those of Drs. Aposhian, Deth, and Kinsbourne.[101] Petitioners' fourth expert witness in the general causation case, Dr. Greenland, provided testimony more focused on rebutting respondent's epidemiological evidence, rather than on causation itself. All three general causation opinions were based on the purported effects of TCVs on the brain, but the mechanisms of causation were either unstated (Dr. Aposhian's opinion) or had different foci from one another (the opinions of Drs. Deth and Kinsbourne). None of these experts offered causation opinions specific to the three test cases.[102]

Whether the opinions expressed related solely to a specific type of autism–regressive autism–or to ASDs in general appears to remain open. Both Drs. Deth and Kinsbourne acknowledged that their proposed causation mechanisms were not limited to regressive autism, but other evidence, including virtually all of Dr. Greenland's testimony, focused on regressive autism.

In addition to opining on causation, each of the experts offered opinions on other matters to support petitioners' assertion that TCVs can cause ASDs. These supporting opinions addressed such diverse issues as whether regressive autism (or a subset of regressive autism called "clearly regressive autism") constitutes a separate phenotype of ASD with an etiology distinct from other forms of ASD; whether the mercury levels in TCVs are sufficient to provoke a neuroinflammatory response in the brain; and whether children with autism are genetically predisposed to a hypersusceptibility to mercury or to oxidative stress.

Doctor Aposhian provided background evidence on mercury toxicology. He discussed a number of *in vitro*, animal, and human studies of mercury's effects. Based on some of these studies, he calculated the amount of mercury from TCVs that would reach the brain. In addition, Dr. Aposhian also offered a causation opinion himself, opining that mercury caused autism in some individuals with a hypersensitivity to

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[101] Petitioners' Post-Hearing Br. and their Reply Brief ["Pet. Reply Br."] appear to rely only on the general causation hypotheses presented by Drs. Deth and Kinsbourne, relegating Dr. Aposhian's contributions to a supporting role. Petitioners' assertions regarding causation in Colin's specific case are addressed in much more detail in Section X, below. Because this is a test case, and other petitioners may rely more on Dr. Aposhian's own causation opinion, I address Dr. Aposhian's opinion at greater length than I would otherwise.

[102] Case-specific opinions on causation were offered by Dr. Mumper in each of the three test cases. Her opinion is addressed in Section X, below.

mercury or with a “mercury efflux disorder,” although he was not clear about how it did so.

Doctor Deth testified that mercury could impair a number of biochemical processes, inducing systemic metabolic abnormalities, particularly in children with a particular genetic predisposition towards developing oxidative injury. These metabolic problems produced oxidative stress and affected gene expression (the mechanisms by which genes are turned on or off). He asserted that these effects interfered with neuronal function in the areas of attention and cognition, producing the major symptoms of ASD. Doctor Deth also opined that oxidative stress could induce the neuroinflammation seen in the brains of individuals with ASD. He relied in some measure on Dr. Aposhian’s opinions regarding the amount of mercury in the brain produced from TCVs, but also based his opinions on experiments performed in his own laboratory. Based on results from these experiments, some of which were, as yet, unpublished, Dr. Deth asserted that very small amounts of mercury could produce the effects he described.

Doctor Kinsbourne’s causation opinion focused only on neuroinflammation. Relying on the opinion of Dr. Aposhian that TCVs could produce sufficient mercury in the brain to induce a state of neuroinflammation, Dr. Kinsbourne opined that neuroinflammation would result in the production of excess levels of an excitatory neurotransmitter, glutamate. The resulting excitatory-inhibitory imbalance would produce a state of overarousal, to which he attributed most of the behavioral symptoms of ASD. Doctor Kinsbourne’s causation opinion was not dependent on Dr. Deth’s explanations of how oxidative stress was induced, but he indicated that Dr. Deth provided an explanation at a cellular level for the production of neuroinflammation. However, for Dr. Kinsbourne’s opinion, precisely how the neuroinflammation was produced was not critical; he opined that anything that could cause neuroinflammation could produce ASD’s behavioral symptoms, including the measles virus hypothesis he presented in the Theory 1 cases.

Doctor Kinsbourne also provided background evidence about ASD. He discussed the phenomenon of regression in ASD, opining that those who experienced a loss of skills as part of the clinical picture in their development of ASD constituted a distinct subtype, with a distinct etiology. He did not dispute the evidence that ASDs are strongly genetic conditions, but opined that the genetic contribution rendered certain children more susceptible to environmental toxins, which produced ASD, rather than the genetic differences being directly responsible for ASD.

All three of the opinions rested, to some degree, on Dr. Aposhian’s testimony about a postulated genetic hypersusceptibility to mercury’s effects, on Dr. Deth’s testimony about metabolic abnormalities in children with ASD, and on Dr. Kinsbourne’s views of gene-environment interactions. Petitioners used the evidence of genetic hypersusceptibility and metabolic abnormalities to explain why mercury induced these problems only in some children, while the vast majority of children who received TCVs

were unaffected.

Because a substantial number of epidemiological studies had failed to detect any association between TCVs and ASD, the general causation evidence also included the testimony of an epidemiologist, Dr. Greenland. Doctor Greenland's testimony was very limited, and largely represented an opinion based on a set of assumptions. Relying on evidence concerning the percentage of children with ASD who experienced a loss of skills, and on evidence that an even smaller percentage of those children had entirely normal development prior to the loss of skills, Dr. Greenland asserted that the resulting small subgroup had a condition he called "clearly regressive autism." Based on the postulated existence of this subgroup, Dr. Greenland opined that the epidemiological studies finding no relationship between ASD and TCVs were irrelevant, because none of the studies could have detected an association of TCVs with this small subtype. Implicit in Dr. Greenland's opinion was that this subtype actually existed as an etiologically distinct phenotype of ASD. Whether the general causation hypotheses are inclusive of all ASDs or limited to cases of regressive autism (or to "clearly regressive autism") remains unclear. The causation experts were questioned about causation as it pertained to regression in ASD, a broader category than that of "clear regression." However, neither Dr. Deth nor Dr. Kinsbourne limited his causation hypothesis to regressive autism, much less to "clearly regressive autism," and both acknowledged that the mechanisms of injury they described were not limited to those with regression.

In order to understand the strengths and weaknesses of the TCV causation hypotheses presented, I begin in Section IV with background evidence explaining what is known about ASD. This includes diagnostic criteria, behavioral symptoms, pathophysiology (including the evidence concerning neuroinflammation in the brains of autistic individuals). The epidemiological studies of TCVs and ASD are discussed in Section V. Next, in Section VI, I discuss the evidence concerning the toxicology of mercury and thimerosal, and in particular, mercury's effects on the brain. Doctor Deth's evidence regarding disruption of sulfur metabolism is in Section VII, followed in Section VIII by explication of the neuroinflammation hypotheses of Drs. Deth and Kinsbourne. My conclusions regarding the general causation hypotheses are set forth in Section IX. Colin's specific causation claim is presented in Section X.

Section IV. Autism Spectrum Disorders.

A. Overview.

This section provides background information on the definitions, diagnoses, presentations, and prevalence of disorders on the autism spectrum. It discusses what is generally accepted about the known causes, genetic and otherwise, of ASDs. Thereafter, this section sets forth other evidence concerning the brain structures pertinent to the neuropathology of ASDs and the causation hypotheses that follow in Sections VI, VII, and VIII. It addresses the pivotal issue of whether cases of ASD that include a loss of previously demonstrated skills ("regression") constitute a separate

phenotype.[103] After considering the evidence presented, I conclude that regressive ASD does not constitute a separate phenotype of ASD, and thus is extremely unlikely to have an etiology distinct from other forms of ASD.

Most of the factual information contained in this section was not in dispute. The matters in dispute primarily involved regressive autism, but the experts also had some disagreements about the prevalence of ASDs; their known or postulated causes (other than the TCV hypotheses presented by petitioners); and the brain pathophysiology found in ASDs.

The citations are primarily to reports and testimony by respondent's experts, largely because of their superior qualifications and greater expertise in autism research and diagnosis and the depth of the background information they provided. Several of respondent's experts are among the most frequently published in the field of ASD research and all of them are acknowledged experts in the field of ASD diagnosis or research.[104]

Two of petitioners' experts,[105] Drs. Kinsbourne and Mumper, had qualifications that warranted consideration of their testimony about autism's symptoms, diagnosis, treatments, and causes, but their testimony was not particularly helpful in providing the background information in this section. Although qualified to testify about autism by virtue of his general training and experience in pediatric neurology, Dr. Kinsbourne's practice never focused on children with ASDs. He no longer sees or treats patients and

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[103] Doctor Lord described a phenotype as a cluster of unique behaviors that are associated with each other. Tr. at 3587.

[104] For example, Dr. Rutter appears as a primary author or co-author of about 50 articles or book chapters filed on petitioners' and respondent's master lists of scientific and medical journal articles, with publication dates ranging from 1965 (*see* M. Rutter, *Classification and Categorization in Child Psychiatry*, J. CHILD PSYCHOL. & PSYCHIAT. 6(2): 71-83 (1965), filed as RML 434) to 2007 (*see* M. Rutter, et al., *Early adolescent outcomes of institutionally deprived and non-deprived adoptees: III. Quasi-autism*, J. CHILD PSYCHOL. & PSYCHIAT. 48(12): 1200-07 (2007), filed as RML 417). He and Dr. Lord were actively involved in creating the instruments used in ASD diagnosis. Tr. at 3549-50. Doctors Rutter and Fombonne were involved in developing the DSM-IV-TR criteria for autism diagnosis and in negotiations between the WHO and the American Psychiatric Association to make the ICD-10 and DSM-IV criteria as comparable as possible. Tr. at 3617-19. Doctor Kemper and his research partner, Dr. Bauman, conducted some of the earliest studies in the pathophysiology of the brains of autistic individuals; Dr. Kemper is still researching and publishing in the area. *See, e.g.*, M. Bauman and T. Kemper, *Histoanatomic observations of the brain in early infantile autism*, NEUROLOGY 35: 866-74 (1985) ["Bauman and Kemper 1985"], filed as PML 509; Tr. at 2797-99. Doctor Rodier's work in the prenatal origins of autism and her ongoing research are also widely cited.

[105] Doctor Aposhian used a number of slides to illustrate what he called his "introductory remarks" about ASD. *See* Pet. Tr. Ex. 1, slides 14-21; Tr. at 147-52. Because he was not qualified to opine on the nature of autism or its diagnosis, I have accorded such evidence little weight. Although he did not concede a lack of qualifications, Dr. Aposhian himself acknowledged that he would "take second place" to a neurologist in answering questions about the neurological aspects of autism. Tr. at 246-47.

has conducted no research into autism's causes, diagnosis, or treatment, other than a review of medical literature. In many cases, his expert report (PML 717) lacked citations for the statements he made[106] and, in some cases, his citations were simply incorrect.[107]

Doctor Mumper is a pediatrician, not a neurologist, psychiatrist, or psychologist, and has had only the standard training provided to pediatricians in these disciplines. Although she has considerable experience in treating children with autism, her testimony was largely anecdotal, rather than based on systematic research, and was thus less helpful in terms of input to this section.

B. The Autism Spectrum.

Autism spectrum disorders[108] are not new, although public and medical awareness of them has grown exponentially over the last two decades. The term "autism" first emerged in 1943, when Leo Kanner described a series of 11 children with distinctly unusual behavior.[109] Tr. at 3250, 3257.

The diagnostic criteria for ASDs are found in the DSM-IV-TR.[110] In general terms, the DSM-IV-TR explains that these developmental disorders are characterized by "severe and pervasive impairment in several areas of development," and require qualitative impairments "distinctly deviant relative to the individual's developmental level

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[106] *E.g.*, PML 717 at 4 ("[C]lassical...and regressive autism differ sharply with respect to their known medical causations.").

[107] *E.g.*, PML 717 at 6-7 (citing to PML 377 for a conclusion absent from and unsupported by that study).

[108] The terms "autism spectrum disorder" and "pervasive developmental disorder" were used interchangeably by the witnesses. The DSM-IV-TR, the diagnostic handbook for mental disorders currently in use in the U.S., uses the heading of "Pervasive Developmental Disorders" in defining disorders on the autism spectrum. DSM-IV-TR at 69. To avoid confusion between the umbrella term of pervasive developmental disorder and its abbreviation, "PDD," and the diagnostic category of "pervasive developmental disorder-not otherwise specified" ["PDD-NOS"], a category of developmental disorder on the autism spectrum, I use the terms "autism spectrum disorder" or "ASD" rather than "PDD." The exception to this practice is when I directly quote a witness or article. Witnesses frequently used the term "autism" when referring to the broad category of ASDs. *See, e.g.*, Report of Dr. Casanova, Res. Ex. C, at 2 (indicating that he would use the terms "autism" and "ASD" interchangeably). Where the evidence is applicable only to the narrower diagnostic category of "autistic disorder," I use that term, rather than "autism."

[109] *See* L. Kanner, *Autistic Disturbances of Affective Contact*, NERVOUS CHILD 2(3): 217-50 (1943), filed as RML 270.

[110] *See* Tr. at 3617-18 (explaining how the criteria were developed). The section of the DSM-IV-TR pertaining to pervasive developmental disorders was filed as RML 123; one specific page was filed as RML 8. For ease in citation, the manual is simply referred to as the DSM-IV-TR throughout this opinion.

or mental age" to make a diagnosis. DSM-IV-TR at 69. The DSM-IV-TR also notes that the disorders are frequently associated with mental retardation and are sometimes associated with a diverse group of other medical conditions, including "chromosomal abnormalities, congenital infections, [and] structural abnormalities of the central nervous system." *Id*. at 69-70.

1. Diagnostic Categories Included in the Autism Spectrum.

A range of disorders comprise the autism spectrum. The behavioral qualities are similar, but the severity of them may vary, even within the same diagnostic category. Tr. at 3254.

a. Autistic Disorder.

A diagnosis of autistic disorder requires a minimum of six findings from a list of impairments divided into the three domains of impaired function: (1) social interaction; (2) communication; and (3) restricted, repetitive, and stereotyped patterns of behavior, interests, and activities. At least two findings related to social interaction and at least one each in the other two domains are required for diagnosis. DSM-IV-TR at 75. Additionally, delays or abnormal functioning in at least one of the following three areas must have occurred prior to three years of age: "(1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play." *Id*.

The diagnosis is one of exclusion as well, since one of the diagnostic criteria is that the disorder must not be better accounted for by Rett's disorder or Childhood Disintegrative Disorder, both of which are discussed below. DSM-IV-TR at 75.

Autistic disorder is frequently associated with mental retardation, but it can occur in individuals of normal intelligence as well. Tr. at 3256. It is approximately four to five times more common in boys and is the second most prevalent of the disorders on the autism spectrum. DSM-IV-TR at 73; Tr. at 3707-08.

b. PDD-NOS.

The DSM-IV-TR defines PDD-NOS as "a severe and pervasive impairment in the development of reciprocal social interaction," coupled with impairment in either communication skills or the presence of stereotyped behaviors or interests. DSM-IV-TR at 84. The diagnosis is made when the criteria for other autism spectrum disorders, or other psychiatric disorders such as schizophrenia, are not met. *Id*. It includes what has been called "atypical autism," which includes conditions that present like autistic disorder, but with onset after age three, or which fail to meet the specific diagnostic criteria in one or more of the domains of functioning. *Id*. It is the most prevalent of the disorders on the autism spectrum. Tr. at 3707-08.

c. Asperger's Disorder.[111]

Asperger's syndrome is a form of high-functioning autism which presents with abnormalities in social interaction and communicative functioning. There are no delays in language or cognitive development. Tr. at 3254; *see also* DSM-IV-TR at 84 (requiring two impairments in social interaction and one in restricted, repetitive, and stereotyped patterns of behavior, interests, and activities for diagnosis).

d. Childhood Disintegrative Disorder ["CDD"].[112]

In CDD, children with apparently normal development by age two experience a profound loss of skills and disintegration of functioning after age three and before age 10. In later years, these children present similarly to children with severe autistic disorder. They usually have severe mental retardation, an increased frequency of seizures, and EEG abnormalities. Tr. at 3255; DSM-IV-TR at 78. This is the rarest of the disorders on the autism spectrum. Tr. at 3707-08. According to Dr. Rutter, it is unclear whether CDD is a variant of autism or something that is confused with autism. Tr. at 3255. *See also* Volkmar and Rutter, RML 497, at 1095.[113]

e. Rett's Disorder.[114]

Rett's disorder differs from the other disorders contained in the PDD chapter of the DSM-IV-TR, in that its cause is known. Tr. at 3255. Rett's disorder is an entirely genetic condition, caused by X-linked mutations in the MECP2 gene.[115] More than 95%

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[111] The DSM-IV-TR refers to this condition as "Asperger's Disorder." *Id*. at 80. The witnesses frequently referred to it as "Asperger's" or "Asperger's syndrome," and, for consistency, I do likewise. *See, e.g.*, Tr. at 388, 1197, 3254, 3558.

[112] In his report, Dr. Kinsbourne referred to CDD as "Heller's disease," a reference to the physician who first described it. PML 717 at 4; *see also* C. Hendry, *Childhood Disintegrative Disorder: Should It Be Considered a Distinct Diagnosis*, CLIN. PSYCHOL. REV. 20(1): 77-90 (2000), filed as RML 232.

[113] F. Volkmar and M. Rutter, *Childhood Disintegrative Disorder: Results of the DSM-IV Autism Field Trial*, J. AM. ACAD. CHILD ADOLESC. PSYCHIAT. 34(8): 1092-95 (1995) ["Volkmar and Rutter"], filed as RML 497 (discussing how CDD cases can be differentiated from those of autism, and similarities and differences in the two categories).

[114] The DSM-IV-TR refers to this condition as "Rett's Disorder." *Id*. at 76. This condition was variously referred to in testimony, reports, and journal articles as "Rett's syndrome," "Rett syndrome," or simply as "Rett's." *E.g.*, Tr. at 3255; M. Shabazian, *Rett Syndrome and MeCP2: Linking Epigenetics and Neuronal Function*, AM. J. HUM. GENETICS 71(6): 1259-72 (2002), filed as PML 128.

[115] R. Amir, *Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2*, NATURE GENETICS 23: 185-88 (1999) ["Amir"], filed as RML 10. *See also* M. Shahbazian and H. Zoghbi, *Molecular genetics of Rett syndrome and clinical spectrum of MECP2 mutations*, CURR. OPIN. NEUROLOGY 14: 171-76 (2001) ["Shahbazian"], filed as RML 446.

of those with the condition are female.[116] Unless otherwise indicated, in spite of the DSM-IV-TR's classification of Rett's disorder as a pervasive developmental disorder, discussion of ASDs does not include Rett's disorder.[117]

In its early stages, it presents with symptoms similar to those of autism (Tr. at 3255), but a loss of hand skills may occur as early as five months of age. It is characterized by severe impairments in language development, psychomotor retardation,[118] and, frequently, severe mental retardation. It has a distinctive pattern of developmental regression. DSM-IV-TR at 76.

2. Domains of Impairment.

Autism spectrum disorders involve unusual qualities of behavior in three areas or domains: (1) social reciprocity, (2) communication, and (3) restricted behaviors and interests. Res. Tr. Ex. 8, slide 3; Tr. at 2362, 3253, 3588. Children with ASDs display behaviors in these domains that are qualitatively different from those of typically developing children. The term "qualitative" describing these behavioral domains is significant. Tr. at 3250. The issue is more than a delay in functioning; the behaviors displayed are abnormal "in type, not just in degree or timing." Tr. at 3250-51.

Issues regarding the social and communicative domains generally manifest earlier than the repetitive and stereotyped behaviors. Tr. at 3253. Examples of impairments in the social reciprocity domain include impairments in eye contact and body language, and an inability to develop appropriate peer relationships. Impairments in the communication domain may include a delay in developing spoken language or in initiating or sustaining a conversation. It also includes the use of repetitive or idiosyncratic language. Impairments in the repetitive and restricted behaviors and interests domain include preoccupation with parts of objects, abnormally intense interest in a subject, and repetitive motor mannerisms, such as hand flapping or twirling. DSM-IV-TR at 75; *see also* Tr. at 2362-66 (Dr. Rust providing examples); 3251-53 (Dr. Rutter providing examples). One of the most important and early recognized symptoms is verbal and nonverbal language impairment. Tr. at 2362.

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[116] Although the DSM-IV-TR indicates that the disorder has only been reported in females, and Dr. Kinsbourne's report stated that it occurs only in females (PML 717 at 4), Dr. Rust testified that there were a very small number of cases in boys. Tr. at 2533-34. His testimony is substantiated by Shahbazian, RML 446, at 173-74. I accept Dr. Rust's testimony as correct, given his greater experience in treating and researching ASD, and in view of this article.

[117] Those conducting ASD research often exclude those with Rett's disorder from studies. *See, e.g.*, S. Rose, et al., *The Frequency of Polymorphisms affecting Lead and Mercury Toxicity among Children with Autism*, AM. J. BIOCHEM. & BIOTECH. 4(2): 85-94, 87 (2008) ["Rose"], filed as PML 430 (study excluded "Rett syndrome" and other genetic disorders associated with symptoms of autism).

[118] Motor skills are generally not impaired in ASDs (Tr. at 3565), one factor setting Rett's disorder apart from ASDs.

3. Diagnostic Criteria and Tools.

There are no objective tests to diagnose ASD. Tr. at 3267. Several subjective testing instruments are used to make the diagnosis.[119] The ADI-R,[120] initially developed by Drs. Lord, LeCouteur, and Rutter in 1989,[121] is a long, semi-structured interview, in which caregivers are asked to describe observations of a child in specific contexts. The examiner uses the information obtained to assess whether the child has specific symptoms or behaviors, which are then coded into a standard format. Tr. at 3549-50. The ADI-R is used worldwide, primarily in research, but also clinically. Tr. at 3253-54.

Doctors Lord and Rutter were also authors of the ADOS,[122] which involves a standard series of activities for children, keyed to age and language ability. Tr. at 3253-54, 3550-51. The ADOS is an observation tool used both in autism diagnosis and in research. Tr. at 3550-52. Even when clinicians do not use the ADI-R and the ADOS, most follow the principles of these tools in a modified way. Tr. at 3254.

Other instruments used to evaluate ASD include the Childhood Autism Rating Scale ["CARS"] and the Vineland Adaptive Behavior Scales,[123] as well as various intelligence and developmental tests such as the Stanford-Binet Intelligence Scale, the Wechsler Intelligence Scale for Children-Revised, and the Bayley Scales of Infant Development. *See* Osterling and Dawson, RML 362, at 250[124] (reporting on various tests used in assessing children for participation in an ASD study).

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[119] One of these instruments, the ADI-R, was listed as an exhibit on respondent's master list (RML 418), but was not actually filed.

[120] *See* C. Lord, et al., *Autism Diagnostic Interview–Revised: A Revised Version of a Diagnostic Interview for Caregivers of Individuals with Possible Pervasive Developmental Disorders*, J. AUTISM & DEV. DISORDERS 24(5): 659-85 (1994), filed as RML 311. Doctor Rutter was a co-author.

[121] The current revised version was published in 1994. Tr. at 3550.

[122] *See* C. Lord, et al., *The Autism Diagnostic Observation Schedule–Generic: A Standard Measure of Social and Communication Deficits Associated with the Spectrum of Autism*, J. AUTISM & DEV. DISORDERS 30(3): 205-23 (2000), filed as RML 310. I note that Dr. Leventhal was a co-author and Dr. Rutter was the senior researcher on the study. The last-listed author on a paper is usually the senior investigator on the study. Tr. at 1913.

[123] *See* A. Carter, et al.,*The Vineland Adaptive Behavior Scales: Supplementary Norms for Individuals with Autism*, J. AUTISM & DEV. DISORDERS 28(4): 287-302 (1998), filed as RML 59. Adaptive behavior measurements are used to diagnose or rule out mental retardation and assess an individual's ability to relate to others. *Id*. at 289-90.

[124] J. Osterling and G. Dawson, *Early Recognition of Children with Autism: A Study of First Birthday Home Videotapes*, J. AUTISM & DEV. DISORDERS 24(3): 247-57 (1994), ["Osterling and Dawson"], filed as RML 362.

4. Natural History and Prognosis.

a. Recognition of ASD Behaviors.

Typically, parents begin recognizing developmental problems at 18-24 months. The timing may vary, based on whether the child with autism is the first child, whether the parents have other children, or whether they know other autistic children. Tr. at 3259-60. Most parents note the communication problems and lack of social reciprocity first, but they may also have noted subtle signs from periods very early in development that tell them their child's behavior is not quite right. Tr. at 3260.

Subtle social abnormalities may be present at 12 months of age in many cases, but a diagnosis cannot readily be made at that time. Tr. at 3260. Doctor Rust testified that co-occurring cerebral palsy or mental retardation may mask autism, resulting in a later diagnosis. Tr. at 2379-80. In general, autistic behavioral symptoms appear to worsen during the second year of life. *See* Dawson 2007, RML 108,[125] Table 4 (summarizing studies showing the loss or decline in skills at various ages).

Home video[126] and "baby sibs"[127] studies demonstrate that at a group level, children with autism and those without it can be reliably differentiated at about 12 months of age, but not generally before. Tr. at 3261. Earlier manifestations occur in individuals, but are difficult to assess reliably, and at an individual diagnostic level, they are too varied to be of much use. Tr. at 3261-62. However, if videos demonstrate clearly abnormal behavior, "that is reasonably good evidence that there were abnormalities present at that time." Tr. at 3262. Videos are less useful if they do not show abnormalities. Tr. at 3262. Doctor Rutter disagreed with Dr. Kinsbourne's assertion (PML 717 at 5) that the majority of children with autism exhibit some level of autistic behavior during the first year of life. Tr. at 3262.

b. Prognosis.

Autism spectrum disorders are generally recognized as a life-long impairment. Tr. at 3255-56. Although some children with ASDs grow up to lead independent lives, qualitative impairments persist. A very small minority of those with ASD appear to

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[125] G. Dawson, et al., *Rate of Head Growth Decelerates and Symptoms Worsen in the Second Year of Life in Autism*, BIOL. PSYCHIAT. 61:458-64 (2007) ["Dawson 2007"], filed as RML 108.

[126] *See, e.g.*, Osterling and Dawson, RML 362; E. Werner, et al., *Brief Report: Recognition of Autism Spectrum Disorder Before One Year of Age: A Retrospective Study Based on Home Videotapes,* J. AUTISM & DEV. DISORDERS 30(2): 157-62 (2000), filed as RML 509 (summarizing earlier home video studies and reporting on the use of videos to detect ASD behaviors in children aged 8-10 months of age).

[127] These studies involve siblings of children with autism, who are at higher genetic risk of developing the condition themselves. Researchers assess the siblings at different ages throughout the child's early development to note when abnormalities first appear. Tr. at 3261.

recover completely. Tr. at 3256.

In general, ASDs are not static conditions. Tr. at 2358. According to Dr. Lord, children with autism improve, but the level of improvement varies from child to child. Tr. at 3568. Behavioral treatments make some difference, but the difference is relatively small as compared simply to the natural course of development. Tr. at 3569. Doctor Rust noted that improvements may be a result of the natural course of the disorder, rather than any treatments in the interim.[128] Tr. at 2451. Most improve in language, with some children developing fluency. Tr. at 3569. The improvement in social skills is lower, with autistic children only rarely having no social deficits. Tr. at 3569. About 25% of those with autism develop seizures in adolescence. Tr. at 3267-68.

5. Prevalence of ASDs.

a. Measurements of Prevalence.

The prevalence of ASD within the U.S. in 2002 can be expressed as 6.6 per 1,000; as 66 per 10,000; as 0.6%, or as one child in 152. Tr. at 3636; *see also* PML 586[129] (2002 CDC data on ASDs in the U.S.) These figures are highly consistent with studies in the U.K., Denmark (including the Faroe Islands),[130] and Canada. All of these countries have prevalence rates in the 60-70 per 10,000 range. Tr. at 3636. However, within the U.S., ASD prevalence rates vary widely among states. For example, New Jersey has a rate of 1.06%, but Alabama reported a rate of 0.33%. The rate from location to location also varies based on methods of case ascertainment. *See* Res. Tr. Ex. 12, slide 6; Tr. at 3636-37. Studies conducted since about 2000 are more precise than earlier studies because they use ascertainment methods across different populations with similar case definitions, producing the more recent estimates of 66-70 per 10,000. Tr. at 3709-10.

b. An Increase in Prevalence?

One of the areas of controversy concerns the dramatic increase in the

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[128] Doctor Lord's report indicated that, based on language level, social deficits, the frequency and severity of repetitive behaviors, and the nature of parental involvement in treatment, changes in behavior over time can be predicted. Res. Ex. O at 2. Using observations made at ages two, three, and five, she and her team identified criteria that would accurately predict behaviors and diagnosis at age nine. Tr. at 3557-58. *See* C. Lord, et al., *Autism from 2 to 9 Years of Age*, ARCH. GEN. PSYCHIATRY 63: 694-701 (2006), filed as RML 309.

[129] CDC, Prevalence of Autism Spectrum Disorders - Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States 2002, MORBIDITY AND MORTALITY WEEKLY SURVEILLANCE SUMMARIES 56 at 12 (February 2007), filed as PML 586.

[130] A. Ellefsen, et al., *Autism in the Faroe Islands. An Epidemiological Study,* J. AUTISM & DEV. DISORDERS 37: 437-44 (2007) ["Ellefsen"], filed as RML 130.

percentage of children who have diagnoses on the autism spectrum. Some, including Dr. Deth, have called this an "autism epidemic." *E.g.,* Deth, PML 563, at 190.[131] Doctor Kinsbourne asserted that "the incidence of the ASD diagnosis is rising spectacularly."[132] PML 717 at 6. The parties were in agreement that the prevalence rates of ASD have increased, not only in the U.S., but also elsewhere in the world, but disagreed on whether the increase could be explained by factors other than a true increase in ASD's prevalence. Petitioners asserted that a true increase in the prevalence of ASDs would be circumstantial evidence that environmental factors are fueling the increase. *See* PML 717 at 7.[133]

However, Dr. Fombonne, who is both a psychiatrist treating children with ASDs and a specialist in the epidemiology of ASDs, testified that it is difficult to determine if the prevalence of ASDs in the U.S. has actually increased in the last 20 years. Tr. at 3715-16. Diagnostic substitution, broadened diagnostic criteria,[134] broader diagnostic concept,[135] better case ascertainment,[136] more aggressive efforts to find and diagnose children with the condition, and an increase in survival rates for premature infants[137] have all played a role in the increased prevalence of ASDs. Tr. at 785-86; 3280-83; Res. Ex. Z at 4-5 (Report of Dr. Rutter); Res. Ex. W at 5-6 (Report of Dr. Rust); Croen,

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[131] R. Deth, et al., *How environmental and genetic factors combine to cause autism: a redox/methylation hypothesis*, NEUROTOXICOL. 29(1): 190-201 (2008) ["Deth"], filed as PML 563.

[132] Doctor Rutter criticized Dr. Kinsbourne's juxtaposition of two concepts in this assertion. He agreed that the diagnosis of autism has increased spectacularly, but disagreed that it means there is a true increase in the condition. Tr. at 3280-81.

[133] Doctor Kinsbourne was unwilling to attribute any particular percentage of cases to TCVs. PML 717 at 7.

[134] For example, a letter to the editor of the British Medical Journal reported on efforts to confirm the reported rate of autism in 1970. At that time, a cohort study identified only five children as having autism at age five, for a prevalence rate of 0.45/1000. Applying current diagnostic criteria to records of individuals in that 1970 cohort, the researchers demonstrated over an eight-fold increase in the prevalence rate to 3.76/1000. *See* H. Heussler, et al., *Prevalence of autism in early 1970s may have been underestimated*, BRIT. MED. J. 323: 633 (2001), filed as RML 234.

[135] A broadened diagnostic concept refers to the fact that individuals with normal intelligence may be autistic. In earlier decades, autism was thought to be limited to individuals with mental retardation and there was reluctance to diagnose autism in individuals of normal intelligence. Tr. at 3282-83.

[136] Better case ascertainment means that pediatricians, family doctors, psychiatrists, and psychologists have become more aware of early manifestations of autism. Tr. at 3281.

[137] Doctor Rust pointed out that autism diagnoses are more likely to occur in children who were premature at birth, and more premature infants are surviving to be diagnosed with autism. Tr. at 2479. Doctor Rodier concurred. Tr. at 3022-23.

RML 97, at 213-14.[138] Doctor Kinsbourne conceded that changes in diagnostic criteria, improved ascertainment, and diagnostic substitution may all have contributed to the rise in prevalence, but asserted that these factors could not account for the actual rise.[139] *See* PML 717 at 6-7; Tr. at 785-86. Doctor Rutter concluded that the increase in prevalence was "mainly methodological," but that the possibility of a true increase could not be ruled out. Tr. at 3282. Petitioners' epidemiology expert, Dr. Greenland, avoided opining on the issue. Tr. at 114.

C. Known Causes of ASD.

1. Overview.

A specific causal factor can be identified in only about 8-20% of cases of ASD.[140] Virtually all the known causes involve either a genetic defect or a prenatal toxic insult or infection. In a few case reports, autism-like syndromes have occurred after postnatal infections; the experts differed over whether these cases truly represented cases of ASD, or simply what Dr. Rutter called "phenocopies," disorders that mimic the symptoms of ASD. Tr. at 3266-67. The experts had few true disagreements regarding ASD's known causes, and agreed that ASDs are highly genetic, but not generally Mendelian[141] conditions. They differed in whether an external factor was necessary to produce ASD in the presence of a genetic susceptibility for the disorder. As the core

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[138] L. Croen, et al., *The Changing Prevalence of Autism in California*, J. AUT. & DEV. DISORDERS 32(3): 207-15 (2002) ["Croen"], filed as RML 97.

[139] Doctor Kinsbourne included a citation to a 2002 article by Dr. Rutter (PML 377) for this point. PML 717 at 6-7. The article filed as PML 377, M. Rutter, *Genetic Studies of Autism: From the 1970s into the Millennium*, J. ABNORMAL CHILD PSYCHOL. 28(1): 3-14 (2000), was actually published in 2000, not 2002. The statement Dr. Kinsbourne attributed to Dr. Rutter is not contained anywhere in it. No 2002 article by Dr. Rutter was filed by either party. Doctor Rutter's CV (Res. Ex. AA) breaks down his publications by year and the titles of his 2000 and 2002 publications do not reflect any articles likely to contain the comment Dr. Kinsbourne attributed to him. *See also* Tr. at 2477-78 (Dr. Rust discussing Dr. Kinsbourne's citation to Dr. Rutter's work).

[140] The experts varied only slightly in their estimates of the percentage of cases in which a cause could be identified. Doctor Rust estimated 8-12%, a rate similar to the rate of known causes for cerebral palsy and mental retardation. Tr. at 2531-32. Doctor Rutter estimated the rate at 10-15% (Tr. at 3266); Dr. Kinsbourne placed the rate at around 10-20% (Tr. at 851).

[141] Mendelian conditions are named after Gregor Mendel, who first described patterns of inheritance. *See* DORLAND'S at 1124. Conditions, such as Huntington's chorea, are called Mendelian when they are controlled by a single gene and those who inherit the gene eventually develop the condition. With the exception of a small number of cases involving single gene inheritance, ASDs are not Mendelian conditions. Tr. at 3275, 3288; *see also* C. Marshall, et al., *Structural Variation of Chromosomes in Autism Spectrum Disorder*, AM. J. HUMAN GENETICS 82: 477-88 (2008) ["Marshall"], filed as RML 326 (listing fragile X, Rett's disorder, and tuberous sclerosis as genetic conditions associated with ASD, and the maternally- derived duplication of chromosome 15q11-q13 as a cause of 1-3% of cases of ASD). Single gene defects that produce autistic symptoms are present in less than 6% of cases. Tr. at 2396.

issue in the Theory 2 cases is whether postnatal administration of TCVs can cause ASDs, I do not resolve the disagreement regarding postnatal causation at this point. To the extent that there is reliable evidence for postnatal causes for ASD, that evidence serves as circumstantial evidence that TCVs might be one as well. The converse also applies.

2. Heritability[142] and Genetics.

Doctor Rust commented that autism is among the most heritable of all neurological conditions. Tr. at 2394. Autism is about four to five times more common in boys than in girls, an early suggestion that ASD had a genetic component. *See* Tr. at 2377-78. Studies of ASD in twins confirmed that ASD is a strongly genetic condition.[143] In identical twins, the concordance rate[144] for autism is about 60% for autism itself, and about 90% for the broader phenotype of ASD. Tr. at 789-90, 2595-96, 3272-73. That is, if one twin has autism, there is a 90% chance that the second twin will have either ASD or some behaviors that are found in those with ASD. *See* Le Couteur, RML 296.[145] Siblings and fraternal twins have a concordance of 2-4% for autism and 10-27% for the broader spectrum of autistic disorders.[146] This is a risk 20-50% times greater than that of the general population. Res. Tr. Ex. 8, slide 14.

Because concordance rates between monozygotic twins are not 100%, factors other than genes play a role, at least in some instances of ASD. Tr. at 3275. Doctor Rutter testified that autism results from the combination of between three and twelve

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[142] There is a distinction between heritability and genetics. Tr. at 3592-93. Heritability refers to whether a genetic condition may be inherited or passed on to offspring. Genetics refers to gene determination of physical characteristics; genetic defects may be inherited or may arise spontaneously, and not all defects in genes result in the same outcome. *See* DORLAND'S at 763, 840. In tuberous sclerosis, a genetic condition, the size, location, and effect of the tumors vary widely among individuals. Tr. at 3264. In ASD, even in identical twins, IQ measurements or autism diagnoses are not necessarily concordant. Tr. at 3595.

[143] *See, e.g.*, A. Bailey, et al., *Autism as a strongly genetic disorder: evidence from a British twin study*, PSYCHOLOGICAL MED. 25: 63-77 (1995) ["Bailey 1995"], filed as PML 90. Doctor Rutter was the senior researcher on this study.

[144] Concordance is the "occurrence of a given trait in both members of a twin pair." DORLAND'S at 404.

[145] A. Le Couteur, et al., *A Broader Phenotype of Autism: The Clinical Spectrum in Twins*, J. CHILD PSYCHOL. & PSYCHIAT. 37(7): 785-801 (1996) ["Le Couteur"], filed as RML 296. Doctor Rutter was the senior researcher on this study.

[146] Doctor Rutter testified that the concordance rate in dizygotic twin pairs is about 5% for autism diagnoses, and about 10% for the broader spectrum of autistic disorders. Tr. at 3272. The Marshall study also used the 5-10% figures. RML 326 at 477.

genes, and from non-genetic factors.[147] Tr. at 3275-76. He noted that the rate of chromosome abnormalities is higher in autism than in the general population. There are more copy number variations[148] in autism. Tr. at 3276. Doctor Rust noted that because there are a number of genetic influences at work, the condition may be the result of varieties of gene expression or modifications that occur after the gene begins to express itself.[149] Tr. at 2396.

Autism is associated with several other genetic disorders, including fragile X syndrome and tuberous sclerosis. Although children with tuberous sclerosis are more likely to have autism than children without this genetic disorder, Dr. Rutter was careful to state that tuberous sclerosis played a part in causation, not that it caused autism. The risk of autism in those with tuberous sclerosis depends on the brain location where the tumors are found, and whether there is associated mental retardation. Thus, it is not clear whether the genes for autism and tuberous sclerosis are interconnected, or only that the parts of the brain involved in tuberous sclerosis are involved with autistic behaviors. Tr. at 3265-66. Doctor Rodier concurred with this testimony, commenting that children with tuberous sclerosis do not show autistic symptoms early on, but as the tumors cause more brain injury, they may develop them. Tr. at 3020.

In families where there are multiple incidences of autism, members of the extended family often have a number of personality characteristics similar to those in autism. Tr. at 2392-93. These characteristics were found in both parents in 38% of family clusters of autism. Tr. at 2392-93; Res. Tr. Ex. 8, slide 13. *See also* Pickles,

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[147] Doctor Rutter preferred the "non-genetic factor" terminology to "environmental factor" because the non-genetic factor need not be an environmental hazard. Tr. at 3276; *see also* M. Fraga, et al., *Epigenetic differences arise during the lifetime of monozygotic twins*, PROC. NAT'L. ACAD. SCI. 102(30): 10604-09 (2005) ["Fraga"], filed as RML 180 (examining epigenetic differences as one explanation for discordances in monozygotic twins). The disputes between the parties regarding the non-genetic factors are set forth below.

[148] Copy number variations are small deletions or substitutions in small bits of the genetic code that are not the result of inheritance. Tr. at 3276.

[149] "Epigenetics" is the term usually applied to this aspect of gene expression. Epigenetics has been defined as "the study of heritable changes in gene function that do not change the DNA sequence but, rather, provide an 'extra' layer of transcriptional control that regulates how genes are expressed." D. Rodenhiser and M. Mann, *Epigenetics and human disease: translating basic biology into clinical applications*, CANADIAN MED. ASSN. J. 174(3): 341-48, 341 (2006) ["Rodenhiser and Mann"], filed as PML 459. The authors further explained that "[a]lterations in ... epigenetic patterns can ... result[] in profound and diverse clinical outcomes" and that "genes can be expressed or silenced depending on specific developmental or biochemical cures, such as changes in hormone levels, dietary components or drug exposures." *Id.* at 341, 342. The MECP2 gene, which is responsible for Rett's disorder, is involved in controlling gene expression, and deficiencies in this expression have been found on autopsy in those with ASD. *Id*. at 341, 346.

RML 381.[150] This suggests that lesser degrees of expression of a genetic condition may be causing disturbances in other family members. Tr. at 2393. *See also* Tr. at 3274-75 (Dr. Rutter describing the Pickles study, RML 381, which compared families with an autistic member to those with a Down syndrome[151] member, finding families with an autistic member were more likely to exhibit the milder conditions than those with a Down syndrome member). This phenomenon is known as "familial loading." Tr. at 3275.

3. Prenatal Insults.

Doctor Rodier testified about five environmental risk factors for autism: rubella, thalidomide,[152] valproic acid,[153] ethanol, and misoprostol.[154] All five are early prenatal exposure risks identified through population studies.[155] Tr. at 3019. She also testified that the prenatal causes are most likely ones that occur in the first trimester. Tr. at 3020.

Doctor Rodier did not include terbutaline on her list of environmental exposures because the information that suggests it is a risk factor for autism is not based on a population study.[156] The Connors study, PML 73,[157] examined cases of autism in twin

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[150] A. Pickles, et al., *Variable Expression of the Autism Broader Phenotype: Findings from Extended Pedigrees*, J. CHILD PSYCHOL. & PSYCHIAT. 41(4): 491-502 (2000) ["Pickles"], filed as RML 381. Doctor Rutter was listed as the senior researcher on this study.

[151] The significance of using families with a Down syndrome member is that Down syndrome is a genetic condition arising from a spontaneous mutation, not an inherited defect. Thus, families with a Down syndrome member might be as aware of behavioral differences in the Down syndrome child as the families with an autistic child, reducing reporting biases, but since autism is an inherited characteristic, the rates of family members with similar behaviors would be different in the two groups. Tr. at 3274-75.

[152] Doctor Rust testified that prenatal thalidomide has been described as having an association with autism, but that he had not looked carefully enough at the data to have an opinion. Tr. at 2572-73. He had a similar opinion about valproic acid, noting that the most common defects associated with it were neural tube defects. Tr. at 2573. Doctor Rodier testified she became interested in autism in 1983 or 1984, when reports of a possible connection between thalidomide and autism suggested a connection with teratology. Tr. at 2917.

[153] Valproic acid (dilantin) is used to treat seizure disorders. DORLAND'S at 2004.

[154] Misoprostol is used to prevent gastric ulcers and to terminate pregnancy. DORLAND'S at 1161.

[155] Doctor Kinsbourne testified similarly, identifying thalidomide, valproic acid, and rubella as causing autism if administered at specific points during gestation. Tr. at 792-93.

[156] A population study would compare rates of autism in those exposed to a possible risk factor, such as terbutaline, to those of the general population. Tr. at 3020.

[157] S. Connors, et al., *β_2-Adrenergic Receptor Activation and Genetic Polymorphisms in Autism: Data from Dizygotic Twins*, J. CHILD NEUROL. 20(11): 876-84 (2005) ["Connors"], filed as PML 73.

pairs exposed and unexposed to terbutaline, with at least one twin in the exposed pair with autism. Tr. at 3020-21. The study initially found that there was no significant increase in the risk of the second twin having autism. However, when a small subset of male twins with no other affected siblings was considered, terbutaline exposure appeared to produce an excess risk of autism. Tr. 3021.

Doctor Rodier explained that the nature of the exposure made it difficult to determine whether terbutaline produced the excess risk or if it was the reason for the terbutaline administration, i.e., the risk of premature labor. If the terbutaline not been administered, the twins might not have survived long enough to be diagnosed with autism. Tr. at 3021-22. Children with very low birth weights as the result of premature delivery have a greater risk of autism, which could be due to the birth weight itself, or the fact that a fetus with autistic injuries is more likely to have low birth weight. Tr. at 3022-23. It is difficult to separate whether terbutaline increases the risk of autism or preserves pregnancies with preexisting risk of autism.[158] Tr. at 3023.

Petitioners relied on the Zerrate rat study, PML 106,[159] to demonstrate that a postnatal exposure could produce brain effects similar to those found in individuals with ASD. *See* Pet. Post-Hearing Br. at 39. The authors noted that the brains of the rat pups resembled "those reported in post mortem examinations of corresponding brain regions in autistic individuals." Zerrate, PML 106, at 17. However, because rat pups are more immature at birth than humans, the period of comparable exposure would have involved late gestation in humans. Tr. at 3024.

4. Postnatal Events Other Than TCVs.

Doctor Kinsbourne asserted, based on case reports,[160] that environmental

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[158] The authors of the Connors study agreed with Dr. Rodier's assessment. They wrote:

> Although twinning itself might or might not directly contribute to the development of autism, it might increase the risk of exposure to other environmental influences. Twin birth rates increased over the past decade in the United States, rising 33% since 1990 and the most pronounced increases occurred in older mothers...Multiple births with attendant uterine size and irritability also increase the risk of premature labor and therefore the risk of exposure to a β_2 -adrenergic receptor agonist drug, such as terbutaline for tocolysis.

Connors, PML 73, at 881 (footnote omitted).

[159] M. Zerrate, et al., *Neuroinflammation and Behavioral Abnormalities after Neonatal Terbutaline Treatment in Rats: Implications for Autism*, J. PHARMACOL. & EXPERIM. THERAPUTICS 322(1): 16-22 (2007) ["Zerrate"], filed as PML 106.

[160] *See, e.g.*, I. Gillberg, *Autistic Syndrome with Onset at Age 31 Years: Herpes Encephalitis as a Possible Model for Childhood Autism*, DEV. MED. & CHILD NEUROL. 33: 912-29 (1991), filed as PML 340 (describing several other case reports, in addition to this particular case).

exposures occurring after birth, including herpes encephalitis, can produce autistic syndromes. Tr. at 793. Doctors Rodier and Rutter agreed that herpes encephalitis occasionally causes autistic-like behaviors, but disagreed that it was a cause of ASD. Herpes encephalitis causes tremendous brain damage; this damage, rather than the disease, causes the autistic behavior (Tr. at 3058). Doctor Rutter concurred, testifying that herpes encephalitis cases have "some autistic features of a kind that are parallel," but are different in the course and in the age of onset (Tr. at 3266). He also commented that he was unconvinced that the herpes encephalitis cases were "the same sort of thing as autism as we ordinarily understand it." Tr. at 3324; *see also* Damasio, PML 328[161] (describing the location of virus damage). I note that the area of damage (the limbic system) described in the Damasio article is similar to areas of anatomical abnormalities found in the brains of those with autism. *See* Section IV.G below.

Doctor Rodier testified that case studies have associated malaria in young children with later presentation of autism (Tr. at 3044), but Dr. Rust expressed skepticism that malaria caused autism. He explained that malaria can produce a severe encephalopathy, but that the co-occurring motor, sensory, and intellectual problems should preclude an autism diagnosis. Tr. at 2574-75.

There are a few cases involving acute postnatal encephalopathies with later development of autistic symptoms, but Dr. Rodier would classify those with the tuberous sclerosis cases: where there is sufficient injury to the brain, some symptoms consistent with autism occur. Tr. at 3044-45. The postnatal damage causes behavior that mimics the symptoms of autism, but has a very different etiology. Tr. at 3059. Doctor Rutter indicated that, on rare occasions, brain abnormalities acquired postnatally can give rise to ASD-like features, but it was difficult to decide whether these were truly postnatal causes of autism or simply phenocopies. Tr. at 3266-67; Res. Ex. Z at 8. Doctor Kinsbourne called these diverse causes for autism "functional convergence," producing clinical appearances of autism. Tr. at 793. Doctor Rust was skeptical that encephalopathies could result in a true autistic regression. *See* Tr. at 2568.

Doctor Rutter summed up the evidence regarding known causes of ASD by saying that all of the evidence that is "reasonably solid" indicates prenatal causes. Tr. at 3267. He was not willing to rule out entirely the possibility of very early postnatal causes, although he knew of no good examples of them. Tr. at 3267.

D. Regression In ASD.

1. Overview.

Initially at least, the phenomenon of regression in ASD appeared to be at the

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[161] A. Damasio and G. Van Hoesen, *The limbic system and the localisation of herpes simplex encephalitis*, J. NEUROL., NEUROSURG. & PSYCHIATRY 48: 297-301 (1985) ["Damasio"], filed as PML 328.

heart of petitioners' case.[162] Doctor Kinsbourne opined that regressive autism is a separate and distinct condition, with environmental causes occurring after birth playing a role in its etiology. PML 717 at 6-7; *see also* Tr. at 780-82, 851-53. He also indicated that the causes of regressive autism may be distinct from those of non-regressive autism. PML 717, at 6. Petitioners' epidemiologist, Dr. Greenland, relied on the existence of a subset of regressive autism, termed "clearly regressive autism,"[163] for his opinion that the epidemiological studies finding no association between TCVs and ASD were irrelevant to the issue of causation because they would have missed an effect of TCVs on this small subgroup. *See* Section V.F. below. Doctor Aposhian postulated a small subgroup of children hypersusceptible to mercury's effects (*see* Section VI below), although he did not expressly state that the subgroup must be composed of children with regression or "clear" regression. Petitioners intimated that Dr. Fombonne had validated the use of this term (Pet. Post-Hearing Br. at 53), but this is either a misstatement or a misunderstanding of Dr. Fombonne's testimony. *See* Tr. at 3683-84. Both Drs. Kinsbourne and Deth presented testimony relating their causation opinions to regressive autism, although Doctor Deth acknowledged that there was nothing in the causal mechanisms he advocated that applied solely to regressive autism. Tr. at 64; *see also* Section VII below. Doctor Kinsbourne did so as well. Tr. at 901, 904 (acknowledging that his neuroinflammation hypothesis was not necessarily limited to regressive autism); *see also* Section VIII below.

Considerable testimony was devoted to explaining the nature of regressive ASD and how it differs from "classic" ASD. Several areas of consensus emerged. It is clear that some proportion of children with autistic disorder and PDD-NOS experience a loss of skills at some point in their development. However, the weight of the evidence is that those who experience regression are not otherwise biologically or behaviorally distinct from other children with ASD.

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[162] Regression occurs in children with classic autism and in those with PDD-NOS or milder forms of the condition. Tr. at 3669. Regression is a part of the diagnostic criteria for Rett's disorder and CDD. DSM-IV-TR at 76, 78.

[163] Doctor Greenland defined "clearly regressive autism" as regressive autism in which there were no developmental problems prior to the regression. Report of Dr. Greenland, PML 715, at 6-7. The existence of "clearly regressive autism" as a diagnostic subtype of regression is one of the matters in dispute. Aside from testimony by Dr. Greenland (who was not qualified to opine on its existence) and some testimony from Dr. Kinsbourne (Tr. at 784 (the percentage of cases where the child is clearly regressive is below 20%); Tr. at 784 (explaining the concept as "when a child is clearly regressive, that's very clear")), there is no evidence that "clearly regressive autism" is recognized as a distinct entity. Doctor Kinsbourne's report did not refer to "clearly regressive autism" at all. It is not listed in the DSM-IV-TR. Doctor Lord, who has performed considerable research into the phenomenon of regression, testified that she had never heard the term and that it was not used in the published literature. Tr. at 3571; *see also* Tr. at 3683-84 (Dr. Fombonne testifying that he had never heard the term, and, contrary to Dr. Greenland's testimony, he was not the source for Dr. Greenland's definition).

2. Existence of Regression.

The terms “classic” or “early onset” are used to describe the majority of children with autistic disorder, as well as most children with other ASDs.[164] Early descriptions of ASDs by Kanner and others[165] included reports that some children with the condition experienced a loss of skills. Tr. at 3284, 3559-60. At one time, there were concerns about whether these reports, largely based on parental recall, were accurate. Although it is now generally accepted that loss of skills occurs,[166] there is still considerable debate about whether the children who experience loss of skills were developmentally normal prior to the loss, how widespread the phenomenon actually is, when regression begins, and how to define it. The general consensus is that it does not represent an etiologically distinct subtype of ASD. Tr. at 3284-85.

3. Definitions.

Doctor Lord was involved in the early efforts to determine whether regression actually existed and to define it. Tr. at 3547-48. She defined the phenomenon of regression in autism as the loss of previously observed and demonstrated skills, or as a reduced frequency of demonstrating those skills.[167] Tr. at 3558.

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[164] In his report and testimony, Dr. Kinsbourne used the term “congenital autism” to refer to autism in which there is no loss of skills. “Congenital” is defined as “existing at, and usually before, birth; referring to conditions that are present at birth, regardless of their causation.” DORLAND’S at 408. To the extent that autism is prenatally and genetically determined, Dr. Kinsbourne’s use of the term may be technically correct, but it would be very rare for autistic symptoms (as opposed to dysmorphology associated with autism) to be detectible at birth.

Perhaps for this reason, Dr. Lord took exception to Dr. Kinsbourne’s terminology. Tr. at 3584-85. She explained that autism cannot be diagnosed in a newborn. In the process of development, autistic behaviors emerge, both in those with regression and in those without. She testified that a distinction between “congenital” and regressive autism is a false one. Tr. at 3585.

[165] *See* S. Wolff and S. Chess, *A Behavioural Study of Schizophrenic Children*, ACTA. PSYCHIATRY SCAND. 40: 438-66 (1964), filed as RML 514 (reporting on a number of cases documenting loss of skills). Childhood schizophrenia was one of the terms then used to describe ASDs.

[166] Doctor Lord was emphatic in stating that regressive autism does exist. Tr. at 3558. Doctor Rutter concurred, commenting that both home video and other studies confirm that regression happens. Tr. at 3285. He testified that he did not like to use the term “regressive autism” because of the implication that it is a distinct subtype of autism. Tr. at 3284.

[167] How broadly or restrictively the phenomenon is defined obviously affects the estimates of the percentage of those with regressive autism. Tr. at 3670. If the threshold for describing regression is how often a child looks at people at nine months of age, compared to how often he looks at them at 15 months of age, then nearly every child with autism would be described as regressed. If the criteria are more restrictive, then the percentage of autistic children with regression declines. Tr. at 3566-67. The length of time a skill loss must persist is another definitional variable. Tr. at 3567-68. Doctor Kinsbourne appeared to be in at least partial agreement with this evidence, as he testified that the definitions for regression vary. Tr. at 783. He noted that some studies use the criterion that a child had words and then stopped using

Doctors Rutter and Lord explained that, in most cases, regression is simply one variable in the early development of those with autism. Tr. at 3579. There are children who experience a dramatic loss of skills, those in whom losses are minor and more difficult to spot, and those who fall somewhere in between. Tr. at 3284-85. Regression is not a condition that either exists or does not exist in a particular child; it is a matter of the degree and type of worsening that occurs. Tr. at 3284, 3579. Aside from the fact of regression itself, children with regression do not form a distinct group. Tr. at 3285.

Doctor Fombonne explained that there is no standardized definition of regressive autism in the ADI-R and no subcategory in it for regressive autism. Tr. at 3769-70. Although there are questions pertaining to regression, they were added to aid in standardizing studies that might look at regression as part of the developmental course in autism, not to define diagnostic subtypes. Tr. at 3771-72.

4. Assessment and Timing of Regression.

Regression typically occurs at the end of the first year or during the second year of life in children with autistic disorder or PDD-NOS. Tr. at 3285, 3558-59. It occurs later, usually after three years of age, in CDD. DSM-IV-TR at 77. It is typically assessed by careful interviews of parents to obtain very specific information about the skills that the children had and when they lost them.[168] Tr. at 3560.

Although loss of words was once thought to be the primary manifestation of regression, research by Dr. Lord and others suggests that what is most common is loss of social skills, such as waving or playing peek-a-boo. Tr. at 3561-62, 3565-66, 3589. However, loss of words is the symptom the parents most often agree upon when interviewed years later. Tr. at 3565-66. Losses in the play domain are less often found. The degree to which the child is losing imaginative play and gaining repetitive behaviors is difficult to quantify. Tr. at 3589-90.

Trajectories of development and loss are similar, but their timing may vary. Tr. at 3564. In some children, the loss of skills is precipitous; in others, it is much more gradual. Tr. at 3566-67. Regaining skills is also variable. Tr. at 3560, 3567. In

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them. Others use stricter language criteria or may look for a change in play or socialization patterns. Tr. at 783. He described "clear-cut" cases where a child who once had a significant amount of language quit talking, or a child who had been playing in a normal fashion suddenly started lining up toys. If the criteria require this clear-cut demarcation, then the percentage of cases will be lower. Tr. at 784.

[168] The skill of the interviewer may confound the data collected. Careful questioning is essential because parents are more likely to remember a dramatic loss, such as a child having five words and then never speaking again, than they are to remember that a child stopped talking for a month. Tr. at 3568. Although parents have a wealth of information about their children, they may not understand everything that is relevant if simply asked about a loss of skills. Tr. at 3561. There is a huge variability in the skills children acquire between 12 and 24 months of age, and children with ASD are no exception. Tr. at 3560, 3579.

interviewing the parents of two-year-olds, Dr. Lord's group found children who lost skills for a month and then began regaining them. They also found children who lost language and who did not talk again for months or years. Tr. at 3568. Most children with regression regain language at levels similar to those who do not experience a loss of skills, but have about a ten point lower verbal IQ than those without regression.[169] Tr. at 3567. There is a large degree of variability in the time between word loss and regaining language skills. Tr. at 3567.

At the time of the hearing, Dr. Lord had been involved for three years in a "baby sibs" study of infants who have risk factors for autism, to determine if regression can be detected as it happens. Tr. at 3548. Because most of what is known about regression is based, at least partially, on retrospective reports, this study provides an opportunity to assess regression as it happens, and a different picture of regression is emerging.[170] Tr. at 3582-83. For almost all children who develop autism, eye contact worsens between 12-24 months. Social engagement and social responsiveness also gets worse. Tr. at 3581. The changes in development in children who are eventually diagnosed with autism are much more complicated than they were once thought to be. Tr. at 3582.

5. Regression and Prior Abnormal Development.

Studies over the last 10 years demonstrate that most children with regression showed deficits prior to the loss. Tr. at 3570-71, 3577. Some did not. Tr. at 3291; *see also* Tr. at 2467, 3290-91, 3570. Doctor Rust testified that about 80% of children with what has been called regressive autism had some abnormalities prior to the time they lost skills.[171] Tr. at 2388.

Both Drs. Rutter and Lord indicated that reviewing pediatric records is not a

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[169] This 10-point figure is based on Dr. Lord's own research. Tr. at 3567. She noted that other studies have found no difference. Tr. at 3567.

[170] Doctor Lord's testimony about this study was based on findings that have not yet been published and peer reviewed. Tr. at 3598-99. No peer reviewed study covering this data was submitted prior to the closure of the evidentiary record in this case. Doctor Lord disagreed with cross-examination questions suggesting that her testimony based on this study was merely anecdotal. She pointed out that her observations were not based on one child, but rather on 50 children who have been followed in a very systematic way for three years. Tr. at 3602. She also noted that her testimony was largely based on her experience over the last 35 years, not simply on the toddler study. Tr. at 3605. Although I have considered this evidence (just as I have considered as evidence Dr. Deth's current unpublished research (*see* Section VII.C. below)), I have not accorded Dr. Lord's testimony about this study the same weight I would give a peer reviewed study published in an indexed journal. Nevertheless, three years of systematic personal observations of children by a trained observer with 40 years of experience in ASD are entitled to some weight.

[171] Doctor Rust testified that this figure was consistent with the medical literature, but was also based on his own, as-yet unpublished research. Tr. at 2520-21.

reliable way to assess whether a child was developing entirely normally during the first year of life. Tr. at 3263, 3571. The physicians creating the pediatric records are not focused on documenting early signs of autism, and if abnormalities are not clear cut, they may not record them. A record that reflects concerns, such as assessments that a child has delayed skills, is likely to be valid, but a record that reflects no problems does not mean that no problems exist, as the physician may not have noticed them or asked the correct questions, or she may simply have failed to record parental concerns. Tr. at 3263, 3571-72.

6. Prevalence of Regression.

Studies vary in the reported percentages of children who experience regression, but the range is about 15-50%.[172] Doctor Fombonne noted that the actual rate of regression depends on the criteria used to define it. The questions in the ADI-R which document regression have been revised to detect more subtle forms of regression, and thus rates may become higher. Tr. at 3670.

The prevalence of regression as a percentage of those with autism does not appear to have changed over time.[173] Using the same definition of regression, the Fombonne and Chakrabarti study,[174] RML 147, examined the trend over time, finding very little difference in the percentage of regression in those born between 1992-95, and those born in 1980 or earlier.[175] Tr. at 3673-74; Res. Tr. Ex. 12, slide 23.

Doctor Kinsbourne did not challenge the evidence regarding the prevalence of regression. However, he drew a causal conclusion from the fact that the percentage of cases of regression had not changed over time. This conclusion is discussed below.

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[172] Doctor Kinsbourne's report contained a 20-30% figure. PML 717 at 7. Doctor Rutter testified that it was about 25-33%. Tr. at 3285. Doctor Fombonne estimated it at 15-35%. Tr. at 3670. *See also* R. Hansen, et al., *Regression in Autism: Prevalence and Associated Factors in the CHARGE Study*, AMBUL. PEDIATRICS 8(1): 25-31, 25 (2008) ["Hansen"], filed as RML 223 (summarizing numbers from several studies and indicating that up to 50% of children in clinical samples experienced regression).

[173] Both parties agreed that the percentage of autistic children with regression was not increasing at a rate faster or slower than that of autism in general. Tr. at 3285; Report of Dr. Kinsbourne, PML 717, at 7.

[174] E. Fombonne and S. Chakrabarti, *No Evidence for A New Variant of Measles-Mumps-Rubella–Induced Autism*, PEDIATRICS 108(4): 1-8 (2001) ["Fombonne and Chakrabarti"], filed as RML 147.

[175] This finding tracks closely with a number of other studies. Tr. at 3674-77. These include the Honda study in Japan (H. Honda, et al., *No effect of MMR withdrawal on the incidence of autism: a total population study*, J. CHILD PSYCHOL. & PSYCHIATRY 44(6): 572-79 (2005) ["Honda"]), filed as RML 243, and the Taylor study in England (B. Taylor, et al., *Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study*, BRIT. MED. J. 324: 393-96 (2002) ["Taylor"]), filed as RML 478.

7. Significant Studies of Regression.

a. The Hansen Study, RML 223.

The Hansen paper is part of the CHARGE study.[176] The study is a very recent examination of 333 California children with ASD diagnoses. When regression was defined as the loss of both social skills and language, 15% of the children were classified as displaying regression. When loss of either language or social skills was used as the defining criterion, an additional 26% of the children were classified as regressed, for a total of 41%. Tr. at 3671; Hansen, RML 223, at 28.

The CHARGE study also looked at whether regression has distinctive characteristics that would merit considering regressive autism as a separate phenotype in terms of family history, a biological marker, or a different response to treatment. Tr. at 3671-72. The CHARGE study failed, as have many other studies, to validate that regressive autism is different than non-regressive autism. The study also examined gastrointestinal symptoms, seizures, and sleep problems, and failed to find any differences between the early onset and regressive groups. Tr. at 3672-73; Hansen, RML 223, at 29.

The only areas of significant difference between the children with early onset and regression were in communication, expressive language, and lethargy. Although statistically significant, the differences were small. Hansen, RML 223, at 27-28. There were no statistically significant differences in demographics or clinical factors. *Id.* at 29. The authors concluded that the differences observed did not suggest any etiologic differences in the two groups. *Id*. at 30.

b. The Richler Study,[177] RML 397.

Doctor Lord was the principal investigator on the Richler study, which was authored by one of Dr. Lord's graduate students. Tr. at 3573. The study used data from a number of sites around the country to investigate whether regressive autism is a separate phenotype of autism. Tr. at 3574-75.

The study began with the hypothesis that children with regression constituted a

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[176] "CHARGE" stands for Childhood Autism Risks from Genetics and the Environment. It is an ongoing case-control study with three categories of subjects: (1) children with either autistic disorder or ASD; (2) children with developmental delays but not autistic disorder or ASD; and (3) typically developing children. Hansen, RML 223, at 26. The Hansen study focused on children in the first category. The authors used standard ASD screening tests, the ADI-R and the ADOS, in preschool populations of children with autistic disorder and those with ASD. *Id.*

[177] 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 & DEVEL. DISORD. 36(3): 299-316 (2006) ["Richler"], filed as RML 397.

distinct autism phenotype, and attempted to determine how they were different. Tr. at 3575. However, the evidence did not support the hypothesis. Tr. at 3578-79. They looked at language and the development and acquisition of social skills before their loss, as well as at gastrointestinal symptoms,[178] gender, ethnicity, and birth order in children with regression. These characteristics were compared to children without regression and to typically developing children to determine if there were characteristics in the regressed children that set them apart. Tr. at 3575.

They found only minor differences. Tr. at 3575. Children with regression had slightly lower verbal IQ scores when older, and there was a slightly higher frequency of parental reports of diarrhea and constipation in children with regression. Tr. at 3575-76, 3578. They did not find a clustering of the characteristics that had been suggested as defining regressive autism as a separate phenotype. Tr. at 3578. The subgroup of children with regression who most closely fit the authors' postulated separate phenotype of regressive autism did not fit petitioners' "clearly regressive" phenotype. This subgroup of children with regression had abnormal development in the majority of the areas studied prior to their loss of skills. Richler, RML 397, at 313.

The weight of the evidence is that children with ASD and regression do not differ in any significant respect from children with ASD who did not experience any loss of skills. There does not appear to be a biological difference between those who experienced a loss of skills and those who did not. Although most of the brain physiology studies discussed below did not identify whether the brains examined were from individuals with regression, the few that did buttress the conclusion that those who experienced regression and those who did not have the same disorder, not two different ones.

E. Brain Physiology.

1. Brain Structures Pertinent to the Neuropathology of ASD.

a. Overview.

A general understanding of the gross anatomical and cellular structures discussed in the neuropathology studies is helpful, particularly in assessing the significance of differences between the brains of typically developing individuals and of those with ASDs. This section covers the gross anatomy of the brain structures and systems discussed in the studies, and the pertinent cell types that comprise them. Most of the material in this subpart was not contested; following my usual practice, I have identified areas of disagreement.

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[178] Children with ASD have a high rate of gastrointestinal problems and dietary selectivity. M. Valicenti-McDermott, et al., *Frequency of Gastrointestinal Symptoms in Children with Autistic Spectrum Disorders and Association with Family History of Autoimmune Disease*, J. DEV. & BEHAV. PEDIATRICS 27(2): S128-36 (2006), filed as PML 299.

A system refers to a number of structures in the brain that work together, such as the limbic system, discussed below. Autism is generally considered to be a "systems disorder." Although ASD was once thought to be due to localized areas of brain abnormality or a focal brain lesion, current research indicates that a systems problem is involved. A systems abnormality occurs when interconnections between different parts of the brain are not working properly. Tr. at 3268, 3338. The presence of systems abnormalities has been confirmed by imaging studies, such as a functional MRI, which examine brain functioning in relation to specific cognitive tasks. These studies have consistently shown a systems problem in ASD. Tr. at 3268-69. The parts of the brain that are working when specific tasks are performed are different in individuals with autism, as compared to neurotypical individuals. Tr. at 3268-69.

b. Anatomy of the Brain.

Grossly, the brain consists of three major portions: the brainstem, the cerebellum, and the cerebrum. See Res. Tr. Ex. 10, slide 2, for an illustration of the parts of the brain.

The cerebrum is the largest and most highly evolved portion of the brain. It occupies the upper part of the cranium.[179] The outer portion of the cerebrum is covered by the cerebral cortex, which consists of a superficial, thin layer of gray matter.[180] The cortex forms folded bulges, called gyri, with deep furrows or crevices, called sulci. In the cerebral cortex, there are six cell layers, which are sometimes referred to as the neocortex. The layers are numbered from brain surface inward and include Layer I (the molecular layer),[181] II (the external granular layer), III (the external pyramidal layer), IV (the internal granular layer), V (the internal pyramidal layer), and VI (the multiform layer). The brain's white matter lies underneath Layer VI.[182] These layers include the most highly evolved type of cerebral tissue.[183] Minicolumnar structures are found between Layers VI and II, consisting of pyramidal neurons[184] ascending vertically,

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[179] *See* DORLAND'S at 336. The cerebrum is subdivided into sections or lobes, but an explication of the subdivisions is not generally necessary to understanding the evidence.

[180] Gray matter ("substantia grisea") consists primarily of neurons, dendrites, and unmyelinated axons. DORLAND'S at 1781-82.

[181] The subplate zone and Layer I of the cerebral cortex are illustrated on Res. Tr. Ex. 10, slides 14, 15, and 17.

[182] White matter ("substantia alba") consists primarily of myelinated axons and nerve fibers. DORLAND'S at 1781.

[183] *See* DORLAND'S at 425, 1006, 1227 (illustration of the layers of the neocortex).

[184] Pyramidal cells are triangular-shaped neurons that are found in the pyramidal layers of the cerebral cortex (Layers III and V) and in Layers II and IV. An illustration of pyramidal neurons appears on Res. Tr. Ex. 10, slide 15.

surrounded by cell-poor areas containing unmyelinated axons, dendritic arborizations,[185] and synapses.[186]

The cerebellum is an area of the brain located at the back of the head below the cerebrum and behind the brainstem.[187] The cortex of the cerebellum consists of three layers, including one of granule cells and one of Purkinje cells (discussed below). Studies relating to Purkinje and granule cells are some of the most significant in both mercury toxicity and the pathophysiology of ASD.

The portion of the brainstem primarily discussed is the medulla (sometimes called the medulla oblongata), which is located in the back of the brain. Tr. at 2807. It is a cone of nerve tissue connecting the pons and the spinal cord.[188] The medulla is illustrated on Res. Tr. Ex. 10, slide 5. The inferior olive is a structure found in the medulla, in an area with many neurons. Tr. at 2810. It is the source of the climbing fibers connecting to the Purkinje cells in the cerebellum. Tr. at 2816. The arcuate nucleus is a small gray matter area of the medulla.[189] It is illustrated on Res. Tr. Ex. 10, slide 7.[190]

The thalamus is a large, dual-lobed mass of gray matter cells located at the top of the brainstem, near the center of the brain. It contains groups of nuclei that relay sensory impulses to the cerebral cortex.[191]

c. The Limbic System.

The limbic system is a group of brain structures involved with autonomic functions and aspects of emotion and behavior.[192] It includes the hippocampus,

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[185] Dendritic arborization refers to the tree-branch appearance of projecting fibers from neurons. *See* DORLAND'S at 122.

[186] Report of Dr. Casanova, Res. Ex. C, at 5; M. Casanova, et al., *Minicolumnar pathology in autism*, NEUROL. 58: 428-32, 428 (2002) ["Casanova 2002"], filed as RML 62. Although he was scheduled to testify, respondent elected not to call Dr. Casanova as a witness for reasons not disclosed. *See* Tr. at 3235.

[187] *See* DORLAND'S at 336.

[188] *See* DORLAND'S at 246, 1113.

[189] *See* DORLAND'S at 1284.

[190] The source of this illustration is A. Bailey, et al., *A clinicopathologicial study of autism*, BRAIN 121: 889-905 (1998) ["Bailey 1998"], filed as PML 220.

[191] *See* DORLAND'S at 1891.

[192] *See* DORLAND'S at 1843.

amygdala,[193] and cingulate gyrus.[194] The amygdala is connected to the limbic cortex, and is connected by fibers to the hippocampus and thalamus. The cingulate gyrus is a part of the cerebrum near the corpus callosum. The hippocampus[195] is a sheet of neurons located within the temporal lobes of the cerebrum, adjacent to the amygdala. Tr. at 2831. Several of Dr. Kemper's slides provided illustrations of these brain structures. *See, e.g.*, Res. Tr. Ex. 10, slides 2, 16, 19, 21.

2. Cellular Structure.

The cellular structures of the brain include neurons and neuroglial cells, which include astrocytes and microglia. Neurons perform the control functions of the brain, while neuroglial cells play a variety of supporting roles. Tr. at 795; DORLAND'S at 1254, 1256. In a normal brain state. the three primary cell types–astrocytes, neurons, and microglia–exist in harmony. Tr. at 2241. Both microglia and astroglia are involved in cortical organization and contribute to the regulation of immune responses in the central nervous system. Pardo, PML 72, at 489.[196] Changes in astroglia and microglia can produce both neuronal and synaptic changes that contribute to central nervous system dysfunction. Pardo, PML 72, at 489.

a. Neurons.

A neuron consists of a cell body, several short arms (called dendrites), and a long arm (called an axon). The axon terminates in a number of small branches and may have other branches projecting from it before its terminus. DORLAND'S at 1256. The axon is covered with a sheath containing myelin and other materials. DORLAND'S at 1256; *see also* DORLAND'S, Plate 36, at 1244.

Prenatally, neurons are created in particular areas of the brain and migrate along glial fibers to other areas. As they migrate, they leave behind a trail of axons, which develop and lengthen. Neurons move in a particular trajectory, which can be interrupted or changed by events such as early damage to the brain. Tr. at 2548-50, 2554; Res. Tr. Ex. 8, slide 77. An early stroke could cause migration to be abnormal, resulting in tangles of cells that do not reach their intended destination. Defects in neuronal migration may also be the result of genetics or other factors. Tr. at 2551-52.

Astrocytes facilitate the migration of neurons, as well as ensuring their survival.

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[193] *See* DORLAND'S at 421 (corpus amygdaloideum).

[194] *See* DORLAND'S at 806.

[195] *See* DORLAND'S at 853.

[196] C. Pardo, et al., *Immunity, neuroglia and neuroinflammation in autism*, INT'L. REV. PSYCHIATRY 17(6): 485-95 (2005) ["Pardo"], filed as PML 72.

Tr. at 2410. Neurons can be grown in culture without astrocytes, but once the neurons mature, astrocytes must be present or the neurons will die off. Tr. at 2410.

(1) Purkinje Cells.

Purkinje cells are a type of GABAergic[197] giant neuron found in the Purkinje layer of the cerebellar cortex. They appear on slides as huge gray cells and are so large that they can be seen on slides with the naked eye. Tr. at 2882, 3027; DORLAND'S at 325. Doctor Kemper called them the "boss cell[s] of the cerebellar cortex." Tr. at 2812.

Axons from other neurons in the inferior olive travel to the cerebellum and form a "basket-like nest"[198] in which each Purkinje cell rests.[199] Purkinje cells appear in discrete layers or rows and can be easily counted, in contrast to small neurons, which do not form such layers. Tr. at 2405.

(2) Granule Cells.

Granule cells[200] are small neurons found in the granular layers of the cerebral and cerebellar cortices. *See also* Res. Tr. Ex. 10, slide 9. They are associated with Purkinje cells such that destruction of Purkinje cells may lead to destruction of associated granule cells. Tr. at 2814.

b. Glial Cells.[201]

Neuroglial cells are the supportive tissue of the central nervous system. They include microglia and astrocytes, as well as several other cell types not discussed. DORLAND'S at 324; Tr. at 509.

(1) Astrocytes.

Astrocytes (sometimes referred to as "astroglia") are star-shaped cells that have caretaker functions in the brain. Tr. at 795. Astrocytes function as a barrier between

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[197] "GABA" is gamma aminobutyric acid. DORLAND'S at 747. "GABAergic" refers to inhibitory neurons, those which secrete GABA, the brain's primary inhibitory neurotransmitter. Tr. at 2812-13, 2882. Neurotransmitters are chemicals used by neurons to communicate cell to cell. Tr. at 795-96.

[198] *See* DORLAND'S at 318 (basket cell).

[199] A photograph of Purkinje cells appears on Res. Tr. Ex. 10, slide 9; *see also* Res. Tr. Ex. 11, slide 12; Tr. at 3028 (the axons forming the basket stain black when treated with an immunocytochemical stain for neurofilaments). Tr. at 2405.

[200] *See* DORLAND'S at 321.

[201] The term "glial" is used to describe brain cells that are not neurons. Tr. at 509.

microglia and neurons, communicating with both and trying to maintain a homeostatic state. Tr. at 2241-42. They comprise between 25% and 50% by volume of the cells in the central nervous system.[202] Astrocytes respond to and prevent the build up of neurotransmitters and affect the permeability of the blood brain barrier. Pardo, PML 72, at 489. In addition to their other functions, astrocytes chemically detect invaders and activate microglia. Tr. at 798-99.

Gliosis is the proliferation of astrocytes. Tr. at 2243. In gliosis, the astrocyte's nucleus and cytoplasm enlarge and they are more readily stained with glial fibrial acidic protein ["GFAP"]. Tr. at 2852. Staining with GFAP is the "gold standard" in identifying astroglial cells, because the stain reacts only with astroglial cells. It will not stain neurons or other types of glial cells. Tr. at 2879-80.

Although Dr. Kinsbourne testified that glial scars are formed from dying astrocytes,[203] Dr. Johnson testified that Dr. Kinsbourne was incorrect. Glial scarring is actually the result of activation of astrocytes moving into an area of the brain that has been damaged. Once there, astrocytes secrete proteins that lay down a matrix that forms the scar. Tr. at 2244. Astrocyte death is not required for and is not a consequence of gliosis. *See* Tr. at 2852.

(2) Microglia.

Microglia play a number of roles in the brain. When activated,[204] they function as the macrophages or phagocytes[205] of the brain, as a part of the brain's innate immune system. Tr. at 2893. They also play a role in the development of the nervous system and brain. Tr. at 2426, 2850. Microglia are primarily dormant, in contrast to astrocytes and neurons, which are always active. Tr. at 798. When activated, microglia undergo chemical changes that cause them to swell. Microglia also emit cytokines[206] and

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[202] *See* M. Aschner, et al., *Involvement of glutamate and reactive oxygen species in methylmercury neurotoxicity,* BRAZILIAN J. MEDICAL & BIOLOGICAL RES. 40: 285-91, 286 (2007) ["Aschner 2007"], filed as PML 570 (50%); M. Aschner, et al., *Methylmercury alters glutamate transport in astrocytes*, NEUROCHEM. INT'L. 37: 199-206, 200 (2000) ["Aschner 2000"], filed as PML 568 (about 25%).

[203] Doctor Kinsbourne testified somewhat inconsistently about gliosis, calling it evidence of astrocytic death (Tr. at 876); "an overgrowth which leads to a scarring" (Tr. at 876); and an excess of astrocytes, which die and leave the appearance of scars in the brain (Tr. at 877).

[204] Microglial activation means that glial cells are more prominent within the tissue. The cytoplasm of the cells is enlarged and the nucleus may also be. Tr. at 2849.

[205] Phagocytes are cells that engulf other cells. Microglia are sometimes called "gitter" cells. DORLAND'S at 321, 323. As part of the brain's immune system, microglia clean up debris, such as dead or dying cells and toxins. Tr. at 2426.

[206] Cytokines are "[h]ormone-like messenger molecules that cells use to communicate." L. Sompayrac, HOW THE IMMUNE SYSTEM WORKS 117 (2d ed. 2003).

defensive chemicals when encountering invaders. Tr. at 799. These cytokines may be either pro- or anti-inflammatory. Tr. at 2243. Microglia also emit reactive oxygen species, which can cause oxidative stress. Tr. at 799. These substances may damage any cell in the vicinity, not simply the invader. Tr. at 799-800.

Microglia also work to repair damage to other cells, such as neurons. Tr. at 2242; Pardo, PML 72, at 489. Microglial activation can be beneficial, as a response to a disease process, dysfunction, or injury, rather than its cause. Tr. at 2851; Pardo, PML 72, at 489.

F. Developmental Abnormalities and Dysmorphology.

1. Overview.

Physical findings, such as co-occurring minor physical abnormalities and increased head circumference and brain volume in some children with ASDs have provided clues to the processes by which ASD originates. Minor abnormalities, such as extra teeth, occur with greater frequency in a number of disorders, including schizophrenia, ADHD, and ASD, than in the general population. The nature of these disorders suggests a prenatal trigger for both the physical abnormality and the developmental disorder. Tr. at 3269-70. Increased head circumference and brain volume in many children with ASD during certain periods of development after birth provide another clue to the origin of ASD symptoms. Tr. at 2389.

This subpart discusses some specific developmental abnormalities that occur with greater frequency in children with ASDs, and when those abnormalities occurred. It also discusses the phenomenon of head and brain overgrowth, which suggests a problem with the brain forming too many connections or failing to prune unneeded ones, which may cause both the brain overgrowth and some of autism's symptoms. The Courchesne 2005[207] literature survey contains a lengthy discussion of studies of brain overgrowth in ASD and its possible connections to ASD symptoms.

2. Dysmorphology, Head Circumference, and Neuropeptide Findings.

a. Dysmorpology.

Doctor Rodier provided most of the testimony and other evidence concerning dysmorphology in ASD. Many children with autism have craniofacial dysmorphologies,

[207] *See* E. Courchesne, et al., *Autism at the beginning: Microstructural and growth abnormalities underlying the cognitive and behavioral phenotype of autism*, DEV. & PSYCHOPATH. 17: 577-97 (2005) ["Courchesne 2005"], filed as PML 104.

including ear abnormalities and wide-set eyes,[208] at a rate exceeding that of the general population.[209] Tr. at 3028-29. She used the ear abnormalities to illustrate the probable timing for ASD's origins.

During gestation, ears form low on the neck of human embryos, and as the embryo ages, the ears migrate and twist to an upright position near the eyes. Tr. at 3029. In many children with autism, a typical ear malposition is found, with the ears lower than the eyes and rotated posteriorly. Because the ears are in place at around the 12th week of gestation, low-set, posteriorly rotated ears are evidence of an insult to development that occurred early in the prenatal period.[210] Tr. at 3029-30. Doctor Rodier could not opine on whether the ear malpositioning was the result of a genetic defect or a prenatally-occurring environmental factor, but she concluded that the co-occurrence of this dysmorphology and autism suggested a common cause early in gestation. Tr. at 3049-50.

b. Head Circumference and Brain Overgrowth.

The brain grows in size between birth and three years of age, when the head is close to adult size. Tr. at 2402. Brain development continues until at least 24 years of age. Tr. at 2402. However, the brains of children with ASD and children with Rett's disorder enlarge at times when typically developing brains do not, suggesting that there is an ongoing elaboration of neural interconnections. Tr. at 2403.

Head circumference increases are not diagnostic indicators for autism, but they are distinctive findings that set ASD apart from other neurodevelopmental disorders. Tr. at 3331. This differs from the more consistent reports of microcephaly seen in Rett's disorder and many cases of intellectual disability. Tr. at 3331-32. Virtually all of the studies of head circumference have found increased head size in cohorts of children with ASD as compared to typically developing children, although the studies vary on when in the first two years of development the increased head circumference manifests.

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[208] Although she did not discuss any studies on eye position abnormalities, Dr. Rodier testified that more children with autism have eyes that are too far apart than the neurotypical population. Tr. at 3030. She provided pictures of two boys with ASD and wide-set eyes. Both boys were exposed in utero to valproic acid, an environmental cause of autism. Tr. at 3030-31.

[209] Based on her own work, Dr. Rodier testified that about 50% of autistic children have some dysmorphology and that her estimate was similar to that of another investigator. Tr. at 3052.

[210] One of her papers recounted a group of children in Nova Scotia with autism, 42% of whom had the ear rotation dysmorphology, versus 18% of the control children. Tr. at 3048-49. P. Rodier, et al., *Minor Malformations and Physical Measurements in Autism: Data from Nova Scotia*, TERATOL. 55: 319-25 (1997), filed as RML 401.

Some studies have shown a smaller head size at birth;[211] others have found no differences in birth head size from typically developing children.[212] Tr. at 2836-37.

Doctor Kemper discussed several of these head circumference and brain volume studies.[213] Tr. at 2835-38. Although the studies were not entirely consistent concerning the precise time frame in which the growth occurs,[214] increased head circumference in those subsequently diagnosed with ASD is a common finding. Tr. at 2870-72. Nearly all the studies found that the increase in head circumference occurs before a diagnosis of ASD can reliably be made. *See, e.g.,* Dawson 2007, RML 108, at 463.

c. Neuropeptide Testing.

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[211] E. Courchesne, et al., *Evidence of Brain Overgrowth in the First Year of Life in Autism*, JAMA 290(3): 337-44 (2003) ["Courchesne 2003"], filed as RML 94. This study found that head circumference at birth was slightly lower than average.

[212] *See, e.g.*, K. Hobbs, et al., *A Retrospective Fetal Ultrasound Study of Brain Size in Autism*, BIOL. PSYCHIATRY 62: 1048-55, 1053 (2007), filed as RML 239 (finding mean fetal brain size at mid-gestation to be normal in individuals later diagnosed with autism, but an increased discrepancy between standardized biparietal diameter and head circumference, suggesting a subtle imbalance in brain growth, with brain width increased relative to brain growth as a whole). *See also* S. Webb, et al., *Rate of Head Circumference Growth as a Function of Autism Diagnosis and History of Autistic Regression*, J. CHILD NEUROL. 22(10): 1182-90, 1187 (2007) ["Webb"], filed as RML 506 (finding no significant difference in head size at birth).

[213] See E. Redcay and E. Courchesne, *When is the Brain Enlarged in Autism? A Meta-Analysis of All Brain Size Reports*, BIOL. PSYCHIAT. 58: 1-9 (2005) ["Redcay and Courchesne"], filed as RML 391; Courchesne 2003, RML 94; Y. Dementieva, et al., *Accelerated Head Growth in Early Development of Individuals With Autism*, PED. NEUROL. 32(2):102-08 (2005)["Dementieva"], filed as RML 116; J. Lainhart, et al., *Head Circumference and Height in Autism: A Study by the Collaborative Program of Excellence in Austim*, AM. J. MED. GENET. PART A 140A: 2257-74 (2006) ["Lainhart 2006"], filed as RML 289. I note that Dr. Rodier was a co-author of this study.

The Redcay and Courchesne meta-analysis, RML 391, demonstrated that, in the year after birth, there was a dramatic increase in brain growth in children with ASD, followed by a period when brain growth slowed. By adolescence, brain size in autistics was about the same as that of controls. Tr. at 2836. The Courchesne 2003 study, RML 94, showed that infants later diagnosed with autism had a steady increase in brain growth over the first five months of life, and by six to 14 months, had a significant increase in head growth. Tr. at 2837. The Dementieva study showed a remarkable level of head growth in autistic children from birth to one month of age. Tr. at 2837. The Lainhart 2006 study indicated that head circumference relative to height tended to be larger in individuals with autism, and increased head circumference was associated with more severe social algorithm scores on the ADI-R. Tr. at 2838; RML 289 at 2257.

[214] *See* H. Hazlett, et al., *Magnetic Resonance Imaging and Head Circumference Study of Brain Size in Autism*, ARCH. GEN. PSYCHIAT. 62: 1366-76, 1371 (2005) ["Hazlett"], filed as RML 230 (finding normal head circumference at birth, with a significantly increased rate of growth beginning at 12 months); Dawson 2007, RML 108, at 461 (head circumference in children with ASD was nearly one standard deviation larger than national norms by one year of age).

The Nelson study, RML 353,[215] found neuropeptide abnormalities in umbilical cord blood of children who were subsequently diagnosed with autism, finding no differences in children diagnosed as having experienced early onset or regression. Nelson, RML 353, at 302. Doctor Fombonne commented that the similarity of the findings suggested biological similarity in children with and without regression.[216] Res. Ex. E, ¶ 62.

3. Discussion.

Although not by any means dispositive of the question of autism's origins, the dysmorphology findings suggest a time frame in common with the early gestational origin of the dysmorphology. Doctor Rodier conceded that co-occurring conditions could have separate causes, with an event early in gestation causing the malpositioning and a later event causing the autism, but she indicated that a scientist would not propose a second event without evidence that it occurred. Tr. at 3050.

Larger head circumference measurements and brain volume increases after birth in children with autism do not conflict with a prenatal origin for ASD. As Dr. Rust testified, at each phase of brain development, genetic signals turn on processes that result in elaboration, development, and elimination of brain structures. Tr. at 2403. This may involve the over-elaboration of connections, which results in the forming of too many connections between brain cells and neurons that are too densely packed. Tr. at 2412. This may account for the increase in head circumference and brain volume seen in ASD. Tr. at 2403.

Doctor Rutter concurred, noting that there is an overgrowth of neurons and neuronal connections between birth and age two and a similar period of growth in adolescence in neurotypical individuals. Along with the growth, there is a pruning of connections that are not working or are no longer necessary. Tr. at 3334. The increase in head size seen in ASD may be due to excessive overgrowth or a failure to prune connections. Tr. at 3335. Environmental insults between birth and age two could affect the pruning or overgrowth, but there is no evidence that indicates this is likely. Tr. at 3335.

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[215] K. Nelson, *Toward a biology of autism: possible role of certain neuropeptides and neurotrophins*, CLIN. NEUROSCI. RES. 1: 300-06 (2001) ["Nelson"], filed as RML 353.

[216] Although only 69 children with autism were studied, the values of two or more of the neuropeptides measured were higher in 97% percent of the children with autism than in any of the 54 control children, a remarkably consistent finding. Nelson, RML 353, at Table 1.

G. Pathophysiology in the Brains and Cerebrospinal Fluid ["CSF"] of ASD Patients.

1. Overview.

Much of what is known about the origins of autism and how the brains of those with the disorder differ from those of neurotypical individuals comes from autopsy studies[217] performed on a relatively small number of brains.[218] Several such studies were filed on the master lists of scientific and technical journal articles, but two of the researchers involved in these studies also testified as respondent's experts, Drs. Rodier and Kemper. Doctor Kemper and his research partner, Dr. Margaret Bauman, published their first paper on the neuropathology of autism in 1985. The prevailing view at that time was that autism was caused by poor parenting or some environmental factor. The autopsy studies found structural differences in the brains, establishing a biological basis for ASD. Tr. at 2798. The origin of many of the differences found could be dated to early in the first trimester of pregnancy. *See* Tr. at 2833.

The findings were relatively consistent among the various studies and research facilities. Although not all brains studied had all of the features that, as a group, distinguished the brains of those with autism from those of neurotypical individuals, there was consistency in the areas in which changes were observed and in the types of changes found. Almost all of the brains exhibited some of the pathological changes found in most autistic brains. Tr. at 2799-2800, 2803, 3056. This consistency extended across the age range of the brains examined. Tr. at 2800.

Several caveats should be noted, in addition to the small numbers of brains upon which these findings are based. First, none of the brains autopsied were from children under the age of three, and thus the neuropathological changes noted may not reflect findings present at the time autism's symptoms first manifested. *See* Tr. at 2800. Second, some of the changes observed in only one or two brains may have been the result of something other than ASD that mimics ASD's symptoms. Third, particularly with regard to the Vargas study,[219] PML 69, some of the findings may, as the authors

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[217] The autopsy studies are important because they can look at brains with a level of detail not achievable in functional MRI scans and PET scans of living brains. Tr. at 2866.

[218] By Dr. Kemper's account, a total of 23 brains have been studied. Tr. at 2864. Doctor Rodier concurred. Tr. at 3037-38.

[219] D. Vargas, et al., *Neuroglial Activation and Neuroinflammation in the Brains of Patients with Autism*, ANN. NEUROL. 57: 67-81 (2005) ["Vargas"], filed as PML 69. The Vargas study examined brain tissue and CSF from autistic patients, looking for neuroglial and inflammatory reactions and for cytokine expression. PML 69 at abstract. Brain tissue from 11 patients was examined for cellular and inflammatory reactions. Additionally, cytokine profiling was performed on fresh frozen brain tissue from seven deceased patients and on CSF from six living patients. All of the living patients had experienced developmental regression. *Id*. at abstract. The brain samples were compared to controls, none of whom had epilepsy or mental retardation. *Id*. at 68, Table 1. The CSF samples of the ASD patients were compared to control

noted, reflect either a response to earlier injury, an on-going pathological process, or both. PML 69 at 78.

The findings from the Bailey 1998[220] and Hutsler[221] studies, as well as those performed by Drs. Kemper and Rodier personally, discussed below, were not generally contested. The petitioners relied primarily on two studies, the Vargas study, PML 69, and the Lopez-Hurtado study, PML 446.[222] Respondent also relied on the Vargas study, with the primary area of disagreement being the interpretations placed on the findings. In this regard, a later paper, Pardo, PML 72, co-authored by three of the Vargas study researchers, provides some insights into interpretation of the Vargas findings. Additionally, a letter from Dr. Pardo to Dr. Kemper, generated as a result of their scientific discussions, was filed as Res. Ex. BB.[223] The letter also helps explain what the Vargas researchers found. *See* Tr. at 2848-49.

The only autopsy study that was seriously criticized was the Lopez-Hurtado study. The criticisms ranged from the statistical methods used to confusion regarding precisely what cells were counted.

2. Early Studies.

Doctors Kemper and Bauman began publishing autopsy studies of autistic brains in 1985. *See* M. Bauman and T. Kemper, *Histoanatomic observations of the brain in early infantile autism*, NEUROL. 35: 866-74 (1985), filed as PML 509. A summary of their

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samples from much older patients who had no evidence of central nervous system inflammatory disorders or pathological processes. *Id.* at 69 and Table 2.

[220] PML 220. Doctor Rutter was one of the researchers on this study.

[221] J. Hutsler, et al., *Histological and Magnetic Resonance Imaging Assessment of Cortical Layering and Thickness in Autism Spectrum Disorders*, BIOL. PSYCHIATRY 61: 449-57 (2007) ["Hutsler"], filed as RML 249.

[222] E. Lopez-Hurtado and J. Prieto, *A Microscopic Study of Language-Related Cortex in Autism*, AM. J. BIOCHEM. & BIOTECH. 4(2): 130-45 (2008) ["Lopez-Hurtado"], filed as PML 446.

[223] In response to petitioners' concerns about whether Dr. Pardo's letter (Res. Ex. BB) constituted an expert report, respondent agreed to contact Dr. Pardo to determine if he would be available for cross-examination about the content of the letter. Tr. at 3374. However, it appeared that petitioners wanted to question him about other matters, rather than simply about the letter. *See* Tr. at 3374. In any event, respondent eventually decided not to call Dr. Pardo. Tr. at 3375. As there is no explcit right of cross-examination in Vaccine Act cases (*see* § 300aa-12(d)(2)(D)), the dispute over the admissibility of Dr. Pardo's letter is largely academic. Because he did not testify as a witness, I have not accorded the letter the weight I would give to a testifying expert's report, and have considered it primarily as evidence clarifying matters contained in the Vargas study, PML 69, and the Pardo paper, PML 72.

work appears in Chapter 7 of one of their books. *See* Bauman and Kemper 1994,[224] RML 38, at 124. Although later papers have described additional brain studies and have reviewed the findings of other researchers in addition to their own (*see, e.g.*, M. Bauman and T. Kemper, *Neuroanatomic observations of the brain in autism: a review and future directions*, INT'L. J. DEVL. NEUROSCIENCE 23: 183-87 (2005) ["Bauman and Kemper 2005A"], filed as PML 306), the book chapter, RML 38, provides significant detail about the first six brains studied and appears to be the source for a number of the photographs used as slides during Dr. Kemper's testimony.

3. Specific Neuroanatomical Changes in Brains of ASD Subjects.

The Pardo paper provided a concise summary of the most prominent neuropathological changes in autism. The authors characterized them as cytoarchitectural organizational abnormalities of the cerebral cortex, cerebellum, and other subcortical structures, including: (1) densely packed small neurons; (2) loss and atrophy of Purkinje cells, primarily in the neocerebellar cortex; (3) a curtailment of normal development of neurons in the limbic system and changes in neuronal size and number in the nucleus of the band of Broca, cerebellar nuclei, and inferior olive; and (4) more numerous, smaller, and less compact minicolumnar structures in the frontal and temporal regions of the brain. PML 72, at 486-87. Many of these relatively consistent findings from the autopsy studies also indicated when in the development of the brain the problems likely arose, based on when those brain structures were created or moved into permanent place.[225]

a. Densely Packed Small Neurons.

In both the Hutsler (RML 249)[226] and Bailey 1998 (PML 220)[227] studies, the

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[224] M. BAUMAN AND T. KEMPER, *Neuroanatomic observations of the brain in autism*, *in* THE NEUROBIOLOGY OF AUTISM Ch. 7 (1st ed. 1994) ["Bauman and Kemper 1994"], filed as RML 38.

[225] As the human brain forms, various structural changes take place. *See* Tr. at 2805; Res. Tr. Ex. 10, slide 4 (template of brain developmental events).

[226] The Hutsler study evaluated cortical layering and thickness in postmortem brains of eight individuals with autism spectrum diagnoses and eight age- and sex-matched controls, using structural MRI to assess cortical thickness in frontal, parietal, and temporal lobes. The researchers also used histological sections to assess the pattern of cortical layering in the superior frontal gyrus, the superior parietal lobule, and the middle temporal gyrus. Hutsler, RML 249, at 449. The Bailey 1998 and Hutsler studies found very similar pathological changes. Tr. at 2804; *see also* Res. Tr. Ex. 10, slide 3 (tables comparing the findings from the two studies).

[227] The Bailey 1998 study involved the more severe cases of autism in the neuropathology studies, examining brain tissue from six subjects with mental retardation and autism, matched with five controls. Tr. at 2875; Bailey 1998, PML 220, at 889, 891. The investigators performed neuronal counts on sections from the medial aspect of the superior frontal gyrus, the hippocampus, and the Purkinje layer of the superior aspect of the cerebellar hemisphere. PML 220 at 892. The whole brains were also visually

researchers found an increased number of neurons in the white matter.[228] Tr. at 2827. The neurons in the cerebral cortex are born between two zones, the subplate and Layer I (the top layer of the cerebral cortex). Tr. at 2822-23; Res. Tr. Ex. 10, slide 14. The subplate, which is very important for the establishment of cerebral cortical circuitry, is present prenatally, but disappears shortly after birth; neurotypical adult brains have very few neurons in Layer I. Tr. at 2823. Autistic brains display an abnormal settling or distribution of neurons within the cerebral cortex. Tr. at 2824, 2828-29; Res. Tr. Ex. 10, slides 15 and 17. These neurons should have disappeared shortly after birth. Tr. at 2828. The increased number of neurons in Layer I and in the white matter in autistic brains represents, according to Dr. Kemper, a persistence of the embryonic zone. Tr. at 2829. These defects likely occurred at 16-20 weeks of gestation. Tr. at 2830-31; *see also* Vargas, PML 69, at 79 (suggesting that their findings might represent a persistent fetal pattern of development).

b. Loss of Purkinje Cells.

A decreased number of Purkinje cells is one of the most consistent neuropathological findings in autism. Tr. at 2804, 2815. This consistency may be due both to the prevalence of the loss in the samples studied[229] and to the relative ease with which Purkinje cells can be detected and counted.[230] When Purkinje cells are lost early in development, the comparable cohort of granule cells decreases.[231] Tr. at 2814.

Based on a number of pathological clues, the decrease in the number of Purkinje

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examined, with a number of abnormal findings grossly apparent. PML 220, Figures 2, 3, 8, 10. The study sets forth the pathological findings in a series of tables, each focusing on a specific area of the brain. *See* PML 220, Table 2 (cerebral cortex and underlying white matter), Table 3 (brainstem), and Table 4 (cerebellum).

[228] The dark blue dots on the photograph at Res. Tr. Ex. 10, slide 17, are neurons. In the control brain pictured on this slide, there are only occasional neurons in the white matter, but a much larger number appear in the autistic brain. Tr. at 2827-28. The photographs also illustrate the lack of a demarcation between the cortex and the white matter in the autistic brain. Tr. at 2828.

[229] The Vargas study found evidence of Purkinje loss in every brain sampled, except one. PML 69 at 71. The Bailey 1998 study found a decreased number of Purkinje cells in five of the six brains studied. *See* PML 220 at 898, Table 4. *See also* Bauman and Kemper 1994, RML 38, at 124 (noting a loss of Purkinje cells in all six brains studied).

[230] Unlike smaller neurons, which are numerous and scattered throughout tissue, the much larger Purkinje cells form rows in the same layers of brain tissue. A series of photographs on Res. Tr. Ex. 10, slide 9, of Purkinje cells in autistic and control brain sections demonstrates the loss. *Compare* Box B (autistic brain) *with* Box C (control brain). Box B shows a profound loss of Purkinje cells and an attendant loss of granule cells as illustrated by the light staining. Tr. at 2813-14.

[231] The photograph on the right side of Res. Tr. Ex. 10, slide 9, shows a mild loss of Purkinje cells with relative preservation of granule cells. Tr. at 2813. Box B on the same slide shows a profound loss of Purkinje cells and an attendant loss of granule cells. Tr. at 2813-14.

cells can be traced to a specific period of prenatal development. The inferior olive projects climbing fibers to the Purkinje cells in the cerebellum, with one projection to about 15 Purkinje cells. Tr. at 2816. A climbing fiber from the inferior olive surrounds the Purkinje cell, creating a basket around it and the surrounding dendritic tree that connects the brain stem to the Purkinje cell. Tr. at 2807, 2816-17, 3028; Res. Tr. Ex. 11, slide 12. Climbing fibers reach Purkinje cells at about 29-30 weeks of gestation.[232] If the Purkinje cells are lost after birth, the inferior olivary neurons are also lost. Tr. at 2817-18. Because the brains of autistic individuals show a loss of Purkinje cells but no loss of the inferior olivary neurons, the Purkinje cells were lost before the relationship between them and the olivary neurons was established. Tr. at 2818-20, 3028.

Using GFAP staining,[233] the Vargas researchers found marked reactivity of a type of astroglia in areas of Purkinje cell loss. PML 69 at 71. Other immunochemical studies and microscopic evaluations found "that microglia and astroglia reactions in the cerebellum were both closely associated with degenerating Purkinje cells...." *Id*. Purkinje cells displaying degenerative changes were strongly immunoreactive for an anti-inflammatory cytokine, tumor growth factor ["TGF"]-β1.[234] *Id.* at 75. Increased levels of the MCP-1 chemokine[235] were found as well. The MCP-1 chemokine is expressed in the cerebellum during prenatal development and may be associated with the maturation of Purkinje cells. *Id*. at 79. The authors speculated that the neuroglia reaction might indicate that the Purkinje cell damage continued beyond early development, and might result from the vulnerability of Purkinje cells to whatever pathogenic process caused the cells to be lost in the first place, or it might reflect "persistent fetal patterns of brain development." *Id*. at 79.

c. Other Neuronal Changes.

Arrested neuronal migration[236] in the inferior olive and arcuate nucleus in the

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[232] The development of the human cerebellar cortex from nine weeks of gestation through seven months after birth is illustrated by a series of sketches on Res. Tr. Ex. 10, slide 11. Tr. at 2818-19. At 25 weeks of gestation, the climbing fibers are present, but they have not yet formed connections with the Purkinje cells. Tr. at 2819. During the next five weeks of gestation, they envelop the Purkinje cells, and, by birth, have done so densely. Tr. at 2819-20.

[233] GFAP measurements were used to assess astroglial activation. Vargas, PML 69, at 69.

[234] The term "transforming growth factor" is also used to refer to TGF-β1. *See* DORLAND'S at 1890.

[235] Chemokines are small molecular weight cytokines. DORLAND'S at 344. In addition to their role in inflammation, they help regulate the immune system, and they may play other roles in the central nervous system. *Id.*

[236] This migration pattern is illustrated by small arrows on the drawing on the right side of Res. Tr. Ex. 10, slide 5. Tr. at 2808. The arrested migration is illustrated on Res. Tr. Ex. 10, slide 6. Tr. at 2808-09.

medulla were reported by both Dr. Kemper[237] and the Bailey 1998 study, PML 220. Tr. at 2808-09. This migration occurs early in gestation. Tr. at 2807-08.

The neurons in the inferior olive do not normally line up in rows. In autistic brains, the neurons show an abnormal layering or lined up appearance, reflecting a problem in neuronal migration at up to 14-16 weeks of gestation.[238] Tr. at 2810-11. This finding has been present in all the brains that Dr. Kemper has examined. Tr. at 2811.

There are distinct differences in the inferior olive itself in the brains of those with autism, with autistic children having larger neurons. Tr. at 2820-21; Res. Tr. Ex. 10, slide 12 (age-matched autistic and control brains of children). A different pattern emerges in adult autistic brains, with large neurons absent and abnormal patterns of layering of small neurons in the same region. Tr. at 2821; Res. Tr. Ex. 10, slide 13. What happens to induce this change between age 13 and adulthood is unknown. Tr. at 2821. Doctor Kemper interpreted the finding as indicating abnormal circuitry in the cerebellum. Tr. at 2821.

Changes that cannot be related to a specific period of brain development have been found in the hippocampus, with densely packed neurons found in the brains of autistic patients. Tr. at 2831-32; Res. Tr. Ex. 10, slides 19-20.

d. Minicolumnar Changes.

Pyramidal cells form into vertical structures called minicolumns which are highly complex networks of neurons connected locally and at longer distances reaching through several layers of the neocortex.[239] *See* Res. Ex. C, at 5. Minicolumns are banded on both sides by the peripheral neurophil space, which contains few cells, but many unmyelinated axon fibers, dendritic arborizations, and synapses. Dendrites from pyramidal cells in Layer V ascend in bundles through or adjacent to the cell column. The edges of the minicolumns contain vertical bundles of fibers containing GABAergic interneurons that distinguish one minicolumn from its neighbors. Casanova 2002, RML 62, at 428.

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[237] *See* M. Bauman and T. Kemper, *Structural Brain Anatomy in Autism: What is the Evidence? in* THE NEUROBIOLOGY OF AUTISM 121 (2d ed. 2005)["Bauman and Kemper 2005B"], filed as RML 39.

[238] This is illustrated on Res. Tr. Ex. 10, slide 8.

[239] Information regarding the minicolumnar studies was presented primarily in Dr. Casanova's expert report (Res. Ex. C) and his studies. The Casanova 2002 study, RML 62, described the general design of minicolumns. It included several photographs and tables illustrating the differences between autistic subjects and neurotypical controls in minicolumns in the cerebellar cortex. The study compared the number of minicolumns, their width, and neuronal dispersion in the columns. Casanova 2002, RML 62, at 428.

In the brains of ASD patients, minicolumns are narrower, smaller, and less compact, with reductions in the neurophil space. Casanova, RML 62, at 430. The neurons are present in equal numbers, but are more dispersed. *Id.* at 431, Fig. 3. The total number of minicolumns is determined at about five to six weeks after conception, before cells migrate from the cortex. Tr. at 2805.

4. The Vargas Study, the Pardo Paper, and the Lopez-Hurtado Study.

Because Drs. Deth and Kinsbourne relied heavily on the Vargas study, the Pardo paper, and the Lopez-Hurtado study, these publications are discussed at somewhat greater length.

a. The Vargas Study.

The brains of the autistic patients showed extensive microglial and astroglial activation. The most prominent histological changes were found in the cerebellum, with a patchy loss of neurons in the Purkinje cell layer and in the granular cell layer. Vargas, PML 69, at 71. Staining for GFAP showed marked reactivity of astroglia in areas of Purkinje cell loss, and marked astroglial activation in the granular cell layer and cerebellar white matter. In the middle frontal gyrus and anterior cingulate gyrus, prominent astroglia reactions were observed in the subcortical white matter.

In the fresh frozen brain tissue, there was increased GFAP expression in the cerebellum. Microglial activation was measured and was observed in the granular cell layer and white matter of the cerebellum. Vargas, PML 69, at 71.

There were no differences in microglial or astroglial activation based on age, developmental regression, or retardation in the autistic patients. Vargas, PML 69, at 71. Microglial activation in the cerebellar white matter was significantly elevated in patients with a history of epilepsy, but no differences were observed in other regions. *Id.* Astroglial activation was similar in autistic patients with and without epilepsy. *Id*.

There were consistently higher levels of certain cytokine subsets in the fresh frozen tissue of the autistic brains. Anti-inflammatory tumor growth factor ["TGF"]-β1 was increased in several areas, and proinflammatory chemokines were increased in similar areas. Vargas, PML 69, at 73. The researchers determined that reactive astrocytes were the main source of cytokines in the brains of the autistic patients. *Id.* at 74-75. Cerebrospinal fluid of patients with autism showed a significant increase in both proinflammatory and modulatory cytokines. *Id*. at 75.

The authors concluded that the microglial and astroglial reactions were neuorinflammatory reactions associated with the central nervous system's innate

immune response.[240] Vargas, PML 69, at 75. The neuroglial activation was consistent with chronic and sustained neuroinflammation.[241] The microglial responses resembled those seen in neurodegenerative disorders, including Alzheimer's, Parkinson's, and ALS, and in those seen in HIV dementia. *Id*. at 77.

Both microglia and astroglia are essential for neuronal activity and synaptic function, neuronal-glial interactions, and cortical organization during brain development. Microglial and astroglial responses may both directly cause and protect against injury. The significant question that remains unanswered by this study is when during development the activation of neuroglial cells occurred. Vargas, PML 69, at 78. The neuroglial reactions in the cerebellum were most prominent, a finding that is consistent with previous observations of prenatal developmental abnormalities in the cerebellar regions of autistic patients (abnormalities in the inferior olive and a reduced number of Purkinje cells), but also indicating that the degenerative processes in the cerebellum continue postnatally and beyond. *Id*. at 78-79.

The authors suggested that the cytokines and chemokines found in increased amounts in autistic patients provided clues to the pathogenesis of autism. Vargas, PML 69, at 79. They linked increased levels of a proinflammatory chemokine (MCP-1) to microglial activation and recruitment of macrophages to areas of neurodegeneration in the cerebellum. The increased levels of TGF-β1 in the cortex and cerebellum suggest a response to an injury, because this anti-inflammatory cytokine is involved in tissue remodeling after an injury. It is also expressed during cell death, perhaps to suppress local inflammation and prevent additional cell degeneration. TGF-β1 was found primarily within reactive astrocytes and neurons in the cerebellum. The pro- and anti-inflammatory cytokine profiles were markedly elevated in the anterior cingulate gyrus, another area associated with dysfunctional brain activity in autism. *Id*. at 79.

Several of respondent's witnesses commented on the significance of the Vargas study's findings. Doctor Johnson noted that brain trauma results in inflammatory responses, including massive microglial activation and gliosis associated with that damage. Tr. at 2245. He also noted that activated microglia may have both positive and negative aspects. Tr. at 2243. Doctor Kemper commented that a likely explanation for the neuroinflammatory process found in the Vargas study is pathology that has its origin in events that occurred prenatally, although postnatal insults are also possible. Tr. at 2895. Doctor Rutter commented that the changes observed were interesting, but their meaning was uncertain given the different roles for glial activation in the brain. Tr.

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[240] There was no evidence of any significant B or T cell reactions; no immunoglobulins were deposited in any neuronal or neuroglial cells. Vargas, PML 69, at 72. Their absence indicates a lack of adaptive immune response. *See id*. at 75.

[241] Neuroinflammation reflects activation of microglia and astroglia and the chemicals they use to communicate with one another to suppress negative effects in the brain. Tr. at 2243. It is a dynamic system, and activated microglia may have both positive and negative aspects. Tr. at 2243.

at 3336. The neuroinflammation does not show what changes are happening or when they are happening. Tr. at 3337.

b. The Pardo Paper and Letter.

Three of the authors of the Vargas study also collaborated on a subsequent article, Pardo, PML 72. This paper discussed the neurobiology of autism and the Vargas' study's findings.

The authors noted that neuronal dysfunction and cortical organizational abnormalities may lead to neuroglial activation. The activated neuroglial responses may actually increase, rather than ameliorate, the magnitude of the neuronal dysfunction. Pardo, PML 72, at 489, 490 (suggesting that the neuroglial activation may have a dichotomous role in brain inflammatory responses). Although the authors suggested that the activated microglia might be a response to genetic or environmental factors, all of the possible environmental factors identified were ones that occur prenatally. *Id*. at 490; *see also id.* at 487-88 (discussing maternal antibodies affecting prenatal brain development).

They concluded the paper by hypothesizing that environmental factors, including neurotoxins, infections, and maternal infections, may, in the presence of genetic susceptibility, play a role in the development of abnormalities in brain structure and in the neuroinflammatory changes they observed. *Id.* at 493. However, Dr. Pardo's letter indicated that the effects found were not consistent with a toxic exposure. Res. Ex. BB at 1; Tr. at 2903.

5. The Lopez-Hurtado Study.

a. Findings.

This was an autopsy study comparing three brain regions associated with language and speech in individuals with autism to age-matched controls. PML 446 at 130. The findings differed remarkably from those of other autopsy studies. Unlike other studies, the authors did not find evidence of altered neuronal migration in the areas examined. PML 446 at 140. Also unlike other studies, the investigators reported "a striking reduction in neuronal density in [specific brain areas] in autism relative to controls." PML 446 at 140. Neuronal density findings suggested that neuronal death ensues as a result of aging, a phenomenon also seen in schizophrenia, bipolar disorder, and major depressive disorder.[242] *See* PML 446 at 140-41. The investigators reported

[242] Doctor Johnson noted that neurodegeneration and chronic astrocytic and microglial activation leads to death, not autism. In autism, patients plateau, but in the chronic neuroinflammatory or neurodegenerative diseases he studies, such as Alzheimer's and Parkinson's, the patients die. Tr. at 2255-56.

a greater density of glial cells[243] in the autistic brains, but not in the granular layers. They found a steep linear increase in glial cell density in the autistic subjects from ages seven to ten, followed by a plateau through age 26. PML 446 at 140.

Two findings similar to those noted in Rett's disorder were made, including increased lipofuscin-containing[244] cells. PML 446 at 141. Since Rett's is considered an entirely genetic disorder, this suggests a response to neuronal maldevelopment, rather than an environmental agent at work.

b. Doctor Kinsbourne's Interpretations.

Doctor Kinsbourne testified that this study found a proliferation of microglia,[245] a diminution in the density of the astrocytes,[246] gliosis, and the loss of some neurons. He noted that the older brains studied had more striking changes, suggesting an ongoing process. Tr. at 807-08. This, according to both Dr. Kinsbourne and the authors, would be compatible with the effect of a toxin on the brain, since metals such as lead, iron, and mercury have been known to cause glial proliferation. Tr. at 810. However, the authors noted that proliferation of glial cells also occurs in ischemia, trauma, toxins, and neurodegenerative disorders. PML 446 at 140.

c. Doctor Kemper's Criticisms.

Doctor Kemper had concerns about the Lopez-Hurtado study as well as considerable difficulty in locating it.[247] Tr. at 2854-55. He summarized the study's findings as a decreased number of neurons, an increased number of glial cells, and an accelerated accumulation of lipofuscin. Tr. at 2856.

However, there was no assurance in the paper that the authors were careful in

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[243] Doctor Kemper commented on the use of the term "glial" as opposed to "microglial." As used, the term could refer to both astroglia and microglia. Tr. at 2857-58.

[244] The authors described lipofuscin as material originating from phagocytosed cellular components that had been engulfed by microglia acting as phagocytes. Lipofuscin is "composed primarily of oxidatively-modified proteins and lipids." They noted that lipofuscin is a "depot for metals, including redox-active and heavy metals." They indicated that higher levels of lipofuscin may be considered as a marker for increased oxidative activity. PML 446 at 141 (footnotes omitted).

[245] The authors used the term "glia" rather than "microglia," making Dr. Kinsbourne's assertion incorrect. *See* PML 446 at abstract.

[246] This interpretation by Dr. Kinsbourne was incorrect. The study did not report changes in the density of astrocytes, but did report morphologic changes in astrocytes. PML 446 at 140.

[247] Doctor Kemper testified that he was unfamiliar with the journal in which the Lopez-Hurtado article appeared, and that the Harvard Medical School Library, the second largest in the nation, did not carry it. Tr. at 2854-55.

identifying the areas they intended to examine; the paper did not contain a proper cytoarchitectonic definition of the areas examined, and thus the findings regarding cell types and density are unclear. Tr. at 2856-57. Additionally, the lipofuscin pigment varies from area to area, and if the researchers did not look in the right area, their findings could be incorrect. Tr. at 2857. He commented that the method of cell counting employed in the study would not be accepted in a critically-refereed journal. Tr. at 2857.

The study did not mention microglia, in spite of using standard stains for neuron densities and GFAP, a stain specific for astrocytes. The way the term "glia" was used in the study may encompass astrocytes. Tr. at 2857-58. Thus, its findings cannot be equated to the microglial activation reported in the Vargas study. Tr. at 2858. A report of increased astrocytic density would not be compatible with astrocyte death. Tr. at 2858.

Doctor Kemper also commented that the authors had a very interesting idea, one he would like to have seen investigated by proper technique, but a reputable journal would not have accepted the paper, as written. Tr. at 2858. He would not rely on its findings for information about the neuropathological basis of autism. Tr. at 2859.

d. Doctor Johnson's Criticisms.[248]

Doctor Johnson noted that the Lopez-Hurtado paper, PML 446, had a significant methodological flaw. Tr. at 4317-18. The paper used statistical analysis and computed standard deviations to compare cell counts from brain samples within the same brain.[249] It is improper to compute a standard deviation based on one sample. Tr. at 4318-19. An examination of Table 1 in the Lopez-Hurtado paper, PML 446, at 133, reveals that the authors did precisely what Dr. Johnson indicated was improper. Thus, the statistical inferences are invalid. Tr. at 4319.

Furthermore, Dr. Johnson testified that the appropriate way to analyze the data would be to compare the rate of change with age in cell numbers for glia, neuronal cells, and the lipofuscin-containing cells. When he analyzed the data, he noted that the rate of change in the control patients and in the autistic patients was almost exactly the same. Tr. at 4319. In the older autistic patients, the number of glial cells increased; the same increase was seen in the control patients as a function of the age of the donor. The significant difference was not in the age-related changes, but in the baseline cell

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[248] Initially, when Dr. Johnson was cross-examined about the Lopez-Hurtado study, PML 446, he declined to comment on it, as he had not read it. Tr. at 2249-50. Between his cross-examination and his recall as a witness in the rebuttal case, Dr. Johnson had an opportunity to examine the paper and evaluate the data contained in it, and in rebuttal, he proffered a number of criticisms.

[249] The study counted the number of neurons in brain sections of an individual and computed an average number. The standard deviation computed is therefore based on counting errors. Tr. at 4318-19.

counts. Although the starting points were different, the lines representing the increasing number of glial cells created from the data in the autistic and control samples were "basically exactly parallel." Tr. at 4320. As the youngest samples were from children aged seven, the cell counts revealed little about the genesis of the initial differences. *See* Tr. at 4320.

6. Implications of Neuroanatomical Abnormalities in ASD.

In summary, most of the structural changes observed in the brains of autistics most likely occurred prenatally.[250] The prenatal origin of the structural changes observed buttresses the conclusions drawn from the testimony about dysmorphology in ASD, and in the neuropeptide findings. What goes awry in ASD most likely does so early in gestation, producing abnormalities in all three major sections of the brain. The Vargas study indicates that brain systems that may respond to or be causal of injury are more active in the brains of those with ASD, reflecting an ongoing process. Whether the microglial and astroglial activation observed are the result of, or even consistent with, administration of mercury via TCVs was not addressed by the study, or even suggested by three of the Vargas study's authors in the Pardo paper. Petitioners' evidence that TCVs could be responsible is addressed in Sections VI, VII, and VIII below.

H. Regressive Autism as a Separate Phenotype with a Distinct Etiology.

1. Overview.

The only evidence suggesting that regressive autism (or clearly regressive autism) is biologically and causally different from classic or early onset autism was provided by Drs. Kinsbourne and Greenland. In his testimony and expert report, Dr. Kinsbourne advanced a number of arguments for a biological distinction between regression and early onset autism, and asserted that regression was consistent with environmental triggers. Doctor Greenland pointed to a few studies that he thought pertinent for the existence of clearly regressive autism as a distinct biological entity, but primarily argued that it was respondent's burden to show that clearly regressive autism was not distinct.

I conclude that the preponderance of the evidence demonstrates that regressive autism is not a distinct phenotype, and overwhelmingly demonstrates that "clearly regressive autism" is, at best, only a hypothetical construct, unsupported by any credible evidence. I likewise conclude that opinions, such as Dr. Greenland's, that are based on the existence of this subtype lack the factual underpinnings to be considered reliable evidence. Thus, I conclude that the impressive body of epidemiological

[250] One finding relating to subplate neuronal migration could have occurred either before or shortly after birth. Tr. at 2833.

evidence that TCVs are not causally associated with ASD is relevant and should be considered in determining whether TCVs do indeed cause or substantially contribute to ASDs. That evidence is discussed in Section V, below.

Not surprisingly, respondent's experts[251] had sharp disagreements with the assertions of Drs. Kinsbourne and Greenland. Those assertions and the criticisms thereof are set forth below.

With respect to Dr. Kinsbourne, respondent's experts noted that some of his assertions were made without any reference to supportive medical literature,[252] were based on "cherry-picked" data, and conflicted with the weight of scientific and medical authority. Other aspects of Dr. Kinsbourne's testimony made analysis of his assertions difficult. For example, he declined to define regressive autism. Tr. at 846. In view of the numerous definitions discussed, Dr. Kinsbourne's reluctance to specify what he considered to be regressive autism was troublesome. He could not state whether regressive autism was considered a separate diagnostic category by either the DSM-IV-TR or the ICD-10. Tr. at 847-49.

2. Doctor Kinsbourne's Opinions.

Initially, Dr. Kinsbourne testified that, based on his experience, children with cases of regression developed more severe forms of autism. Tr. at 780. Almost immediately thereafter, he retreated from this position, testifying that there was no difference in the pattern of disabilities or behaviors between regressive and non-regressive autism. Tr. at 781. It was unclear whether this was indeed his own opinion, or merely his response to leading questions.[253]

Doctor Kinsbourne's opinions on regression in autism can be placed into four broad categories. They are: (1) regressive autism is not associated with any of the

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[251] During his testimony, Dr. Kinsbourne claimed that Dr. Rutter had written "something along" the lines of clearly regressive autism being a distinct disease category. Tr. at 848. He did not specify where Dr. Rutter made this statement. Doctor Rutter's testimony clearly indicated that he did not consider regressive autism to be a separate disease category. *See, e.g.*, Tr. at 3284-85.

[252] Petitioners cannot be required to have medical literature supporting their claims in order to prevail in establishing biological plausibility. *Capizzano*, 440 F.3d at 1325. However, when petitioners alone filed roughly 700 medical and scientific journal articles and textbooks, the fact that none were referenced for several contested points in Dr. Kinsbourne's report is a factor in assessing the weight to be given to his specific assertions.

[253] Formal rules of evidence do not apply to Vaccine Act proceedings. However, the prohibition in both the common law and Fed. R. Evid. 611(c) against asking a party's own witness leading questions has a practical basis in the concept that testimony should come from the witness, not the attorney examining the witness. The frequency with which leading questions were used to steer Dr. Kinsbourne's testimony detracted from its impact, and occasionally left me in doubt about who was actually presenting evidence–Dr. Kinsbourne or petitioners' attorney.

known medical causes for non-regressive autism; (2) regression in autism has unique characteristics that set it apart from non-regressive autism; (3) the prevalence of regression is increasing faster than early onset autism; and (4) genetics cannot explain the phenomenon of regression in autism.

a. Regressive Autism and Known Medical Conditions or Causes.

Doctor Kinsbourne's report stated: "Moreover, with few exceptions, the known medical conditions that feature autistic behavior do not do so in isolation, without other abnormalities. Nor do they feature the virtually unique time course of the developmental regression observed in many children who become autistic during the first 12-24 months of life." PML 717 at 4. In the next paragraph of his report, Dr. Kinsbourne continued: "Classical ('congenital') and regressive autism differ[] sharply with respect to their known medical causations. A large number of causative medical factors have been associated with children with non-regressive autism, and a differential diagnosis excluding those possible causes is possible." PML 717 at 4; *see also* Tr. at 902-03. He explained further: "Only a few medical conditions that cause autism feature a regression with loss of previously attained developmental skills, leading to an autistic endpoint." PML 717 at 4. He noted that loss of skills does not happen in most other developmental disorders, and "ruled out" three conditions that feature regression, but do not lead to an autism diagnosis: Rett's disorder, Landau-Kleffner Syndrome[254] ["LKS"], and Heller's disease (CDD). Tr. at 782; PML 717 at 4. In cases of regression, when these conditions are "ruled out," "a reasonable differential diagnosis would then consider other potential causes that might have contributed to the regression." *Id*. at 5.

Doctor Kinsbourne's logic is difficult to follow. Starting with the premise that an otherwise normal and healthy child suddenly loses skills, he lists disorders in which loss of skills appear, rules them out, and then looks for another cause. This process assumes the point that he seeks to prove: that loss of skills cannot be caused by ASD alone. Doctor Kinsbourne assumes the phenomenon of regression sets CDD, Rett's disorder, LKS, and regressive autism apart from other conditions with an "autistic endpoint." And, because the process of differential diagnosis establishes that

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[254] Doctor Kinsbourne briefly described LKS in his report, PML 717, at 4-5. He noted that the first sign of LKS is typically seizures, which appear much later in autism, and that onset of LKS is usually after three years of age. *Id*. at 4-5 (emphasis added). However, articles concerning LKS filed by petitioners indicate that Dr. Kinsbourne's description of LKS was not entirely accurate. According to the Connolly paper (A. Connolly, et al., *Serum autoantibodies to brain in Landau-Kleffner variant, autism, and other neurologic disorders*, J. PEDIATRICS 134(5): 607-13 (1999) ["Connolly"], filed as PML 501), LKS is acquired epileptic aphasia, and involves loss of language skills after 24 months of age, associated with epileptiform EEG or seizures. *Id.* at 608 (emphasis added). The Mikati study (M. Mikati, et al., *Efficacy of Intravenous Immunoglobulin in Landau-Kleffner Syndrome*, PEDIATRIC NEUROL. 26(4): 298-300 (2002), filed as PML 376) described the syndrome as one "characterized by loss of previously acquired language skills, auditory agnosia," and specific EEG findings "of spike and slow wave activity more prominent in sleep." *Id*. at 298. Both studies noted that individuals who have both LKS and symptoms consistent with ASD are referred to as LKS variant ["LKSV"]. PML 376 at 298; PML 501 at 608.

regressive autism cannot be CDD, Rett's disorder, or LKS, it is, therefore, a separate condition. However, this conclusion that regressive autism is different is dictated by the premise that regression alone is enough to establish it as different. Unlike ASD in general, Rett's disorder, CDD, and LKS all have additional factors, aside from regression, that lead to their separate diagnostic categories.

As evidence for the proposition that regression is a distinct phenotype, Dr. Kinsbourne claimed that regressive and non-regressive autism "differ[ ] sharply with respect to their known medical causations." PML 717 at 4. According to Dr. Rutter, there is no evidence for this statement, as there have been no systematic studies comparing regressive autism and non-regressive autism with regard to medical factors that might be causal. Tr. at 3291. Doctor Rust also noted that there was no basis for Dr. Kinsbourne's statement that classic and regressive autism are epidemiologically and biomedically separate disorders. Tr. at 2391; Res. Tr. Ex. 8, slide 58.

Doctor Kinsbourne did not cite to any studies demonstrating that the few known medical causes of autism are found solely or even predominantly in non-regressive cases. On the other hand, Drs. Rust and Rutter did not offer any evidence that those known causes are also seen in cases in which regression occurs. Tr. at 3020. With one side asserting one position, and the other party asserting the other, the disparity in the background and experience of the witnesses leads me to favor the opinions of respondent's experts. Doctors Rutter and Rust are likely to be better informed about this issue, as they both see, treat, teach, research, and write about patients with autism; Dr. Kinsbourne does not.

Even if I concluded that the known medical causes of autism are not found in regressive cases, the small number of cases of ASD in which causal factors can be identified renders this point largely irrelevant. It would be only one small factor to consider in determining whether regressive autism is a separate phenotype, and thus may have causes distinct from the majority of the cases of ASD.

b. Regressive ASD and "Unique Characteristics."

Doctor Kinsbourne's report referred to a number of characteristics that he believed set regressive autism apart from non-regressive autism. These included regressive autism as: (1) more frequently associated with seizures (PML 717 at 5); (2) more often associated with gastrointestinal symptoms (*id*.); (3) more likely to occur after "a previously normal developmental trajectory" (*id.* at 6); and (4) having a "sharply contrasting natural histor[y]" from that of non-regressive autism *(id*. at 6).

(1) Seizure Disorders.

Doctor Kinsbourne reported that there are more overt seizures or epileptiform EEGs in children who have lost language skills. PML 717 at 5. He cited to two studies

for this statement, Tuchman, PML 329,[255] and McVicar, PML 375.[256] Neither provided much support.

The Tuchman study examined nearly 600 children, divided into those with and without epilepsy and compared the rates of regression within these two groups. About 12% of those with regression had epilepsy; about 11% of those without regression had epilepsy. In the group without epilepsy, 73% of the children with regression had EEGs performed, as compared to 61% of those without regression. PML 329 at Table 1. The authors noted that because the EEGs were performed at different facilities, varied in number, were not independently reviewed, and may have differed in quality, their data "must be interpreted with caution." PML 329, at 563. The authors found that in children without epilepsy, "regression seemed to be a risk factor for an epileptiform EEG." *Id*. at 563.

However, because not all of the children in the study had EEG records, and a disproportionately high number of the children who had EEG records also had regression, the study does not support Dr. Kinsbourne's statement. It is impossible to conclude from this study that more children with regression have overt seizures or epileptiform EEGs.

Doctor Rust explained that the reason more EEGs are performed on those with regression because an EEG can rule out Landau-Kleffner syndrome.[257] He asserted that there is no evidence that children with regression actually have more seizures.[258] Tr. at 2390, 2468. Doctor Rust also testified that EEG profiles do not distinguish between classic and regressive autism.[259] *See* Tr. at 2390. He indicated that the issue of whether children with regression were more likely to have seizures or epileptiform EEGs had not been systematically studied. Tr. at 2468.

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[255] R. Tuchman and I. Rapin, *Regression in Pervasive Developmental Disorders: Seizures and Epileptiform Electroencephalogram Correlates*, PEDIATRICS 99(4): 560-66 (1997) ["Tuchman"], filed as PML 329.

[256] K. McVicar, et al., *Epileptiform EEG abnormalities in children with language regression*, NEUROLOGY 65: 129-31 (2005) ["McVicar"], filed as PML 375.

[257] *See supra* note 254. Landau-Kleffner syndrome presents with regression, seizures, and characteristic patterns of discharge on an EEG, but onset generally occurs after age three. Because LKS is a condition that can be treated with some drugs, an EEG may be performed on a child under three who experiences regression in order to rule out LKS, accounting for the increased number of EEGs in children with regression. Tr. at 2390.

[258] He added that, even if they do, seizures are more likely the result of developmental brain abnormalities than toxic events. Tr. at 2468.

[259] LKS and Lennox-Gastaut syndrome are among the disorders that can be identified by EEG patterns. *See supra* note 254 (LKS); DORLAND'S at 1823 (Lennox-Gastaut).

The McVicar study, PML 375, examined language regression, in children with and without ASD diagnoses. PML 375 at abstract. It found that seizures and epileptiform EEGs were more common in those who had language regression but not ASD. PML 375 at 129. Because regression, with or without ASD, was required of all study participants, the study cannot support Dr. Kinsbourne's assertion that children with ASD and regression are more likely to have seizures or epileptiform EEGs than children with ASD and no regression.

Neither the Tuchman nor the McVicar study support the proposition for which Dr. Kinsbourne cited them: that children with ASDs and regression have more seizures or more epileptiform EEGs than children with ASDs who do not experience regression. As Dr. Rust treats a large number of children with ASD and has specialized expertise in EEG research, his assertions regarding regression, seizures, and the similarity of EEG profiles in children with ASD carry greater weight than those of Dr. Kinsbourne, who misstated the support found in these two studies he cited.

(2) Gastrointestinal Symptoms.

Citing to the Richler study, RML 397, Dr. Kinsbourne asserted that the increased frequency of gastrointestinal symptoms in children with regression than in those without regression was a factor that indicated regressive autism was a separate phenotype. PML 717 at 5. Although this study did find more gastrointestinal symptoms in children with regression, Dr. Kinsbourne's use of this study as support engendered a comment by Dr. Rust regarding "cherry picking" data. *See* Tr. at 2469.

The study's findings and conclusions amply support Dr. Rust's accusation. The authors concluded:

> [T]he few children who showed near-normal development prior to loss were not the same children who manifested the "possible regressive phenotype" (i.e., regression, GI symptoms, onset of autistic symptoms after vaccination). In fact, the results from the present study indicated that all those children who most clearly fit the "possible regressive phenotype" showed abnormal development in the majority of areas on the [communication skills test used] prior to loss. If there is a "regressive phenotype" of ASD, then, it does not appear to be characterized by normal or near-normal early development.

Richler, RML 397, at 313 (emphasis added).[260]

Taken as a whole, the Richler study does not support the hypothesis that

[260] The Richler authors further noted that the information regarding gastrointestinal symptoms was based on parental reports and was not corroborated by medical records. RML 397 at 313.

increased gastrointestinal symptoms occur with greater frequency in "clearly regressive" autism, or in regressive autism in which previous development was normal or near-normal.

(3) Previously Normal Development.

Doctor Kinsbourne's report described some autistic children who "develop relatively normally as infants, but regress in their developmental skills and begin to exhibit the behavioral hallmarks of ASD in the second year of life, or even later." PML 717 at 5; *see also* Tr. at 780. The fact that children regress is not contested, nor is it contested that some children who regress had "relatively" normal development during their first year of life. However, the weight of the evidence, discussed in Section IV.D.5., above, is that most children who lose skills did not have completely normal development prior to their loss.

There remains a small minority of children who regress in whom no previous abnormalities of development have been identified. This is not the same as saying that their development before the loss of skills occurred was entirely normal. Assuming, *arguendo*, that this small group truly had completely normal development prior to the loss of skills, there must be other factors that distinguish them from the larger group of children with regression in order to constitute a separate phenotype or diagnostic category. *See* Tr. at 3585, 3588. Evidence of those factors was not produced.

(4) Contrasting Natural History.

Respondent's experts confirmed that a loss of skills could present very suddenly. Doctor Lord described regression as a very striking phenomenon, one that could be heartbreaking and hard to forget, but noted that subtler forms of regression were common. Tr. at 3576, 3579; *see also* Tr. at 3313-14 (Dr. Rutter explaining that dramatic regressions are unusual and that most cases involve subtle changes over time). However, Dr. Lord's research showed that there were no other clear-cut distinctions between regression and classic autism. Tr. at 3576-77, 3587. The reason that regression is not a separate phenotype is the lack of association of regression with any factors, other than the regression itself. Tr. at 3588.

In the large population of children with autism he treated, Dr. Rust did not see any meaningful distinction, biologically or behaviorally, between children with regression and children without it. Tr. at 2391, 2577. Loss of skills happens at a variety of ages and with no clear association with other events. Tr. at 2592. The prognosis in regression does not differ from the prognosis in early onset of ASD. Tr. at 3569; Res. Tr. Ex. 8, slide 12.

The Vargas study found no differences in the immune responses in patients with regressive autism and those with early onset autism. Vargas, PML 69, at 71; Tr. at 2853-54. Aside from the Vargas study, the neuropathological studies did not compare

brains of ASD patients with regression to those without it. Tr. at 3042. I note, however, that the first neuropathological case study performed by Drs. Bauman and Kemper was that of a man who experienced regression.[261] *See* Bauman and Kemper, PML 509, at 866. He shared most of the neuroanatomical features found in the other cases. *See* RML 38 at 125.

The rate of head growth is not different in ASD children with regression versus those with early onset of the disorder. *See* Webb, RML 506. Both children with early onset and children with regression had similar increases in head circumference between four and ten months of age. Webb, RML 506, at 1187. Neuropeptide abnormalities at birth were not different in children later found to have ASD, regardless of whether they lost skills. Nelson, RML 353, at 302.

In families with multiple incidences of autism, members of the extended family often have a number of personality characteristics similar to those found in autism, a phenomenon often referred to as the "broader autism phenotype." Tr. at 2392-93; Lainhart 2002, PML 91.[262] These characteristics include rigidity, aloofness, anxiety, deficits in speech and pragmatic language, and limited friendships. Such characteristics were found in both parents in 38% of family clusters of autism.[263] Tr. at 2392-93; Res. Tr. Ex. 8, slide 13. In these familial clusters of ASD, both classic and regressive autism are found. Tr. at 2389-90; Res. Tr. Ex. 8, slide 12; Lainhart, PML 91, at abstract. This indicates that the two are not biologically distinct. Or, as the authors of the Lainhart 2002 study stated:

> Assuming that features of the [broader autism phenotype] represent genetic liability to autism, our data suggest that genetic factors may be just as important in regressive autism as they are in nonregressive autism. Environmental factors, if involved in the pathogenesis of autism, do not appear to be preferentially involved in regressive vs. nonregressive autism in our sample.

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[261] If the regression status of the subsequent eight subjects was reported in any of the articles filed, I was unable to find it. Table 7.2 of RML 38 lists the first six cases Drs. Kemper and Bauman examined; it appears that the initial case with regression is listed on the far right column of the table.

[262] J. Lainhart, et al., *Autism, Regression, and the Broader Autism Phenotype*, AM. J. MED. GEN. 113: 231-37 (2002) ["Lainhart 2002"], filed as PML 91.

[263] Doctor Rust cited a 1997 study by Piven for this figure. Res. Tr. Ex. 8, slide 13. Although a 1997 article by Piven was filed as RML 382, it does not stand for this proposition. I note that the Lainhart article, PML 91, cites to another 1997 study by Piven that was likely the study Dr. Rust had in mind, as it is entitled *Cognitive deficits in parents from multiple-incidence autism families*. I could not use Dr. Rust's references in his expert report, Res. Ex. W, to determine which article he meant because his report did not reference any article by Piven. This was likely because Dr. Rust's report was filed before that of Dr. Kinsbourne, and thus it did not include responses to Dr. Kinsbourne's assertions.

Lainhart, PML 91 at 236 (citations omitted).

Doctor Kinsbourne also stated that "autistic regression is self-limiting...." PML 717 at 6. Once again, Dr. Rust disagreed. He noted that there is an additional deterioration during the second decade of life, which is inconsistent with "self-limiting." Tr. at 2474; Res. Tr. Ex. 8, slide 60. Doctor Kinsbourne also stated that, as a result of the encephalopathy, autism "may...become more severe." PML 717 at 6. Doctor Rust noted that this statement is inconsistent with a self-limiting condition. Tr. at 2472.

Doctor Kinsbourne's assertions that regression has a distinct natural history and probable postnatal etiology were not supported by the weight of the evidence.

c. Prevalence and Regression.

Because the percentage of cases of regression has not changed over the decades, Dr. Kinsbourne concluded that the real number of regressive cases must be rising. PML 717 at 7. He based this conclusion on two factors: (1) the definition of regression has not changed; and (2) sudden regression is unlikely to be missed or mistaken for something else. *Id*. Thus, diagnostic substitution could not account for any of the increased cases of regression, even if it did account for some of the overall rise in the number of cases of ASD. In Dr. Kinsbourne's words, "the rise in the number of cases of regressive autism is no artifact, but is very real." PML 717 at 7. Attributing regression to both genetic and environmental factors, he blamed the increase on the the environmental factors "correspondingly increasing." *Id.*

Doctor Rutter testified that there was a lack of evidence that the proportion of regressive cases had changed, "rather than a solid finding of no change...." Tr. at 3287. He also stated, contrary to Dr. Kinsbourne's assertion, that the diagnostic criteria for regression had changed, but agreed that it was unlikely these changes accounted for any differences. Tr. at 3287. He also took issue with Dr. Kinsbourne's assertion that regression could not be mistaken for mental retardation or developmental delay, commenting that this assertion indicated that Dr. Kinsbourne had little experience with patients with autism. Tr. at 2475-76; Res. Tr. Ex. 8, slide 61.

I conclude that Dr. Kinsbourne was correct in stating that "striking and even shocking" cases of regression could not be mistaken for anything else. However, there was ample testimony that these striking cases account for only a very small proportion of the cases of regression, and even in these cases, prior development may not have been entirely normal. Thus, there are many cases of regression that could be affected by diagnostic substitution, better ascertainment, and the other factors indicating that the increase in prevalence is largely artifactual. There is inadequate evidence for Dr. Kinsbourne's assertion that regressive autism is truly increasing.

d. Genetics and Regression.

Doctor Kinsbourne testified that, because the concordance rate in autism is between 60% and 90%, some 10-40% of cases of autism cannot be explained by genetics alone. Tr. at 790. In his words, environmental factors must account for the triggering of "a strong susceptibility into a clinical actuality." Tr. at 791; *see also* PML 717 at 7. According to Dr. Kinsbourne, genetic concordance may not be for a gene that causes autism, but for a gene that renders the children susceptible to some environmental factor. Tr. at 791, 853. When both of a twin pair encounter the same factor, they succumb and develop autism.[264] Tr. at 791. Because regressive autism has a timing that is consistent with an environmental "second hit" and such a dramatic change, it requires an explanation, and, in most cases, there is no causal option other than a postnatal environmental insult or exposure. Tr. at 901-02; PML 717 at 9,13. In his report, he indicated that regression and relapse are more understandable if autism is the result of a disease rather than the result of congenital maldevelopment. PML 717 at 14. Although his opinion regarding environmental causes was not limited to cases of regression, he pointed to the sudden onset of regression as implicating a postnatal event. He testified that this concept of gene-environment interaction is generally accepted. Tr. at 791-92.

Respondent's experts proffered more testimony about Dr. Kinsbourne's assertion that genetics could not account for regression than about any of his other points, except the neuroinflammation hypothesis. The evidence was overwhelming that genetics alone can account for regression, as regression is present in a number of entirely genetic conditions, some with striking similarities to autism. A postnatal environmental cause for regression is highly unlikely, but not impossible. The lack of 100% concordance in identical twins indicates that something other than genetics alone affects who develops ASD, but the "something else" is more likely epigenetic influences, rather than a postnatal toxic insult.

(1) Twin Studies and Concordance.

Doctors Rutter, Lord, and Fombonne made many of the same points regarding the concordance rate in ASD. All three noted that even if both monozygotic twins have ASD, there can be huge variability between them in the severity of the affliction. One may be high functioning while the other may be mentally retarded. Tr. at 3264, 3595, 3777.

The autism phenotype is not entirely genetically determined, but differences in twins may be simply the result of random effects in neuronal development. Tr. at 3776-

[264] Doctor Kinsbourne did not account for the converse: if both twins share the same genetic predisposition, but only one has ASD, then the environmental trigger must be something that one twin encounters but the other does not. It is highly unlikely that in cases of ASD, one twin received TCVs but the other did not. Both monozygotic twins would share the genetic susceptibilities to environmental toxins.

77. Other variations between identical twins do not require an external environmental cause. In tuberous sclerosis, an entirely genetic disorder, some individuals have skin abnormalities so subtle that only an expert can detect them. Others have large tubers in the brain that are associated with severe intellectual impairments and epilepsy. Tr. at 3264. Environmental factors do not cause these variations. Tr. at 3265. The genetic contribution in autism is very high, and, overall, genetic factors are more important than non-genetic ones. Tr. at 3279.

(2) Gene Environment Interactions.

Doctor Rutter also disagreed that, as Dr. Kinsbourne stated in his report, "[t]he causal role of gene-environment interaction has become firmly established in the mainstream of autism research and theory" (PML 717 at 9). Tr. at 3279-80. Doctor Rutter commented that there is a distinction between genetic and non genetic factors playing a role in ASD and the term "gene-environment interaction." Tr. at 3280. Doctor Rutter agreed that genetic and non-genetic factors both play a role in autism.

However, he disagreed with the way Dr. Kinsbourne used the term "gene-environment interactions," and with his assertion that their causal role in ASD was firmly established. As Dr. Rutter put it: "that's not only not firmly established; it's not established at all." Tr. at 3280. He conceded that it is a possibility, but one that is entirely speculative with respect to autism. Tr. at 3280. I note that Dr. Rutter has written and lectured about, and chaired high-level governmental committees regarding, gene-environment interaction. *See* Tr. at 3245. Doctor Kinsbourne has not demonstrated any similar expertise.

In his report, Dr. Rutter explained the concept of developmental perturbations. Genetics sets a general pattern for development, but the details may be modified by chance factors. The non genetic factors at work in ASD "may involve random variations brought about by features that increase the risk of developmental perturbations, rather than by some specific environmental insult." Res. Ex. GG at 11. Gene expression can be affected by other genetic elements and environmental influences. Res. Ex. GG at 57.

Respondent's experts agreed that environmental events can influence genetically determined conditions. Tr. at 3277. For example, human height has about the same heritability as autism, about 90%. Tr. at 3278. During the period 1900-1950, the average height rose significantly, by about 12 centimeters. The cause is not certain, but environmental factors such as improved nutrition and reduced infections undoubtedly played a role. Tr. at 3278.

They also agreed that environmental factors play a role in the development of ASD, but asserted that they do so very early in gestation. Tr. at 2575. It is possible that some environmental factors may affect the brain in the very early postnatal period, but the evidence indicates that prenatal effects are more likely. Tr. at 3278. Doctor

Rust explained that the theory that postnatal environmental interactions could interact with genetic predispositions merits examination, but there was insufficient evidence to indicate that it actually happens, other than prenatally, in autism. Tr. at 2575-76. Doctor Rodier testified that there is an outside possibility that a late injury may result in autism, or the behavioral effects that are seen in autism. Tr. at 3051.

(3) Regression in Genetically Determined Conditions.

A great deal of genetic research demonstrates that genes influence developments later in life as much as they influence the beginning of development. Tr. at 3288. Huntington's disease is caused by a single gene, without an environmental contribution, and causes loss of skills in middle age. Tr. at 3288; *see also* Tr. at 2604, 3584. Genetics strongly influences when girls reach menarche, an event that occurs long after birth. Tr. at 3288-89. Schizophrenia has high heritability, with the first manifestations (difficulties with language comprehension and motor coordination) occurring in early childhood. Tr. at 3289. No environmental hazard in early childhood influences these events; they are simply a part of the genetically influenced condition. Tr. at 3290.

Another example that contradicts Dr. Kinsbourne's assertion that an environmental trigger is necessary for regression involves children with congenital nerve deafness. Although they are born deaf, they vocalize normally for about the first six months of life before developing a guttural vocalization pattern characteristic of deaf children. Tr. at 3292. The change in their vocalization patterns at about six months of age is based on when the input of language becomes important to vocalization, and has nothing to do with when the deafness occurred.[265] Tr. at 3292. Brain systems that are necessary for specific functions change over the course of development, and, in this change, skills may be lost or acquired as a result of biological programming. Tr. at 3293.

Doctor Rust spent a considerable portion of his testimony discussing the parallels between Rett's disorder, an entirely genetic condition, and ASD. His testimony helped explain why, despite the lack of 100% concordance in autism, no external triggering event was needed to produce it.

Rett's disorder manifests with regression, which is also present in a substantial minority of children with autism. *See* Tr. at 2399. Rett's disorder produces EEG abnormalities during the first phase of regression; similar abnormalities are seen in some autistic children in the second half of the first year of life. Tr. at 2400. Bruxism[266]

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[265] Doctor Rutter also noted that the sounds babies make the world over are much the same during the first six months of life, but thereafter, the babies lose the ability to make the sounds that are not a part of their native language environment. Tr. at 3293.

[266] Bruxism is teeth grinding. Tr. at 2444.

is almost universal in Rett's disorder, and is commonly seen in autism. Tr. at 2443-44.

The neuropathology of the brain found in Rett's disorder has several similarities to the neuropathology found in ASD: abnormal development of the inferior olivary nucleus in early gestation, likely associated with language disturbances (Tr. at 2409); increased density of neurons, particularly small neurons (Tr. at 2411); less dendritic arborization in selected cortical areas (Tr. at 2411-12); and dysregulated expression of GABA in some with Rett's disorder, leading to seizures, which are common in both disorders (Tr. at 2413).

3. Doctor Greenland's "Clearly Regressive Autism" Hypothesis.

Using Dr. Fombonne's statement in Res. Ex. E, ¶ 121(a), that regression or loss of skills occurs in about 20% of cases of autism,[267] and the findings from the Richler study[268] that in about 72% of cases of regressive autism, some form of abnormal development preceded that regression, Dr. Greenland calculated that the maximum number of cases in which there were no signs of abnormal development prior to the regression was about 6% of all autism cases, and 28% of all regressive cases. Tr. at 78-79, 100. These are the cases to which Dr. Greenland referred when he used the term "clearly regressive autism."

The evidence for regressive autism constituting a separate phenotype was singularly unpersuasive. The evidence for an even smaller subtype of regression, "clearly regressive autism," was non-existent. Doctor Greenland lacked the professional qualifications to opine that autism has distinct "clinically recognizable subtypes with distinct development[al] trajectories and possibly different etiologies." Tr. at 76. Unlike Drs. Fombonne, Rutter, and Goodman, Dr. Greenland is not a medical doctor and his CV does not reflect any education, training, or experience in diagnosing or treating autism. *See* PML 714 (CV of Dr. Greenland). Doctor Greenland is thus not qualified to opine on subtypes of autism or whether subtypes of autism have distinct causes. He acknowledged this lack of expertise himself. Tr. at 111.

Other than Dr. Greenland's assertions, petitioners offered absolutely no evidence that "clearly regressive autism" is considered a separate diagnostic category by anyone

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[267] Estimates of the extent of regression vary widely in the autism literature. *See supra* Section IV.D.6.

[268] Richler, RML 397. Doctor Fombonne noted that Dr. Greenland misinterpreted the premise upon which the 28% figure was based. The authors did not conclude that 28% of children with ASD and regression were entirely normal before they experienced regression, just that no earlier abnormality could be documented. Richler, RML 397, at 306-07. Doctor Fombonne also referred to Dr. Lord's testimony that the proportion of children with regression and evidence of some earlier abnormal development is likely to rise to close to 100% with better and prospective assessments, such as in the baby sibs studies. Tr. at 3689, 3761-62; *see also* Tr. at 3570-71 (testimony of Dr. Lord) and Dwyer Tr. at 257-58 (testimony of Dr. Leventhal).

with expertise in diagnosing autism. The medical literature does not use the term. Tr. at 3684. Doctor Greenland was unable to present any evidence indicating that regressive autism is biologically distinct from nonregressive autism. Tr. at 126-27.

4. Conclusions Regarding Regression.

Most of Dr. Kinsbourne's assertions about regressive autism were simply wrong. He failed to demonstrate that regression is a separate phenotype. In Dr. Rust's words, his assertion that regressive and classic autism are different conditions is an artificial one. Tr. at 2467. There are a very small number of children with apparently normal development who suffer "sudden and even shocking" regression in their second year of life. Aside from this regression, which is not unique to autism, there is nothing else that sets them apart from children whose regression manifests more slowly or who have sudden regression after some slow or abnormal development. *See* Tr. at 3570-71.

His assertion that regression is caused by a disease process rather than genetics does not follow logically from what is known about regression in other conditions. Tr. at 3313. Brain development in human infants occurs in phases. At each phase of brain development, genetic signals turn on processes that result in elaborations, development, and eliminations of brain structures. *See* Tr. at 2403. These changes in the brain result in behavioral changes as well. The evidence establishes that whatever sets the development of the brain of an autistic child apart from a typically developing peer likely occurs early in gestation. On a theoretical basis, some changes might be postnatally influenced, but the evidence for such postnatal events is scant. Even when disease processes such as herpes encephalitis postnatally induce autistic-like symptoms, the behaviors induced are similar to, but qualitatively different from, those seen in most children with autism.

Regressive autism cannot be distinguished biologically from other forms of ASD. Tr. 3105-07, 3113-14. There is no evidence of any brain abnormality that sets those with regression apart from those with classic or early onset ASD.

With regard to "clearly regressive autism," it was petitioners' burden to demonstrate its existence as a separate phenotype. I find that petitioners failed to do so. Because the facts that formed the basis for his opinion were not satisfactorily established, Dr. Greenland's opinion that the existing studies cannot rule out a substantial causal role for TCVs in one form of autism is not relevant or persuasive.[269]

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[269] *See Proveris Scientific Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1268 (Fed. Cir. 2008); *Nimely v. City of New York*, 414 F.3d 381, 399 n.13 (2d Cir. 2005) ("[I]t is worth emphasizing that, because a witness qualifies as an expert with respect to certain matters or areas of knowledge, it by no means follows that he or she is qualified to express expert opinions as to other fields."). Doctor Greenland is a qualified expert on epidemiology, but he lacked the qualifications to opine on the existence of "clearly regressive autism." In the absence of evidence that the condition exists, opinions from someone unqualified to opine on its existence are neither relevant nor reliable.

What follows in Section V is the epidemiological evidence that strongly suggests that TCVs are unlikely to be a postnatal cause of ASDs in general. Thereafter, the evidence upon which petitioners rely for their assertions that postnatal environmental exposure to mercury in the form of TCVs causes or substantially contributes to ASD is set forth and critiqued in Sections VI, VII, and VIII.

Section V. Epidemiology.

A. Introduction.

Petitioners began their case with the testimony of their epidemiologist, Dr. Greenland. Doctor Greenland's testimony was a pre-emptive strike in an attempt to render irrelevant the many studies that had failed to detect any relationship between TCVs and ASD. In addition to offering criticisms of many of these studies, Dr. Greenland attempted to carve out a hypothetical phenotype of autism, which he called "clearly regressive autism," and asserted that the epidemiological studies introduced as evidence would be unable to detect an association between TCVs and this small subgroup. Respondent's experts agreed that, in theory, a small subgroup could have escaped detection by the epidemiological studies performed. However, they disagreed that there was any evidence that a subgroup such as the one hypothesized by Dr. Greenland actually existed. Because I have concluded that petitioners failed to establish the underlying premise for Dr. Greenland's opinion, I find that the published epidemiological studies are highly informative, albeit not dispositive, of the general causation issue before me. Doctor Greenland's criticisms of individual studies are generally well-taken, and I have considered his criticisms in determining what weight to give the epidemiological studies on the issue of general causation.

To place the expert opinions on epidemiology in perspective, I begin with a brief overview of the science of epidemiology. An explication of the different types of epidemiological studies, along with their inherent strengths and weaknesses, follows. I then discuss some of the many studies of TCVs and ASD filed as evidence.

In addition to petitioners' expert Dr. Greenland, three experts in epidemiology, Drs. Goodman, Fombonne, and Rutter, testified for respondent. All were well-qualified as experts. The witnesses were in general agreement about epidemiology's strengths and weaknesses, including most issues related to specific studies.[270] Unlike Dr. Greenland, Drs. Fombonne, Goodman, and Rutter are physicians. Additionally, Drs. Fombonne and Rutter have conducted a number of epidemiological studies of ASD, and they both diagnose and treat children with ASD. Thus, their opinions on the ASD epidemiological studies were generally better informed than those of Dr. Greenland.

[270] Where there was disagreement, it largely concerned the factual underpinnings of Dr. Greenland's opinion about a "clearly regressive autism" subgroup.

B. Epidemiology as a Scientific Discipline.

Epidemiology is the science that studies the patterns or distributions of diseases in human populations and attempts to identify risk factors for those diseases. Tr. at 3088-89, 3625. Epidemiology undergirds virtually all of what we know about medicine. Tr. at 3089; *see also Hodges v. Sec'y, HHS*, 9 F.3d 958, 967 (Fed. Cir. 1993) (Newman, J., dissenting).

Observational epidemiology focuses on patterns of diseases in discrete groups, and attempts to determine if differences in disease rates are due to differences in exposures. Tr. at 3089-90. Thus, it is the observational studies that have relevance to the general causation issue in this case: whether TCVs cause some types of ASD.

1. Selection Bias and Confounders.[271]

Every observational epidemiological study has some weaknesses because such studies examine the world as it is. Tr. at 3089. Common weaknesses in observational studies include selection biases in the groups observed[272] and the failure to account for confounding factors.[273] In interpreting results from observational studies, epidemiologists must determine if the differences in outcome are due to differences in exposure, or to something about the individuals that determines or is linked to the exposure. Tr. at 3090.

Whether something is a potential confounder depends on what is being studied. If, in a particular study of smoking, all the tall people in the study were smokers and all the short people were nonsmokers, height could be a confounding factor. Tr. at 3090. However, if the outcome being examined by the smoking study is lung disease, height may be an unlikely confounder, at least in the absence of some reasonable explanation about why height might affect rates of lung disease. Tr. at 3090.

2. Statistical Analysis and Biological Plausibility.

Epidemiology is not entirely about statistics; it is also about the biology of what is being studied. The factors studied must be relevant to the disease. Tr. at 3091. When

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[271] A confounder is a variable that is not a cause of the condition being studied, but is associated with the causal factor and outcome, and therefore creates a misleading impression of causality. Tr. at 3298.

[272] In examining ASD rates in an unvaccinated group versus a vaccinated group, selection bias in how the two groups are chosen may affect the outcome. A study must address the possibility that lifestyle factors might affect which children are vaccinated and when or if the vaccinations occur.

[273] Confounding factors might involve birth weight, multiple births, maternal age, maternal education, medications used during pregnancy, and many others, and results must be analyzed to determine if such factors account for any differences observed between the two groups.

unexpected findings occur, the underlying biology helps to determine which are spurious and which are not. Tr. at 3092.

To illustrate this principle and the problem with subgroups, Dr. Goodman used an example of a study of a drug used to treat cardiac problems that reduced mortality by 30% in the group that received it. To demonstrate the problem with subgroups, one of the study's authors used astrological signs of the patients to assign them to subgroups.[274] Those in the treated group born under the signs of Gemini or Libra had an adverse effect from aspirin. Because there was no biological reason for Zodiac signs to affect drug reactions, the subgroup effect detected was meaningless.[275] Unless subgroups are selected using scientific criteria, grounded in legitimate biological distinctions, a subgroup effect, such as the adverse response of Geminis and Libras to aspirin, is simply an anomaly. Res. Ex. G, Report of Dr. Goodman, at 5.

3. Effect of Multiple Studies.

Although biases exist in each epidemiological study, their effects can be minimized by multiple studies done in different ways, in different populations, using different measurements. If the multiple studies come to a similar conclusion about a particular risk factor, the likelihood that biases affected the conclusion is considerably reduced. Tr. at 3091.

4. Statistical Significance.

To make a causal inference between an exposure and an outcome, an

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[274] The study was identified in Dr. Goodman's report (Res. Ex. G at 5) and testimony (Tr. at 3111) as the Peto study. Two studies involving drug trials in heart disease were filed: (1) First International Study of Infarct Survival Collaborative Group, *Randomised Trial of Intravenous Atenolol Among 16,027 Cases of Suspected Acute Myocardial Infarction,* LANCET 2(8498): 57-66 (1986) ["ISIS-1"], filed as RML 258; and (2) Second International Study of Infarct Survival Collaborative Group, *Randomised Trial of Intravenous Streptokinase, Oral Aspirin, Both, or Neither Among 17,187 Cases of Suspected Acute Myocardial Infarction*, LANCET 2(8607): 349-60 (1988) ["ISIS-2"], filed as RML 259. The "Zodiac sign" subgroup analysis occurs at page 356 of RML 259, and precedes a discussion of subgroup effects. This discussion emphasized the need for biological plausibility and other evidence before giving credence to subgroup differences, noting: "'Lack of evidence of benefit' just in one particular subgroup is not good 'evidence of lack of benefit.'" ISIS-2, RML 259, at 356-57. Although Dr. Goodman's report discussed a beneficial effect on "Leos," I could not find that discussion in the article itself. However, the discussion of the Zodiac sign subgroups of Libras and Geminis makes the same point.

[275] Doctor Greenland castigated Dr. Goodman's use of this example, and suggested that Dr. Goodman could not defend its use in a meeting of his peers. Tr. at 105-06. Either Dr. Greenland was being disingenuous or he failed to understand the purpose for which the study was referenced. Doctor Goodman was not equating possible autism phenotypes to astrological signs; he was illustrating a fundamental principle of epidemiology: there must be biological plausibility to make a finding credible. Tr. at 3111-12. The epidemiological principle of biological plausibility parallels the legal principle found in the first *Althen* factor: a theory must be biologically plausible and reliable. *See Althen*, 418 F.3d at 1281.

epidemiologist must find a relationship that is beyond what might be found by chance alone. Epidemiologists refer to this concept as "statistical significance." In performing an epidemiological study, a "p-value" (the probability of getting, by chance alone, a statistic as large or larger than the observed value) is computed. If a p-value is smaller than 5%, the result is generally considered statistically significant. Federal Judicial Center, Reference Manual on Scientific Evidence (2d ed. 2000) at 168. Lack of statistical significance does not mean that no association exists; it means that no association was detected. Tr. at 83-84.

Any relationship found to be statistically significant should not violate biological or physical rules and, ideally, should have a coherent biological explanation. Tr. at 3092-93. If the relationship found is weak, the corresponding biological explanation must be much stronger in order to draw a causal connection. Tr. at 3093.

5. Risk Ratios and Confidence Intervals.

Risk ratios are computed by comparing the risk of exposure in two groups, one exposed to the factor under study and the second unexposed. If the risk ratio is one, the incidence of disease is unaffected by the exposure under study. Tr. at 3626-27. A risk ratio of two or more would indicate that exposure is a probable cause of the disease. Tr. at 3627. A risk ratio under one indicates a protective effect. Tr. at 3362.

A "confidence interval," expressed as a range, is the margin for error in a computed result, such as a risk ratio. Estimates of a 95% confidence interval means there is a 95% likelihood that the true risk is between the numbers comprising the range. Narrow confidence intervals mean that the risk ratio is more likely to be accurate; wide confidence intervals indicate a greater margin for error. If a risk ratio of 1 (no association) is reported, but the 95% confidence interval is between 0.5 and 2.0, the actual risk ratio could extend to 0.5 or 2.0. Tr. at 83-85. A wide confidence interval means that many other outcomes are within the same range of possibility. Chance alone could have produced an observed risk ratio of 1.0, even if the true risk were as low as 0.5 or as high as 2.0. Tr. at 85-86.

C. Types of Epidemiological Studies.

The type of study performed affects the significance that may be attached to it and whether conclusions regarding causality may be drawn. The evidence included

cohort studies,[276] case-control studies,[277] prevalence and incidence studies,[278] and ecological studies.[279]

In observational epidemiology, the cohort study is one of the strongest study designs because it does not involve retrospective reports of exposures, a factor that affects case control studies. Tr. at 3625. The critical factor in a case-control study is selecting the controls to ensure that they mirror the case group in any factor that might affect outcome, other than in the exposure under study. Tr. at 3628.

A prevalence study first determines the magnitude of the problem disease, and may then, depending on the study design, look at risk factors. Tr. at 3628-29. Doctor Fombonne described prevalence as a snapshot, documenting the extent of a condition at a particular time. Tr. at 3813. If, in a sample of 100 people, five have blue eyes, those with blue eyes are the numerator and the total population is the denominator, making the prevalence rate (or proportion) of blue eyes 5%. Tr. at 3814. If, however, 100 children are followed from birth to age 10, the number with the studied condition are counted at age 10. If 15 of the children have the disease at age 10, the incidence rate is 15%. Although this computation looks like a prevalence rate, it is subject to change over time and, if measured at additional five-year intervals, the incidence rate would likely rise. *See* Tr. at 3814-15.

Ecological studies often begin with a hypothesis. If the trend lines are similar for the outcome and the proposed cause, further study is warranted, but an ecological study cannot determine if one event is caused by another. Interpreting two similar trend lines in causal terms is called the "ecological fallacy." Tr. at 3630-31. In Dr. Fombonne's example, illustrated on Res. Tr. Ex. 12, slide 3, similar trend lines are

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[276] In a cohort study, one group is exposed to the particular risk factor under study, and a second group, known as the control group, is not exposed. The two groups are followed over time to determine how many in each group develop new cases of disease, the incidence of which is compared in risk ratios. Tr. at 3626-27.

[277] A case-control study involves a group of people with the condition (the case group) and a similarly situated group of people without the condition (the control group), and examines, retrospectively, their exposures to possible risk factors. If more of the case group has a particular exposure than the control group, that risk factor can be identified as a possible or even a probable cause of the condition. Tr. at 3627-28.

[278] A prevalence rate is the proportion of a population that has a particular disease or condition at a given point in time. Tr. at 3634. In contrast, an incidence rate involves observations, made over time, in an at-risk population, with new onset of disease measured in the population at calculated intervals. Tr. at 3634-35.

[279] Ecological studies use aggregate data to look at disease trends over time to find risk factors that may correlate with the disease. They are sometimes called time trend analyses. Tr. at 3630. Drawing causal inferences from an ecological study is problematic, because populations are examined in the aggregate, rather than examining diseases and risk factors person by person. Tr. at 3629-30.

found for suicide rates and unemployment rates. Attributing suicide to unemployment would be an ecological fallacy in the absence of data showing that the individuals who committed suicide were more likely to be unemployed. The population level data must be analyzed at the individual level in order to make a causal association. *See* Tr. at 3631.

When the rates for two trend lines fluctuate in a similar fashion, a causal connection between the two events is more likely; if they do not similarly fluctuate, a causal connection is unlikely. Tr. at 3633; Res. Tr. Ex. 12, slide 4. In essence, an ecological study can rule out a causal association in the aggregate, but cannot serve as evidence of causation.

Ecological studies are not considered adequate substitutes for controlled studies. They are unable to reliably distinguish a small association from no association. Tr. at 92. Ecological studies are more subject to bias than controlled studies, and thus their conclusions are not entitled to as much weight as controlled studies. Tr. at 3126.

A meta-analysis involves aggregating the data from two or more studies, providing a larger studied population and thus narrowing confidence intervals and increasing the power of the analysis to detect causal associations. The combined estimate of risk is almost always more precise than the estimate of risk from any single study. Tr. at 3108.

D. Epidemiological Studies of TCVs and Autism.

Epidemiology is particularly relevant to the relationship of TCVs with ASD because epidemiology is the only science that looks specifically at humans exposed to thimerosal and an outcome involving autism to determine if there is a higher risk of autism based on such exposure. Tr. at 3094. Doctor Fombonne testified about ten separate studies of a possible relationship between TCVs and ASD, with none detecting any relationship. Tr. at 3635-59. Doctor Goodman discussed how the Institute of Medicine used the studies published between 2001 and 2004 to conclude that the "evidence favors rejection" of the hypothesis that TCVs cause autism. Tr. at 3085. In Dr. Greenland's words, the epidemiological studies can be summarized as "support[ing] the idea that the association of [mercury-containing vaccines] with autism is small or nonexistent." PML 715, at 16; Tr. at 122.

1. Hviid Study,[280] PML 238.

This very large 2003 cohort study examined all children born in Denmark

[280] A. Hviid, et al., *Association Between Thimerosal-Containing Vaccine and Autism*, JAMA 290(13): 1763-66 (2003) ["Hviid"], filed as PML 238.

between 1990 and 1996.[281] Because thimerosal was not used in Danish vaccines after 1992, it was possible to examine retrospectively children who had received TCVs and to compare them to children who had not. Tr. at 3638-39. Children who had received no TCVs were compared to those who had received at least one TCV. The incidence of ASD was the same in both groups, with a risk ratio of 0.85, with a 95% confidence interval ["CI"] of 0.6 and 1.2. Tr. at 88, 3640.

The study also looked at dose response to determine if ASD diagnoses were higher in those who received more TCVs. There was no evidence of any increase in diagnoses at any level of exposure. Those who received the highest amount of mercury in TCVs had a risk ratio of 0.96, with a CI of 0.63-1.47. Tr. at 88; 3640.

Although Dr. Greenland criticized this study (Tr. at 88-89) because the thimerosal levels were lower in Denmark than in the U.S.,[282] the thimerosal exposure levels in U.S. and Danish children were comparable at three months of age. At the highest dosage levels (125 micrograms of mercury ["µg"]), there was no observed effect from TCVs on ASD rates. Tr. at 3640-41. Although the study does not directly address the U.S. levels of thimerosal exposure, a strength of the study is that the unexposed group was not self-selected, removing one possible source of bias. *See* Tr. at 3641-42. The removal of thimerosal from Danish vaccines was based on a change in the vaccine manufacturing process, and thus the unexposed group was not self-selected. Tr. at 3642.

2. Verstraeten Study,[283] PML 247.

This cohort study used the Vaccine Safety Datalink ["VSD"] database[284] retrospectively to create cohorts of children. The cohorts were examined for exposure

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[281] The Danish national registry, which contains health data on the entire population of Denmark, includes both immunization status and diagnosis codes.

[282] In view of the position of petitioners' causation experts that they could not determine how much mercury would be enough to tip a genetically susceptible child over the threshold into autism, Dr. Greenland's criticism carries less weight than it might otherwise. *See* Tr. at 622-28 (Dr. Deth's testimony); 859-60 (Dr. Kinsbourne's testimony). Doctor Aposhian posited a hypersusceptible group of children, but was likewise unwilling to say how much mercury might be enough to cause ASD. Tr. at 369-70.

[283] T. Verstraeten, et al., *Safety of Thimerosal-Containing Vaccines: A Two-Phased Study of Computerized Health Maintenance Organization Databases*, PEDIATRICS 112(5): 1039-48 (2003) ["Verstraeten"], filed as PML 247.

[284] The VSD database was created in 1991 by the CDC to link medical events, vaccine history (by manufacturer and lot number), and demographic information from several health maintenance organizations, providing a method for monitoring vaccine safety issues. Verstraeten, PML 247, at 1040.

to TCVs from birth to seven months of age[285] and for ASD diagnoses. The study found no association of TCV exposure with ASD diagnoses. Tr. at 3642-45; Res. Tr. Ex. 12, slide 10.

Doctor Greenland noted that the confidence intervals in this study were wide, from 0.62 to 1.46, and at the highest category of exposure from 0.55 to 3.48. He also pointed out that Dr. Verstraeten stated that an association between TCVs and ASD could neither be confirmed nor refuted by this study,[286] and that Dr. Verstraeten recommended more study of the issue.[287] Tr. at 90.

According to Dr. Rutter, "[t]he Verstraeten study is in many ways the most satisfactory of the studies...." Tr. at 3301-02. For that reason, he looked very carefully for problems that might invalidate the findings. He found several strengths: a large sample, a standard methodology, and thorough and appropriate analysis. It found no association between thimerosal and autism. Tr. at 3302. Doctor Rutter was aware that the preliminary findings may have been different from the final ones. He noted that such discordance is usual when "dealing with multivariate analyses of complex data sets...."[288] Tr. at 3302. Doctor Rutter was also critical of Dr. Verstraeten's failure to declare his pending employment with a pharmaceutical company at the time the study was published, but noted that he did so shortly afterwards. Tr. at 3303. Having looked very carefully at these issues, Dr. Rutter nevertheless rated the Verstraeten study as

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[285] The seven month cut-off would measure cumulative exposure at ages when exposure to thimerosal would be the highest relative to body weight. Verstraeten, PML 247, at 1040. Additionally, the childhood vaccination schedule reflects that most TCVs were administered by seven months of age. Verstraeten, PML 247, at Table 1; *See* CDC, Past Childhood Immunization Schedules, http://www.cdc.gov/vaccines/recs/schedules/child-schedule.htm#past ["CDC Childhood Immunization Schedules"] (providing links to the Recommended Immunization Schedules for Persons Aged 0 Through 18 Years - - United States for each year beginning in 1995). No vaccines are scheduled between the six and 12 month vaccinations. As 12 months of age is considered the first point at which ASD can be reliably diagnosed (*see* Section IV.B.4.), the vaccines most likely to be implicated as causal are those administered in the first six to seven months of life.

[286] T. Verstraeten, *Thimerosal, The Centers for Disease Control and Prevention, and GlaxoSmithKline*, PEDIATRICS 113(4): 932 (2004) (letter to the editor), filed as PML 19. Doctor Greenland's testimony accurately summarized Dr. Verstraeten's position regarding the study.

[287] Doctor Rutter testified that these additional studies recommended by Dr. Verstraeten had been performed and all failed to show a connection. Tr. at 3380.

[288] In 2005, Special Master Hastings granted a PSC discovery request (*see* Discovery Order, OAP Master File, filed April 14, 2005) that Dr. Harlan Austin and Ms. Cathy Lally be permitted access to the Verstraeten study data in order to resolve some apparent discrepancies between the findings appearing in the published manuscript and the findings in an earlier unpublished report. PSC Expert Reanalysis of the Thimerosal Screening Analysis ["OAP Ex. 91"], OAP Master File, filed December 13, 2006, at 4. Doctor Rutter noted that Dr. Austin and Ms. Lally came to the same conclusion as the Verstraeten researchers in their reanalysis of the data. Tr. at 3302; *see also* OAP Ex. 91 at 5 ("[W]e generally believe that the methodology employed by the CDC investigators was sound and that their findings are valid.").

sound. Tr. at 3303.

3. Stehr-Green Study,[289] PML 230.

This ecological study examined trend lines between ASD diagnoses and levels of thimerosal in vaccines. Using data from California, where the amount of thimerosal increased during the time frame studied, and two Scandinavian countries, where the use of thimerosal in vaccines was discontinued in the early 1990s, the authors plotted the amount of thimerosal in birth year cohorts against the incidence of ASD in children ranging from two to ten years of age. The rate of increase in ASD in Scandinavia continued after the removal of thimerosal from vaccines. Tr. at 3305, 3646-47; Res. Ex. 12, slide 11. The authors concluded that the data were "not consistent with the hypothesis that increased exposure to Thimerosal-containing vaccines [is] responsible for the apparent increases in the rates of autism in young children being observed worldwide." Stehr-Green, PML 230, at 106.

In epidemiology, what happens when a particular risk factor is introduced into one population and not another, or when a risk factor is removed in one population but not another, is particularly important. According to Dr. Rutter, the Stehr-Green results make it "really rather unlikely that thimerosal played a role in the overall rate of autism." Tr. at 3305.

4. Madsen Study,[290] PML 239.

This 2003 ecological study examined the rate of autism[291] in Denmark from 1971-2000. Before 1970, children in Denmark were exposed to up to 200 µg of thimerosal, amounts comparable to U.S. exposure in the late 1990s. Tr. at 3648. Rates of ASD diagnoses from 1970 through about 1982 were essentially flat, but began gradually to climb in 1984, and climbed rapidly after about 1992. *See* Res. Tr. Ex. 12, slide 12. Although thimerosal was discontinued in vaccines in 1992 in Denmark, the trend line continued to climb after its removal. If there were an effect of TCVs on autism rates, the complete discontinuance of TCVs would have produced a change in the rate of autism, and none was observed. Tr. at 3648-50.

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[289] P. Stehr-Green, et al., *Autism and Thimerosal-Containing Vaccines*, AM. J. PREV. MED. 25(2): 101-06 (2003) ["Stehr-Green"], filed as PML 230.

[290] K. Madsen, et al., *Thimerosal and the Occurrence of Autism: Negative Ecological Evidence From Danish Population-Based Data*, PEDIATRICS 112(3): 604-06 (2003) ["Madsen"], filed as PML 239.

[291] Because the study used the ICD-10 codes for autism, 84.0 and 84.1, the prevalence rates did not include cases of PDD-NOS. Tr. at 3745-46. Although the prevalence rates found undoubtedly reflected an underestimation of the actual prevalence of ASD in Denmark, Dr. Fombonne was confident than an effect in the reduction of the amount of thimerosal received would have resulted in a change in the trend line if TCVs caused even a small number of cases of ASD. Tr. at 3745-46.

5. Andrews Study,[292] PML 4.

This large 2004 cohort study from the U.K. was performed using a computerized database maintained by general practice physicians in the U.K. It compared TCV exposure and autism rates, finding a relative risk below one, with narrow confidence intervals of 0.88 to 1.12. Tr. at 89, 3651-52. No effect from TCV exposure was observed, even in those exposed at earlier ages when the dose per kilogram of body weight would be higher. Tr. at 3652. This study looked separately at preterm infants, who would have lower body weights at the time of vaccination, with similar negative results. Tr. at 89, 3651-52.

The 75 µg exposure level was similar to that of U.S. infants at four months of age, but U.S. infants would have received more TCVs later in infancy, for more than double the thimerosal exposure. *See* Tr. at 89, 3652; Res. Tr. Ex. 12, slide 13. However, finding no effect at levels up to 75 µg exposure during the earliest, and presumably most vulnerable, periods of development suggests that this level of exposure does not cause ASD. The finding weakens any argument that even small amounts of thimerosal may causally affect the development of ASD.

6. Jick and Kaye Study,[293] PML 92.

Although both Drs. Greenland and Fombonne testified about this study, I have not relied upon it. The results were reported in a letter to the editor, rather than in a peer reviewed article, and the study was performed by researchers who reported serving as consultants to a law firm representing vaccine manufacturers involved in vaccine safety litigation. Therefore, I have accorded this particular study no weight.

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[292] 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): 584-91 (2004) ["Andrews"], filed as PML 4.

[293] H. Jick & J. Kaye, *Autism and DPT Vaccination in the United Kingdom*, N. ENGL. J. MED. 350(26): 2722-23 (2004) ["Jick and Kaye"], filed as PML 92. Similar to the Andrews study in using the U.K. general practice database, the Jick and Kaye study was a case-control, rather than a cohort, study. The authors identified 122 cases of autism, and matched the children to 587 controls, based on age, sex, and treating physicians. The sample size was relatively small, which resulted in fairly wide confidence intervals (0.7-3.3), but no association between TCV exposure and autism diagnoses was observed. Tr. at 90, 3652-53; Res. Tr. Ex. 12, slide 14. As in the Andrews study, the exposed children received lower levels of TCVs than their U.S. counterparts. Tr. at 90.

7. Heron Study,[294] PML 14.

This prospective cohort study of 13,000 women and their children did not directly measure autism rates. Instead, the study examined special educational needs and thimerosal exposure. Tr. at 3654-55. The study adjusted for a number of confounding variables, including fish consumption, and found no relationship between thimerosal exposure and 68 of 69 measured outcomes, with the authors noting that the one positive correlation would be expected by chance alone. Tr. at 3654-55; Heron, PML 14, at 580. Because the study did not separately measure ASD diagnoses and was also based in the U.K., where TCV exposure was lower, the study is less informative than others on the issue of TCV causation of ASDs. Tr. at 89-90. However, the study strongly suggests that TCV exposure is unlikely to produce neurological effects in general. Tr. at 3301.

8. Fombonne 2006 Study,[295] PML 40.

Doctor Fombonne also discussed one of his own recent studies, an ecological study in Quebec of varying levels of thimerosal exposure (which were similar to U.S. levels at their highest) and ASD trends. He found a higher prevalence of ASD after discontinuation of TCVs. Tr. at 3656-57. The study was small, and did not adjust for confounding variables, but was able to examine several different exposure levels, based on changes in vaccines. Tr. at 3655-57. No relationship between TCV exposure and ASD trend lines was observed. Tr. at 3656. The cohort that received entirely TCV-free vaccines had a significantly higher prevalence of ASD diagnoses, 80.6 per 10,000, than did any of the TCV-exposed cohorts. Tr. at 3656-57.

Doctor Greenland correctly noted that Dr. Fombonne looked broadly at PDD diagnoses, rather than focusing on autism alone, and that, as an ecological analysis, the study design did not require a determination that children in the group purportedly exposed to thimerosal were actually vaccinated. Tr. at 93-94.

9. Schechter and Grether,[296] RML 439.

This 2008 ecological study examined a database unique to California to

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[294] J. Heron & J. Golding, *Thimerosal Exposure in Infants and Developmental Disorders: A Prospective Cohort Study in the United Kingdom Does Not Support a Causal Association*, PEDIATRICS 114(3): 577-83 (2004) ["Heron"], filed as PML 14.

[295] E. Fombonne, et al., *Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links with Immunizations*, PEDIATRICS 118(1): e139-50 (2006) ["Fombonne 2006"], filed as PML 40.

[296] R. Schechter & J. Grether, *Continuing Increases in Autism Reported to California's Developmental Services System*, ARCH. GEN. PSYCHIATRY 65(1): 19-24 (2008) ["Schechter and Grether"], filed as RML 439.

determine ASD rates before and after the removal of thimerosal from vaccines. Although thimerosal was removed from vaccines produced in 2001, the shelf life of vaccines meant that some children still received TCVs until 2003 and trace amounts in vaccines thereafter. Tr. at 3657-58. Thus, although exact amounts of thimerosal exposure were difficult to ascertain during the period from 2000-2003, rates of exposure certainly declined from the beginning to the end of that period. If TCVs contributed to ASD rates, a decline in ASD rates beginning in 2004 or 2005 would be expected, because children diagnosed then would have been exposed to lower[297] or only trace amounts of thimerosal. Tr. at 3658. No decline was noted between the end of 2003 and the beginning of 2007. Tr. at 3658-59. I note that Dr. Deth commented that this study was "troubling" for his hypothesis of TCV causation. Tr. at 616-17.

On cross-examination, Dr. Fombonne conceded that the prevalence rates in the earlier years of this study were almost certainly underestimates, but he nevertheless believed the study accurately illustrated the lack of impact on prevalence rates from the removal of TCVs. Tr. at 3739-40. A strong effect of thimerosal would have resulted in a changed trend line, and no effect was observed. Tr. at 3741-42.

10. Thompson study,[298] PML 192.

This 2007 CDC cohort study did not look specifically at ASDs, but it examined neurodevelopmental outcomes, based on the level of thimerosal exposure by seven months of age. Tr. at 3659-60. The study included direct assessment of the children by psychologists blinded as to vaccine or thimerosal exposure. Tr. at 3660. Prenatal exposure, including the mother's vaccinations, receipt of immunoglobulin (which contained thimerosal preservatives), number of dental amalgams, and diet, as well as postnatal exposure of the child to TCVs were measured. Thompson, PML 192, at 1283. Like the Heron study in the U.K., Thompson found no evidence of a thimerosal effect on neurodevelopmental outcomes. Tr. at 3661.

E. Additional Analysis of the Epidemiological Studies.

1. Analysis of Epidemiological Evidence Showing No TCV-ASD Relationship.

Doctor Fombonne properly conceded the limitations of each of the epidemiological studies showing no relationship between TCVs and ASD or neurological difficulties. Tr. at 3661-62. He noted, however, that with the exception of the Young study, discussed below, none showed any increased risk of ASD associated with TCVs.

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[297] Influenza vaccine recommended for administration to children are available in single dose vials (without thimerosal) and multi-dose vials (with thimerosal). IOM, IMMUNIZATION SAFETY REVIEW: VACCINES AND AUTISM 55-62, 65 (2004) ["IOM 2004 Report"], filed as RML 255

[298] W. Thompson, et al., *Early Thimerosal Exposure and Neuropsychological Outcomes at 7 to 10 Years*, N. ENG. J. MED. 357(13): 1281-92 (2007) ["Thompson"], filed as PML 192.

All of the studies showed a risk ratio close to one, with most of the risk ratios falling below one, suggesting a protective effect. Tr. at 3662. Because there is no biologically plausible reason for TCVs to have a protective effect, the studies showing risk ratios below one are interpreted as being inconsistent with TCVs causing ASD. *See* Tr. at 3101-02. The results are consistent across different populations in studies with different designs. Tr. at 3662. These factors, taken together, make the findings of no relationship between TCVs and ASD robust, and favor rejection of any causal hypothesis. Tr. at 3662.

Doctor Rutter commented on the time-trend and ecological studies, noting that they have "manifest strengths" in that they were based on very large numbers, but they have important limitations, the most significant of which is that they are studies of populations, not individuals. Tr. at 3304.

2. Analysis of the Young Study,[299] PML 665.

The only studies demonstrating a relationship between TCVs and ASD are those in which Dr. and Mr. Geier appear as co-authors, including the Young study published in May, 2008, and funded by the OAP PSC. Tr. at 3665; Young, PML 665, at 117. Because petitioners' own expert commented that the Geier studies were not reliable as evidence (Tr. at 122-23) and they were thus not addressed by respondent's experts, I do not discuss the earlier Geier studies any further. In view of the numerous criticisms of the earlier Geier studies[300] and petitioners' own expert's dismissal of them, I have placed no reliance on them.

The Young study was an ecological analysis using the VSD database. Tr. at 3665. Doctor Greenland did not comment on this study during his testimony, as the

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[299] H. Young, et al., *Thimerosal exposure in infants and neurodevelopmental disorders: An assessment of computerized medical records in the Vaccine Safety Datalink*, J. NEUROLOGIC. SCI. (electronic publication with no further citation provided) (2008) ["Young"], filed as PML 665.

[300] *See* IOM 2004 Report, RML 255, at 55-62 (calling their work uninterpretable and noncontributory). A number of judges have had similar concerns about Dr. Geier's work. *See, e.g.*, *Graham v. Wyeth Labs.*, 906 F.2d 1399, 1418 (10th Cir. 1990) (Dr. Geier's calculation error was of sufficient magnitude so as to warrant a new trial); *Redfoot v. B.F. Ascher & Co.*, No. 05-2045, 2007 WL 1593239, at *11 (N.D. Cal. June 1, 2007) (excluding Dr. Geier as an expert, finding his testimony "not reliable"); *Doe v. Ortho-Clinical Diagnostics, Inc.*, 440 F. Supp. 2d 465, 474 (M.D.N.C. 2006) (excluding Dr. Geier's testimony as based on "hypothesis and speculation"); *Jones v. Lederle Labs.*, 785 F. Supp. 1123, 1126 (E.D.N.Y. 1992) ("the court was unimpressed with the qualifications, veracity, and bona fides" of Dr. Geier); *Militrano v. Lederle Labs.*, 3 Misc. 3d 523, 537-38 (N.Y. Sup.Ct. 2003) (characterizing Dr. Geier's affidavit as "conclusory and scattershot" and "undermined by many of the materials submitted in support of it"). *See also* S. Parker, et al., *Thimerosal-Containing Vaccines and Autism Spectrum Disorder: A Critical Review of Published Original Data*, PEDIATRICS 114(3): 793-804 (2004) ["Parker"], filed as RML 368.

article was introduced after his appearance and excusal.[301] The study found an increased risk of ASD, based on increasing exposure to TCVs.

Doctor Fombonne offered several criticisms of this study.[302] In a critique common to many of the studies performed by Dr. and Mr. Geier,[303] Dr. Fombonne commented that the Young article did not provide the data that would allow others to verify the calculations performed. Tr. at 3666.

Doctor Fombonne reproduced one chart from the article on Slide 20 of Res. Tr. Ex. 12. Using the chart, he explained that the birth cohorts used in the study did not all contain the same number of individuals, with most representing 40,000 children. Tr. at 3666-67. One birth cohort, that of children born in 1990, contains only 2,000 children. Tr. at 3667. When this "outlier" is removed, the purported statistical relationship between ASD and TCVs during the first four years of the sample disappears. Tr. at 3667.

Doctor Fombonne was also highly critical of the authors' addition of invented numbers to the 1995 and 1996 data from the VSD.[304] Tr. at 3667-68. If the adjustments are removed, there is no correlation at all between the increase in thimerosal exposure and increase in autism cases per 10,000. Tr. at 3668. Doctor Fombonne commented: "It's dishonest to impute like 45 new cases which are just invented to top up the prevalence in a way which is supportive of their hypothesis. It's clear that these investigators have a clear track record to do with the data that supports their hypothesis. And I've seen that in their previous papers." Tr. at 3757-58.

Doctor Rutter offered similar criticisms of the Young study, PML 665, calling it "a poor study for several different reasons." Tr. at 3387. It began with a cohort design, but ended up being analyzed as a time trend study. That required the authors to make

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[301] The Young study did not appear on the master list of petitioners' medical and scientific journals filed as exhibits on May 5, 2008, although the final version of the PML notes that it was published electronically on May 1, 2008. As it was funded by the PSC, it is unlikely that petitioners' counsel were unaware of its publication. It was not provided to the special masters during the general causation hearing until after Dr. Greenland testified, and was finally filed as PML 665 on August 4, 2008. This timing precluded any comment by Dr. Greenland on the study.

[302] In response to some of the criticisms by Dr. Fombonne, Dr. Young provided a letter explaining restrictions placed on her access to the VSD data. Pet. Tr. Ex. 17 at 1-2. She did not explain why the restrictions were placed on her use of the data, a matter explained in several of respondent's filings. *See, e.g.*, Respondent's Response to Petitioners' Second Motion to Compel and Motion for Issuance of Third-Party Subpoenas, OAP Master File, filed Jan. 19, 2007, at 16 and attached declarations A and B.

[303] *See* IOM 2004 Report, RML 255, at 55-62, 65.

[304] The authors made adjustments to these numbers because they believed the follow up of these children was truncated, based on the numbers they expected. Therefore, they added in notional numbers, increasing the numbers of cases by 45 in 1995, and 80 in 1996. Tr. at 3668.

adjustments to the first and last cohorts. Doctor Rutter described this as "putting together chalk and cheese in the hope of gazpacho soup coming out." Tr. at 3387. The "analytic design and strategy was not a satisfactory one." Tr. at 3388.

He pointed to Table 3 as a striking example of the poor design. Tr. at 3388. Table 3 compares "neurodevelopmental disorders" to several control disorders, measuring the difference in rates of the disorder developing in the cohorts that received 100 micrograms more mercury. The table shows higher rate ratios for autism, ASD, ADD/ADHD, developmental or learning disorders, disturbance of emotions, and tics.[305] Young, PML 665, at 4. Doctor Rutter called this table an example of demonstrating a statistical effect without showing a causal effect. Tr. at 3388. If the neuroinflammation hypothesis is correct, it is difficult to explain how neuroinflammation causes tics or disturbance of emotions. The study reported TCV effects across a very broad range of unconnected disorders having different ages of onset, different genetic factors, and different disease courses. Tr. at 3388. The broad range of effects in these diverse disorders caused Dr. Rutter to be "immediately skeptical as to what [the study] shows. Tr. at 3388-89.

He also questioned why "disturbance of emotions" was listed in the category of neurodevelopmental disorders, noting that anyone knowledgeable about the field of neurodevelopmental disorders would not have categorized it as one, and would have placed it with the control disorders. Tr. at 3389-90. To prove their hypothesis that increased mercury exposure causes increases in neurodevelopmental disorders but not control disorders, the authors have to demonstrate that mercury is associated with increased rates of one but not the other. If "disturbance of emotions" was properly placed with the list of control disorders, it would undercut the authors' hypothesis. Their comparison between the two groups is therefore invalid. Tr. at 3390-92.

Doctor Young's subsequently-filed letter indicated that she reanalyzed the data to respond to Dr. Fombonne's criticisms. After she removed the 1990 birth cohort (the one containing only 2,000 cases) and the notional cases for 1995 and 1996, the results for autism, ASD, and unspecified developmental disorders lost statistical significance.[306] Pet. Tr. Ex. 17 at 3-4. She nevertheless defended the use of the 1990 birth cohort and her adjustments to the numbers for 1995 and 1996. *Id*.

For the reasons indicated in the criticisms proffered by Drs. Fombonne and Rutter, I have accorded the Young study little weight. An additional reason for viewing

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[305] I note that for each of these disorders, the authors found a statistically significant increase based on mercury exposure. However, the confidence intervals were extremely large. The risk ratio for autism, for example, was 2.87, with a confidence interval ranging from 1.19 to 6.94. Young, PML 665, at 4.

[306] The results for ADHD, tics, and emotional disturbances retained statistical significance. Pet. Tr. Ex. 17 at 3-4.

this study as unreliable is the conflict of interest generated by the PSC's funding of the study. In its opinion on remand in *Daubert*, the Ninth Circuit considered whether the matters an expert proposed to testify about flowed from research conducted independently of involvement in the litigation in question, noting that this factor provides objective proof that the research was conducted for scientific purposes. *Daubert v. Merrell Dow Pharmaceuticals*, 43 F.3d 1311, 1317 (9th Cir. 1995); *see also Exxon Shipping Co. v. Baker*, 128 S. Ct. 2605, 2626 n.17 (2008) (the Supreme Court declined to consider research funded in part by a party to the litigation).

3. The Institute of Medicine Report on TCVs and ASD.

Doctor Goodman was a member of the IOM Immunization Safety Review committee that considered the effect of TCVs on ASD in both 2001 and in 2004. His testimony provided an unusual insight into the IOM decision-making process. Although IOM reports on vaccine safety have received special deference in Vaccine Act cases, the nature of the IOM decision-making process has not been discussed in the opinions. so holding. *See Stroud v. Sec'y, HHS*, 113 F.3d 1258 (Fed. Cir. 1997); *Cucuras v. Sec'y, HHS*, 993 F.2d 1525, 1529 (Fed. Cir. 1993); *Kelley v. Sec'y, HHS*, 68 Fed. Cl. 84, 91 n.11 (2005).

The Institute of Medicine is an independent body chartered by Congress as a branch of the National Academy of Sciences. It is specifically tasked with providing independent, objective, expert scientific advice to Congress, federal agencies, and other official governmental groups, but it remains independent of them. It is one of the most highly regarded organizations in the scientific community. Election to the Institute of Medicine is one of the highest honors that a scientist can receive. Tr. at 3072-73.

The Immunization Safety Review Committee included a neurologist, a pediatric neurologist, a neonatologist, an immunologist, an epidemiologist, biostatisticians, and experts in risk communication, public health, and vaccine biology, but no toxicologist. Tr. at 3078. In 2001, it concluded that the evidence was inadequate to make a judgment on whether TCVs played a role in developmental disorders, because studies of the TCV hypothesis were fragmentary. Additional studies were recommended. Tr. at 3079-80.

The committee used the phrase "biologically plausible" to describe the hypothesis in 2001. Tr. at 3080. At that time, the term "biologically plausible" was used in the sense that the hypothesis was possible, in that it did not violate physical principles. *See* IOM, IMMUNIZATION SAFETY REVIEW 13 (2001) ["IOM 2001 Report"], filed as RML 254. Because mercury is a known neurotoxin, the idea that it could produce neurologic damage was quite possible, not biologically implausible or impossible. Tr. at 3080-81. However, the term "biologically plausible" was later misinterpreted as stating that the hypothesis was likely or probable, which is not what the IOM meant. Tr. at 3081; IOM 2004 Report, RML 255, at 3.

Because of this misunderstanding, the committee decided to be more precise about how it evaluated the biological evidence in the subsequent report. In evaluating a proposed biological mechanism of how vaccines cause injury, the committee used three categories: (1) theoretical only (which is where "biologically plausible" could fall); (2) experimental; and (3) proven[307] or demonstrated. Tr. at 3081-82. "Theoretically plausible" would not include "crackpot" theories; a minimum level of credibility would be necessary. Tr. at 3081-82; IOM 2004 Report, RML 255, at 29. "Experimental" would involve theories, some parts of which had been experimentally tested, but the entire mechanism of injury had not been established. "Experimental" hypotheses would be rated as weak or strong. "Proven" would require that an exposure was virtually certain to have caused an outcome.[308] Tr. at 3082.

In reconsidering the TCV-autism hypothesis in 2004, the committee examined more recent epidemiological evidence and animal studies, took evidence in public session, and considered written submissions. Tr. at 3083-84. The evaluation options available to the committee were: (1) no evidence; (2) a causal connection established; (3) evidence favors a causal connection; (4) evidence is inadequate to establish a causal connection; and (5) evidence favors rejection of a causal connection. Tr. at 3084-85; *see also* IOM 2004 Report, RML 255, at 2-3. The committee concluded unanimously that the evidence favored rejection of a causal connection. Tr. at 3085; IOM 2004 Report, RML 255, at 16. This conclusion meant that "all the evidence point[ed] away from a causal relationship," with "no countervailing biological or mechanistic evidence that...would contravene that evidence." Tr. at 3085. It did not absolutely rule out the possibility of a relationship, but indicated that one was highly unlikely. Tr. at 3085-86.

It is unusual for an IOM committee to conclude that the evidence favors rejection of a hypothesis. Tr. at 3086-87. The committee recommended that research into the biology of autism and the risk factors for autism be conducted, but recommended against additional studies into the epidemiology of autism in the general population as results were unlikely to be different. Tr. at 3087-88; IOM 2004 Report, RML 255, at 16-17. It was both the strength of the epidemiological evidence, which included some of the studies discussed above,[309] and the absence of any laboratory or mechanistic evidence controverting it that led to the committee's conclusion. IOM 2004 Report, RML 255, at 13. Since that conclusion was issued, all of the major studies discussed above, except the Young study, PML 665, have buttressed the IOM's conclusion.

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[307] The IOM committee identified this category as "[e]vidence that the mechanism results in known disease in humans." IOM 2004 Report, RML 255, at 29.

[308] Challenge-rechallenge reactions in a given individual would rise to this level of virtual certainty. Tr. at 3082.

[309] These included the Hviid, Verstraeten, Stehr-Green, and Madsen studies. Tr. at 3650.

F. Issues Relating to Dr. Greenland's Opinions.

1. Doctor Greenland's Opinions.

Doctor Greenland conceded that the epidemiological studies have not found any association between TCVs and ASD, while asserting that it is theoretically possible that such an association exists in a small subgroup. Tr. at 121. Any association would have to be either small or nonexistent. Tr. at 122. He correctly noted that none of the studies of TCVs and ASD considered regressive autism separately. Tr. at 87. He asserted that, if TCVs only affected regressive autism, the studies would be unable to detect it, based on the dilution effect.[310] Tr. at 76; PML 715, at 12.

However, the main focus of Dr. Greenland's testimony was predicated on the existence of clearly regressive autism as a subgroup. Because I have determined that there is no evidence that such a subgroup with an etiology distinct from other forms of autism exists, it is unnecessary to consider his opinions about the inapplicability of the existing epidemiological studies to this subgroup. Assuming, *arguendo*, that it does, I would still find the epidemiological studies of TCVs and ASD to be relevant on the issue of general causation.

Doctor Greenland explained that in each 100 cases of autism, only 6 would be in the clearly regressive subtype.[311] Tr. at 80. If TCV exposure increased the risk of clearly regressive autism by a factor of 2,[312] then exposure to TCVs would change the number of clearly regressive autism cases to 12. Pet. Tr. Ex. 1 at 13-14; Tr. at 79-80. These six extra cases would change the total autism cases to 106.[313] Tr. at 80. The risk ratio would be 106 over 100, or 1.06, a figure which is not detectable by the

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[310] The failure to analyze the data separately by type of condition can dilute the association of the exposure with the disease category to the point that the association is undetectable. Tr. at 77. In his report, Dr. Greenland used types of cancer to illustrate this principle. Smoking is significantly associated with lung cancer, but not with skin cancer. PML 715 at 4. Thus, if smoking is subject to an epidemiological analysis with all forms of cancer, an effect will not be detected, but one will be detected if smoking is examined in conjunction with lung cancer. This analogy fails if the types of autism are more akin to types of lung cancer than to cancer in general. *See also* Dr. Goodman's discussion at Tr. 3105-06, indicating that it makes no sense to analyze data separately by categories unless there is something to indicate that the categories are different on a biological basis.

[311] How this 6% figure was derived and criticisms of that process were addressed in Section IV.H.3., above. For purposes of this analysis only, I accept Dr. Greenland's calculations.

[312] Doctor Fombonne testified that only when a risk ratio is greater than 2 is the exposure considered to have increased the risk of the outcome being examined. *See* Tr. at 3627.

[313] The number of cases of autism attributable to TCVs based on Dr. Greenland's postulate would not be inconsiderable in human terms. If the risk of "clearly regressive autism" is in the range of a 6-10% increase in risk from TCV exposure, there would be "hundreds and hundreds" of increased cases of autism. Tr. at 95-96.

epidemiological studies of autism. Tr. at 94. If the studies consider ASD, or developmental delay, rather than just autistic disorder, the dilution is even greater, and the increased risk would be even closer to one. Tr. at 81-82.

For purposes of his analysis, Dr. Greenland assumed that an increased risk of autism from TCVs was only applicable to the "clearly regressive" group. Tr. at 125-26. This opinion required a specificity of association[314] of TCVs to cases of clearly regressive autism. *See* Tr. at 77. He used the term "pre-specified"[315] in his report to reflect that the term may have been defined after the introduction of the hypothesis that TCVs cause only that form of autism. Tr. at 127. He conceded that if there is an effect of TCVs on autism, "it must be concentrated in a very small group to have gone undetected to this point in time." Tr. at 135.

2. Criticisms of Dr. Greenland's Opinions.

a. Regression and TCVs.

Doctors Fombonne and Rutter disagreed with Dr. Greenland regarding detection of an effect of TCVs on regression alone. They asserted that if TCVs had an effect on regressive autism, it was a large enough category that epidemiological studies would detect it. Res. Ex. E, ¶ 121(f) (Report of Dr. Fombonne); Tr. at 3307-08, 3310-11 (testimony of Dr. Rutter). Doctor Fombonne noted that in the 2002 CDC study, the state with one of the lowest rates of immunization (Utah) had the highest rate of regression. The state with the highest immunization coverage (South Carolina) had one of the lowest rates of regression. Tr. at 3675-77; Res. Tr. Ex. 12, slide 27. In view of Dr. Greenland's statements that the subgroup effect must be small in order to escape detection (*see, e.g.*, Tr. at 122, 135), the estimates of the substantial percentage of all ASD cases involving regression, and the greater experience and research focus into the epidemiology of ASD by Drs. Rutter and Fombonne, I accept the position of respondent's experts. If regressive autism as a whole were affected by TCVs, at least some of the existing epidemiological studies would have detected an effect.

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[314] Specificity of association means that an exposure has little or no association with most types of a disease category, but some association with one or a few of those types. Tr. at 77.

[315] According to Dr. Fombonne, the term "pre-specified" has a particular meaning in epidemiology, and Dr. Greenland's use in this context was incorrect. "Pre-specified" is used when there is some preliminary evidence that a subgroup might react differently to a drug or a treatment and a study might plan in advance to consider the subgroup separately. Tr. at 3682-83. This contrasts with *post hoc* subgroup analyses, which are, like the Peto astrology example, known to produce spurious associations. Tr. at 3681-82. Doctor Greenland's use of the term was incorrect because there is no evidence that his "clearly regressive autism" subgroup reacted differently to TCVs. Tr. at 3683.

b. Doctor Greenland's Computations Are Correct, But One-Sided.

Respondent's experts agreed with Dr. Greenland's calculations, if not the assumptions underlying them, but noted that his analysis was one-sided. Doctor Goodman began by explaining the concept of "mathematical bounds," referring to the uncertainty in any estimate of risk. Tr. at 3097-98. If there is absolutely no effect, the estimate would be zero, but in any study or combination of studies, there is a small plus or minus around the estimate, and it is in that plus or minus that a rare individual case might fit. Tr. at 3098. The only way to rule out the possibility of a possible effect is to prove the existence of a protective effect. Tr. at 3099. Doctor Goodman agreed that the bounds calculated by Dr. Greenland were the appropriate limits for how high a risk a TCV effect might be in any small subgroup without affecting the largely negative evidence regarding an association between TCVs and ASD. Tr. at 3097-98.

However, confidence intervals are two-sided. The estimate is in the middle; to each side is a range within which relationships are consistent with the data. Tr. at 3101. A protective effect is as consistent with the data as an excess risk for the small subgroup. Tr. at 3102. The larger studies tend to show a protective effect from TCVs. Because there is no biological basis for such a protective effect, epidemiologists do not call it one. However, because the numbers tend toward protection, the conclusion that there is no excess risk of ASD from TCVs is buttressed. Tr. at 3101-02.

By taking the upper limit of the confidence intervals for each study individually, Dr. Greenland could "fit in" a small subgroup. While it is mathematically possible that such an effect exists, it is not probable that it does. Tr. at 3099-3100. The IOM committee examined whether it was <u>likely</u> that such an effect existed, and it concluded that it was not. Tr. at 3100.

c. The Postulated Effect Requires Biological Implausibility.

Claims of subgroup effects in medicine are common, but the evidence that they exist is scant. Tr. at 3115. Assuming, *arguendo*, that clearly regressive autism is a separate and distinct form of ASD, in order for TCVs to affect it while simultaneously having no effect at all on any other form of ASD, clearly regressive autism must have a biological basis distinct from all other forms of ASD. Tr. at 3104. To fit into the small niche he carved out, Dr. Greenland's mathematical calculations require that TCVs have an effect only on children with clearly regressive autism and no effect at all on the remaining 90-95% of the ASD population. Tr. at 3103-04. What this requires from a biological standpoint is that there is a dramatically different causal pathway for those with clearly regressive autism such that TCVs would trigger it, but not trigger any of the other forms of autism. Tr. at 3104. In essence, Dr. Greenland's hypothesis requires that those with clearly regressive autism have "a fundamentally different biology than children who don't present with that phenotype." Tr. at 3104.

Assuming an entirely different causal pathway for a subgroup of regressive

autism is reasonable only if there is some reason to suspect a different causal mechanism at work. As Dr. Goodman pointed out, neither Dr. Greenland nor any of petitioners' other expert witnesses presented biological evidence that suggested a different biological basis for regressive autism as distinguished from early onset autism. Tr. at 3127-28. To the contrary, there were ample reasons proffered for doubting that regressive autism has any separate biological mechanism. *See, e.g.*, Tr. at 3570, 3689-91; Dwyer Tr. at 256-57.

G. Conclusion.

Epidemiological evidence has limitations. It cannot speak to causation in an individual case. It can, however, sufficiently undermine a hypothesis or theory regarding causation, making reliance on such a theory unreasonable under all the facts and circumstances of an individual case.

To use *Althen's* terms, epidemiological studies point out possible logical connections between two events; further scientific effort must ensue to establish whether the connections are biologically plausible and therefore truly logical. After studying the evidence available, the IOM concluded that the evidence favored rejection of the TCV-ASD hypothesis. Since that 2004 conclusion, all of the reliable epidemiological studies have buttressed the finding of no relationship.

Each epidemiological study filed has limitations that affect the data acquired and may affect the conclusions drawn. However, when numerous well-designed studies have looked at a particular issue and arrived at the same or similar conclusions, the likelihood that the studies' limitations have caused the negative results becomes vanishingly small. Epidemiology can never be direct proof that vaccines do not cause ASD, but it can be strong circumstantial evidence that causation is improbable. In this case, the epidemiological studies furnish powerful evidence refuting a causal association between TCVs and ASD.

Section VI. Mercury and the Causation Theories.

A. Mercury[316] Toxicology.

1. Overview.

The causation hypotheses in the Theory 2 cases rest on mercury's effects on the brain. Doctor Deth theorized that mercury affected the body's sulfur metabolism at several critical junctures, operating in such a way that small amounts of mercury could produce devastating effects. Doctor Kinsbourne relied on a mercury-triggered

[316] Many of the scientific and medical journal articles and some of the expert reports used mercury's scientific symbol,"Hg."

imbalance in excitatory and inhibitory neurotransmitters.

Underpinning both causation theories were Dr. Aposhian's testimony and reports on mercury's toxicology.[317] The very cursory report of Dr. Haynes added virtually nothing to the general causation case.[318] Aside from a tendency to conflate the various forms of mercury, Dr. Aposhian's testimony on mercury's basic chemistry did not differ in most respects from that of Dr. Brent, respondent's medical toxicologist. Their areas of disagreement related to the effects of different species of mercury, the importance of the dose-response relationship, their interpretations of the various studies of mercury's effects, and the quantity of mercury from TCVs that would reach the brain. As a medical doctor who is board certified in medical toxicology and who has treated patients for mercury and other heavy metal poisoning, Dr. Brent's testimony carried greater weight on matters relating to mercury's effects on the human body.

Some aspects of Dr. Aposhian's testimony were troubling. He occasionally cited studies in support of his testimony, that, when examined, did not support that testimony.[319] In spite of his acknowledgment that the various species[320] of mercury had

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[317] Although Dr. Aposhian also offered causation opinions, testifying that some autism is caused by the failure of cells to efflux mercury, and some is caused by a teratogen which produces neuroinflammation (Tr. at 234), he lacked the qualifications in medicine in general and neurology or teratology in particular to proffer these causation opinions. I have considered his opinions on mercury's causation of autism, but have placed little reliance on them, both because of his lack of qualifications to opine, and because of problems with the studies or other evidence he relied upon in reaching those opinions. *See* Section VI.D. A considerable portion of Dr. Aposhian's testimony was devoted to developmental biology and autism. Tr. at 147-52 (autism), 211-15 (developmental biology). The slides that accompanied this testimony were drawn from the IOM Forum on Autism and the Environment in April, 2007. *See, e.g.*, Pet. Tr. Ex. 2, slide 73 (footer). A review of Dr. Aposhian's CV, PML 710, establishes that the causation opinions he offered were outside his area of expertise. However, I have relied in some measure on Dr. Aposhian's testimony about mercury's toxicology, an area in which he is qualified to opine.

[318] Doctor Haynes was not called as a witness, and his very short expert report appears to have been filed in an effort to bridge the gap created by Dr. Aposhian's lack of qualifications to testify about medical matters. As indicated in Section I.D.6 above, Dr. Haynes was less qualified to opine about mercury's toxicology and effects on the human body than Dr. Brent. He does not appear to have published any papers dealing with mercury, conducted any research into mercury's effects on the human body, or treated children or adults with mercury toxicity. His expert report (Pet. Ex. 15) is less than three pages long, is devoid of any citations to medical or scientific literature, and consists primarily of conclusory statements. It does not address the critical factors of dose, speciation, or many of mercury's known effects, and does not address the *Althen* factors. Doctor Brent's opinions, which were based on his experience in treating children with mercury exposure and autism, well-supported by scientific literature, and cogently explained, were entitled to significant weight. Additionally, they were tested in the crucible of cross-examination and in questioning by the special masters. For all of these reasons, I did not find Dr. Haynes' report illuminating or persuasive on the general causation issue. His opinions specific to Colin's medical condition are addressed in Section X.G.3., below.

[319] For example, although an article (G. Harry, et al., *Mercury concentrations in brain and kidney following ethylmercury, methylmercury and Thimerosal administration to neonatal mice*, TOXICOL. LETT. 154: 183-89 (2004) ["Harry"], filed as PML 296) appears in the title area of Pet. Tr. Ex. 2, slide 53, most of

different toxicokinetics, he often attributed the effects of one species to another. Much of his direct testimony appeared scripted, consisting of reading his slides (Pet. Tr. Ex. 2) verbatim.[321] On cross-examination, he provided wandering, anecdotal, and non-responsive answers. *See, e.g.*, Tr. at 248-49, 271-73, 407-08, 421-22, 458-59. He avoided responding to cross-examination questions with comments such as "it depends on how you define ..." (Tr. at 245) or "this is a court of law and I must tell the truth" (Tr. at 409). *See also* Tr. at 150, 244, 247, 256, 272-73, 380-81, 386, 408, 454.

Because mercury's chemistry and toxicology provided the basis upon which the testimony of Drs. Deth and Kinsbourne rested, this section necessarily begins with a short discussion of mercury and its compounds and how human exposure to mercury occurs. However, most of the section discusses the studies that inform the critical issue in petitioners' case: the effects specific quantities of mercury have on human bodies. In examining and weighing the evidence submitted, including the numerous scientific and medical journal articles filed and the testimony concerning them, I considered the following factors: (1) the species of mercury involved in the study; (2) the dose received; (3) the route of administration employed; (4) the length of exposure; (5) the type of study (*e.g.*, human, animal, or cell culture and type of cell); (6) the effects measured; (7) how the effects were detected and in what tissues; (8) whether the reported effects could be or had been duplicated by other researchers; and (9) whether the effects reported in experiments were consistent with those from other types of exposure to the same substance, such as those in accidental poisonings. Applying this methodology, I conclude that the brain levels of inorganic mercury produced by infant vaccinations are, as Dr. Brent testified, minuscule, compared to the brain mercury from other sources. Tr. at 1960. There is no evidence that these levels are high enough to generate the widespread neuroinflammation found in the Vargas autopsy study, PML 69.

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the data on the slide does not appear in the article cited. Only the first and last bullet points are drawn from that article. His report had similar problems. For example, he cited N. Morton, *Genetic Epidemiology of Hearing Impairment*, ANN. N.Y. ACAD. SCI. 630: 16-31 (1991), filed as PML 208, for the proposition that a genetic predisposition and a fever may increase the impact of a stress-causing agent. The article does not mention stress or fever. *See* Tr. at 273-74.

[320] The term "species" refers to different mercury compounds. *See* Tr. at 155.

[321] *See, e.g.*, Tr. at 204-05 (presiding Special Master's comments indicating that Dr. Aposhian did not need to read his slides). A comparison of Dr. Aposhian's testimony to the corresponding slides from Pet. Tr. Ex. 2 reflects the extent to which his testimony involved reading the prepared slides. *E.g.*, Tr. at 170-73 and Pet. Tr. Ex. 2, slides 32-33 (near verbatim reading of slide content as testimony).

2. Mercury and Its Compounds.[322]

Mercury is the only metallic element to exist in nature in liquid form. Clarkson and Magos 2006, PML 35, at 610. It is extremely reactive and readily forms compounds with other substances, particularly thiols,[323] and is present in varying concentrations in nearly all marine life. *Id*. at 612.

Inorganic mercury[324] compounds are those which do not contain carbon atoms, and, by this definition, include elemental mercury, mercuric mercury, and mercurous mercury. Clarkson 2007, PML 622, at 1.[325] However, elemental mercury ("metallic mercury") is often put into a separate category because its toxicological properties differ from those of other inorganic mercury compounds. Pet. Tr. Ex. 2, slide 25;[326] Tr. at 155-56; *Toxicological Profile for Mercury*, RML 6, at 1-2.

Organic mercury consists of mercury compounds containing carbon atoms, and includes methylmercury, ethylmercury, and phenylmercury compounds. Tr. at 157-58; *Toxicological Profile for Mercury*, RML 6, at 2; Clarkson 2007, PML 622, at 1-2. Thimerosal, the vaccine component implicated in petitioners' theories of causation, consists of about 49.6% ethylmercury (Andrews, PML 4, at 584), and is thus classed as an organic mercury compound.

Thimerosal contains a mercury-sulfur bond that is broken very rapidly after injection into the body, where it metabolizes quickly to ethylmercury. Tr. at 173. Both methylmercury and ethylmercury are further metabolized in the body (ethylmercury is

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[322] Much of the information presented in this section is derived from *Toxicological Profile for Mercury*, published by the Agency for Toxic Substances and Disease Registry ["ATSDR"] (1999) ["*Toxicological Profile for Mercury*"], filed as RML 6, in addition to the testimony and expert reports from Drs. Aposhian and Brent. This publication is written in plain language, unlike many of the scientific and technical journal articles filed as exhibits. I have also relied heavily on T. Clarkson & L. Magos, *The Toxicology of Mercury and Its Chemical Compounds*, CRIT. REV. TOXICOL. 36(8): 609-62 (2006) ["Clarkson and Magos 2006"], filed as PML 35 (it was also filed as PML 289). Doctors Clarkson and Magos are two of the most widely published authorities on mercury toxicology, and much of this overview is drawn from this review article. Although Dr. Aposhian made a disparaging comment about their work in his expert report (PML 711 at 9), he withdrew that comment during his testimony. Tr. at 374-76.

[323] Thiols are sulfur-containing compounds. *See* Section VII.B.2. below.

[324] Inorganic mercury is often abbreviated as "Hg++." Doctor Kinsbourne used this abbreviation throughout his expert report, PML 717.

[325] T. Clarkson, et al., *Mechanisms of Mercury Disposition in the Body*, AM. J. INDUST. MED. (electronic publication with no further citation provided) (2007) ["Clarkson 2007"], filed as PML 622.

[326] This slide quotes from an article by Goyer and Clarkson *in* CASARETT & DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS (6th ed. 2001) ["Goyer and Clarkson"], listed as PML 664. Petitioners did not actually file this source. Respondent filed excerpted pages as RML 276, but the filed pages do not contain this quotation.

deethylated and methylmercury is demethylated), forming inorganic mercury, often called mercuric mercury. Tr. at 466-67. Once methyl- or ethylmercury has been converted to inorganic mercury, it is impossible to determine its original source. Mercuric mercury (inorganic mercury) is a mercury ion and all mercury ions are identical. Tr. at 1804.

3. Measurements.

One difficulty in analyzing the evidence in this case is that the numerous studies in evidence used different quantities and species of mercury in experiments, making it difficult to compare results. The studies also referred to the same quantity of mercury in different ways. For example, one study might refer to "micrograms" or "mcg" while another study would use the symbol "µg" for the same quantity of measurement. Doctor Aposhian included a slide that compared quantities and covered standard abbreviations as Pet. Tr. Ex. 2, slide 6. The following tables are extracted from that slide and other evidence. *See, e.g.*, Res. Ex. EE, Supplemental Report of Dr. Brent, at 2; Tr. at 1813 (discussing page 2 of Res. Ex. EE). Occasionally, I have translated measurements in a study or testimony in accordance with this table to aid in comparisons to a study using a different term for the same quantity of measurement.

a. Weight Measures.

Unit	**Symbol**	**Quantity**
kilogram	Kg	1 Kg = about 2.2 pounds
gram	g	1 g = 1/1000 Kg
milligram	mg	1 mg = 1/1000 g
microgram	µg	1 µg = 1/1,000,000 g or 1/1000 mg; one millionth of a gram
nanogram	ng	1 ng = 1/1,000,000,000 g; 1/1,000,000 mg; 1/1000 µg; one billionth of a gram.

b. Liquid Measures.

Unit	**Symbol**	**Quantity**
liter	L	1 L= approximately one quart
milliliter	ml or mL	1 ml = 1/1000 L
microliter	µl	1 µl = 1/1000 ml; 1/1,000,000 L

nanoliter	nl	1 nl = 1/1000 µl; 1/1,000,000 ml; 1/1,000,000,000 L

c. Dose Measurements.

Many of the studies involved doses of mercury based on body weight, or quantifications of the amount of a substance contained in a cell or a volume of fluid. *E.g.*, T. Burbacher, et al., *Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methylmercury or Vaccines Containing Thimerosal*, EVNTL. HEALTH PERSP. 113(8): 1015-21 (2005) ["Burbacher"], filed as PML 26 (dose based on kilograms of body weight; measurements of mercury per gram of tissue). The following table illustrates those comparisons.

Unit	**Abbreviation**	**Quantity**
parts per million	ppm	1 µg per g (µg/g); 1 mg per Kg (weight measures) 1 µg per mL (µg/mL); or 1 mg per L (liter) (liquid measures)
parts per billion	ppb	1 ng per g; 1 µg per Kg (weight measures) 1 ng per mL; 1 µg per liter (liquid measures)

The studies and testimony also discussed dose over time. For example, an experimental animal might be administered 1 µg/Kg/day (one microgram of the substance per kilogram of body weight per day). *See, e.g.*, M. Vahter, et al., *Speciation of Mercury in the Primate Blood and Brain Following Long-Term Exposure to Methyl Mercury*, TOXICOL. & APPL. PHARMACOL. 124(2): 221-29 (1994) ["Vahter 1994"], filed as PML 60.

d. Measurements Based on Molecular Weights.

Some studies discuss concentrations of mercury within certain solutions, such as blood, based on molecular weight. *E.g.*, M. Pichichero, et al., *Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal*: *a descriptive study*, LANCET 360(9347): 1737-40 (2002) ["Pichichero 2002"], filed as PML 223. Determining these concentrations involves the atomic weight of the solute, in this case either mercury or thimerosal. The atomic weight of mercury is 200.59 atomic mass units ["AMU"]; the atomic weight of thimerosal is 404.6 AMU. The following table provides pertinent comparisons between nanamolar measurements and the "parts per billion" measurements in most studies cited. *See* Pet. Tr. Ex. 3, slide 22.

Unit	Abbreviation	Quantity
parts per billion mercury	ppb mercury	1 ppb mercury= 4.99 nanoMolar ["nM"] mercury, approx. 5 x 10^{-9} Molar ["M"]
parts per billion thimerosal	ppb thimerosal	1 ppb thimerosal=2.48 nM of thimerosal, approx. 2.5 x 10^{-9} M

4. Sources of Human Exposure to Mercury.

Human exposure to mercury begins in utero. The fetus is exposed to mercury present in the mother's blood as the result of diet, dental amalgams, TCVs, and other medical products (such as immunoglobulins given to Rh negative women in pregnancy[327]). *Toxicological Profile for Mercury*, RML 6, at 16; Tr. at 364-65. Of note, the fetus may acquire a higher or lower level of mercury than that of the mother, depending on the species of mercury to which the mother is exposed. *Toxicological Profile for Mercury*, RML 6, at 16; Clarkson and Magos 2006, PML 35, at 627; Clarkson 2007, PML 622, at 3.

Dental amalgams (fillings), which contain approximately 50% metallic mercury, are the primary source of elemental mercury exposure, with very small amounts coming from water and airborne sources, including power plant[328] and volcanic emissions. Tr. at 158-59; Pet. Tr. Ex. 2, slide 27; Clarkson and Magos 2006, PML 35, at 625.

Exposure to ethylmercury is almost exclusively from vaccines (Clarkson and Magos 2006, PML 35, at 645) and other pharmaceuticals, although there have been some cases of exposure from ethylmercury-containing fungicides and treated grain products. Clarkson and Magos 2006, PML 35, at 647.

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[327] *See* S. James, et al., *Thimerosal Neurotoxicity is Associated with Glutathione Depletion: Protection with Glutathione Precursors*, NEUROTOXICOL. 26: 1-8, 2 (2005) ["James 2005"], filed as PML 7 (discussing the use of thimerosal-containing "Rho D immunoglobulin" in pregnancy); *see also* DORLAND'S at 1630 (RhoGAM).

[328] According to Dr. Aposhian, coal-fired utility plants produce 70% of the mercury vapor in the general environment, which is highly concentrated in the immediate area of the plant. Tr. at 159. An article by L. Trasande, et al., *Public Health and Economic Consequences of Methyl Mercury Toxicity to the Developing Brain*, ENVTL. HEALTH PERSP. 113(5): 590-96, 590 (2005), filed as PML 86, lists other sources as well as coal-fired utility plants: "[A]nthropogenic emissions from coal-fired electric power generation facilities, chloralkali production, waste incineration, and other industrial activities now account for approximately 70%...of mercury."

However, most human organic mercury exposure comes from methylmercury, primarily in dietary sources. Tr. at 1803. Methylmercury enters the environment through natural sources (such as volcanic emissions), mining, and the burning of fossil fuels. *Toxicological Profile for Mercury*, RML 6, at 4. Once released from rocks and soil or precipitated from the air, mercury enters the food chain through the action of microorganisms that convert inorganic mercury to methylmercury. *Toxicological Profile for Mercury*, RML 6, at 5. In infants, dietary mercury is ingested through breast milk, which contains both inorganic and methylmercury.[329] *Toxicological Profile for Mercury*, RML 6, at 16-17. If an infant is fed breast milk exclusively, infant hair and blood levels are in the same range as that of the mother. Clarkson and Magos 2006, PML 35, at 627. In older infants, children, and adults, the primary dietary sources of mercury are from fish, and possibly chicken.[330] Tr. at 152-53; Tr. at 1802-04.

Inorganic mercury is also present in food sources, but it is poorly absorbed through the gastrointestinal tract, and thus has a minimal effect on body burden of mercury.[331] The WHO has estimated that the European and North American general population ingests approximately 4 µg of inorganic mercury per day, compared to a total daily intake of 6.6 µg of all forms of mercury daily.[332] Clarkson and Magos 2006, PML 35, at 613.

5. Dose-Response Relationships.

Notwithstanding Dr. Aposhian's testimony to the contrary (Tr. at 144, 253-54),[333] the dose-response relationship remains central to the science of toxicology. CASARETT

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[329] Inhaled mercury vapor is also expressed in breast milk at concentrations of about 55% of blood mercury concentrations. Clarkson and Magos 2006, PML 35, at 622.

[330] Doctor Aposhian testified that chicken is a source of dietary mercury exposure because chickens are often fed fish meal, which would contain methylmercury. Tr. at 152-53. He provided one citation for his statement (*see* Pet. Tr. Ex. 2, slide 24), but the article referenced was not filed. One of Dr. Aposhian's references, Committee on the Toxicological Effects of Methylmercury, Board on Environmental Studies, National Research Council, *Toxicological Effects of Methylmercury* (2000), ["*Toxicological Effects of Methylmercury*"], filed as PML 228, indicated that mercury ingestion from poultry or other animals fed fish meal was possible, but that no data were available. *Id*. at 40.

[331] According to Dr. Aposhian, about 15% of ingested mercuric mercury is absorbed from the digestive tract. Tr. at 160; Pet. Tr. Ex. 2, slide 28 (quoting Goyer and Clarkson, PML 664 (not filed), RML 276, at 834).

[332] The mercury content of many fish and marine mammals, as well as that of breast milk, is listed in *Toxicological Profile for Mercury*, RML 6, at 402-31 (fish and mammals) and 444-45 (breast milk). Estimates of daily mercury exposure from diet are found at *Toxicological Profile for Mercury*, RML 6, at 432-39.

[333] Doctor Aposhian also acknowledged that dose is an important consideration even though he denied that dose plays a central role. Tr. at 144, 253.

& DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS ["CASARETT & DOULL'S"] (6th ed. 2001), filed as RML 276. Doctor Brent emphasized that, although not everyone responds in exactly the same way to an identical dose of a substance, almost all processes are dose-related. With few exceptions, at very small doses even toxic substances are not harmful. The corollary is that at very large doses, almost everything can be harmful. Tr. at 1799.

Other factors that may affect toxicity of a specific substance include: the chemical form of the substance; the age,[334] health status, genetic makeup, diet,[335] and immune status of the individual; the route of administration; and the amount of the substance that reaches areas of vulnerability (the concentration at the site of action). *See* Tr. at 144-45. It may also depend on the effectiveness of the body's detoxification process. *See* Section VII below.

Doctor Brent illustrated the concept of dose-response with examples of dose-response curves. Res. Tr. Ex. 4, slide 4. Most substances produce what is called a threshold dose-response curve. Tr. at 1800. At a very small dose, there is no effect in anyone. As the dose becomes higher, those most sensitive to the agent begin to show effects and, at higher doses, nearly all those exposed show effects. *See* Tr. at 1801. A threshold dose-response curve resembles a ski slope, with an initial flat area where no effects are observed, and an increasingly steep slope as the dose increases and more individuals experience an effect. *See* Tr. at 1800-01.

The dose needed to produce a specified effect resembles a bell curve, as shown on slide 5 of Res. Tr. Ex. 4; Tr. at 1800-01. A small number of people respond to a

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[334] In general, fetuses and very young children are the most vulnerable to toxic agents. Doctor Aposhian testified that it takes a premature neonate about four times longer than an adult to get rid of a chemical, citing a study by G. Ginsberg, et al., *Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature*, TOXICOL. SCI. 66(2): 185-200 (2002), filed as PML 439, in support. Tr. at 146. Unfortunately, petitioners filed only one page from this article. A chart appearing on Pet. Tr. Ex. 2, slide 13, was extracted from the filed page and reflects drug half-time for specific types of drugs, which included lorazepam, morphine, and valproic acid. The study did not address mercury at all, but it is generally recognized that fetuses may be severely affected by maternal mercury levels that have little effect on the mother. The age-dependent effects of mercury are discussed *infra*.

[335] Dietary factors play a role in mercury's toxicology. Tr. at 168-69, 278; Report of Dr. Aposhian, PML 711, at 7. *See* S. Hojbjerg, et al., *Effects of Dietary Lipids on Whole-Body Retention and Organ Distribution of Organic and Inorganic Mercury in Mice*, FOOD CHEM. TOXICOL. 30(8): 703-08 (1992) ["Hojbjerg"], filed as PML 271. A diet of 50% of cod liver oil resulted in a retention of significantly less mercury than a diet of 50% coconut oil. PML 271 at 705. The authors concluded that diet composition was of major importance in assessing the toxicokinetics of methylmercury and mercuric mercury. PML 271 at 707; *see also* C. Passos, et al., *Epidemiologic Confirmation that Fruit Consumption Influences Mercury Exposure in Riparian Communities in the Brazilian Amazon*, ENVTL. RES. (electronic publication with no further citation provided) (2007), filed as PML 325 (fruit consumption reduces mercury uptake); I. Rowland, et al., *Effects of Diet on Mercury Metabolism and Excretion in Mice Given Methylmercury: Role of Gut Flora*, ARCH. ENVT. HEALTH 36(6): 401-08 (1984) ["Rowland"], filed as PML 187 (antibiotic use enhances mercury uptake).

small dose; most people require a higher dose; and a small number of people require a very large dose before a given effect is observed. Nearly everyone falls within two standard deviations of the dose at which most experience an effect. Tr. at 1801.

6. Toxicokinetics.

a. Overview.

Different species of mercury have different toxicological properties. They generally enter the human body through different mechanisms (metallic mercury through inhalation, methylmercury through the gastrointestinal system, and ethylmercury through injection), are excreted in different amounts over time, and may have affinities for different organs. They may be metabolized to the same substance (inorganic mercury) but the transport and metabolization mechanisms also differ. Mercury is generally acknowledged to be the metal with the most diversity of effects among its species. CASARETT & DOULL'S, RML 276, at 834. A drop or two of dimethylmercury on the skin is fatal;[336] a drop or two of metallic mercury on the skin is unlikely to have any effect at all, unless heated and the vapors inhaled. Clarkson and Magos 2006, PML 35, at 612; Tr. at 156-57.

Both elemental and organic mercury compounds are metabolized in the body. Some of the mercury is excreted, primarily in feces and to a lesser extent in urine, and some is converted to inorganic mercury (mercuric mercury) which binds to body tissues and is thus not readily excreted. Clarkson and Magos 2006, PML 35, at 611. Precisely how much mercury is excreted from a given dose is difficult to determine, because few studies attempted to quantify the mercury contained in feces.[337]

Differences in toxicokinetics mean that effects seen in studies conducted on one species of mercury cannot be automatically extrapolated to another species, without some evidence that the two substances have similar toxicological properties and similar effects on human metabolism. Unfortunately for elucidation of the issues presented in the Theory 2 test cases, most studies have focused on the effects of methylmercury or metallic mercury, rather than the ethylmercury contained in TCVs. In equal doses, methylmercury is more neurotoxic than ethylmercury. Tr. at 1969 (discussing L. Magos, et al., *The comparative toxicology of ethyl- and methylmercury*, ARCH. TOXICOL. 57: 260-67 (1985) ["Magos 1985"], filed as PML 175). About a 20-30 percent higher dose of ethylmercury is necessary to show the same neurotoxic effects. Tr. at 1969; Magos

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[336] *See* D. Nierenberg, et al., *Delayed Cerebellar Disease and Death after Accidental Exposure to Dimethylmercury*, N. ENG. J. MED. 338(23): 1672-76 (1998), filed as PML 3 (recounting the death of a laboratory worker who spilled one or two drops of dimethylmercury onto her gloved hand).

[337] The Pichichero 2002 study, PML 223, conducted spot measurements of fecal excretion at the same time blood mercury levels were measured. This study is discussed in more detail below.

1985, PML 175, at 260.

However, unlike the Theory 1 cases, where the petitioners were attempting to demonstrate immune system effects of ethylmercury by relying on methylmercury studies, in the Theory 2 cases, the methylmercury studies carry somewhat greater weight. Because the "agent of action" in the Theory 2 cases is inorganic mercury, and both ethylmercury and methylmercury are metabolized to inorganic mercury (mercuric mercury), anything that produces inorganic mercury may produce the postulated result. Thus, with certain caveats, studies of the effects of inorganic mercury in the brain are relevant to petitioners' theory, regardless of the species of mercury that produced the inorganic mercury.

One caveat is that, although both methylmercury and ethylmercury metabolize to form inorganic mercury, attributing ill effects to TCVs is complicated by the vastly greater quantity of methylmercury to which humans are exposed.[338]

A second caveat is that identical amounts of methylmercury and ethylmercury will not produce the same amount of inorganic mercury in the human body. *See* Magos 1985, PML 175, at 260 (based on a rat study). Thus, in extrapolating from methylmercury studies to possible effects of ethylmercury, it is necessary to examine closely the dose required.

A third caveat is that methylmercury demethylates to inorganic mercury much more slowly than ethylmercury deethylates (*see* Clarkson and Magos 2006, PML 35, at 624), and thus the time period during which the inorganic mercury is present and acting as hypothesized must be considered in extrapolating from methylmercury studies to ethylmercury's possible effects.

Finally, the excretion rates of methyl- and ethylmercury differ dramatically, with ethylmercury removed from blood and tissue much more rapidly than methylmercury, leaving far less ethylmercury available in the body to be deethylated to inorganic mercury. Clarkson and Magos 2006, PML 35, at 646-47.

[338] For example, in adult Americans, fish consumption results in the ingestion of 11,000 µg of methylmercury annually (Tr. at 1805), compared to the very small amount of ethylmercury present in a single annual influenza vaccine (12.5 µg) or which was once present in the series of hepatitis B vaccines (12.5 µg in each of the three vaccinations recommended) (IOM 2001 Report, RML 254, at 28). Even when most non-viral vaccines contained thimerosal, breast-fed infants received more mercury from breast milk (estimated to be approximately 280 µg over six months) than they did from TCVs administered during the first six months of life (187.5 µg from the recommended vaccine schedule on average). Tr. at 1805; IOM 2001 Report, RML 254, at 28.

b. Half-time.[339]

Half-times for mercury in the body vary based on species of mercury and the body tissue or fluid involved. Half-time in the brain differs from that in the blood and kidneys, with a generally biphasic pattern, a short initial half-time for organic mercury, followed by a much longer secondary half-time for the inorganic mercury produced by demethylization or dealklyzation. Clarkson and Magos 2006, PML 35, at 617, 619.

c. Measurement Methods.

Urinary excretion rates (expressed either as µg/g of creatinine[340] or as µg/L) are the most frequently used measurements for total body burden of inhaled mercury.[341] Clarkson and Magos 2006, PML 35, at 618. Hair measurements are not useful in measuring excretion of inhaled mercury vapor because inorganic mercury is not readily accumulated in hair. Clarkson and Magos 2006, PML 35, at 618-19.

Levels of total mercury in scalp hair are probably the best indicator of mercury levels in the brain after methylmercury exposure. Clarkson and Magos 2006, PML 35, at 629. Hair mercury levels contain about 80% methylmercury and about 20% inorganic mercury after methylmercury exposure, with the inorganic mercury the probable result of metabolization of methylmercury in the hair follicle, not other inorganic mercury exposure. *Id.*; *see also* Cernichiari, RML 72,[342] at 1019-20.

Brain mercury levels are about five times higher than blood mercury levels and scalp hair levels are about 250 times higher than blood concentration after

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[339] "Half-time" refers to the period of time required to reduce mercury levels by half. DORLAND'S at 810. Thus if the initial blood level of mercury is measured at 8 µg, the half-time (sometimes called half life) is the number of days required before the blood level is reduced to 4 µg. Half-time measurements do not necessarily mean that half the mercury was eliminated from the body, simply that half the mercury was eliminated from the tissue or fluid in which it was measured.

[340] Adults excrete approximately 1.6 g of creatinine per day; therefore, 1 g of creatinine is equal to about 15 hours of urine flow. A mercury level of 1 µg/g of creatinine is approximately the same as a mercury level of 1 µg/L of urine. Clarkson and Magos 2006, PML 35, at 619. *But see* L. Bjorkman & M. Vahter, Letter to the Editor, TOXICOL. LETT. 169: 91-92 (2007), filed as PML 200. This letter describes factors that affect creatinine levels in urine, noting that "there are major differences in urinary creatinine by gender, physical activity, and nutrition." *Id.* at 91. The authors suggest using specific weight of the urine samples to account for variations in the dilution of solutes in urine samples. *Id.*

[341] Urinary mercury levels correlate with the number of dental amalgam surfaces. Clarkson and Magos 2006, PML 35, at 622. Ten amalgam surfaces cause, on average, an increase of 1 µg/L of urinary mercury. Brain levels in the occipital lobe on autopsy also correlated with the number of amalgam fillings. Clarkson and Magos 2006, PML 35, at 622.

[342] *See* E. Cernichiari, et al., *The biological monitoring of prenatal exposure to methylmercury*, NEUROTOXICOL. 28: 1015-22 (2007) ["Cernichiari"], filed as RML 72, at 1015-16.

methylmercury exposure. Hair levels increase or decline commensurate with blood levels of 20 days earlier, reflecting the time required for hair growth. Clarkson and Magos 2006, PML 35, at 627. However, brain-to-blood concentration ratios[343] for methylmercury are useful for estimating brain levels only when a steady state[344] of mercury is attained. Cernichiari, RML 72, at 1018 (noting that the ratios also differ from species to species).

Data on blood and brain levels in ethylmercury exposure are less well established. The available data come from studies discussed below.

d. Symptoms and Damage.

In general, the symptoms of methylmercury and ethylmercury intoxication are similar, but those receiving high doses of ethylmercury may also experience renal effects. Clarkson and Magos 2006, PML 35, at 646-47; *see also* Tr. at 194-95.

Methylmercury has an affinity for the central nervous system, which is illustrated in the symptoms observed in victims, and in the brain damage found on autopsies. Paresthesia[345] is the first symptom, but numbness, ataxia, incoordination, loss of vision and hearing, and slurred speech are all common symptoms. Clarkson and Magos 2006, PML 35, at 630-31, 632. Constriction of visual fields is a frequently reported symptom. *E.g.*, Clarkson and Magos 2006, PML 35, at 630. A threshold dose must be received before toxic effects are observed. Clarkson and Magos 2006, PML 35, at 653.

Onset of symptoms of paresthesia occurs at blood mercury levels in excess of 200 µg/L of whole blood and at levels above 50 µg/g of hair.[346] Clarkson and Magos 2006, PML 35, at 631. Human exposure to 200-500 µg/Kg for 18 days or chronic

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[343] Doctor Brent described the brain-to-blood ratio as a ratio derived from a number of studies that allows an estimate of a brain level of mercury to be drawn from the actual blood level. See Res. Ex. EE, at 10 (describing how a ratio that Dr. Aposhian relied on was improper because of how it was derived). However, a ratio from one species of mercury should not be used to estimate brain levels of another species of mercury. Tr. at 1876-80; Clarkson and Magos 2006, PML 35, at 629. Problems also exist in using brain-to-blood ratios from an animal study to estimate human brain-to-blood ratios. *See, e.g.*, Res. Ex. EE, at 7.

[344] Steady state is the point at which blood levels cease to rise in response to additional mercury intake. It represents a state of dynamic equilibrium. *See* DORLAND'S at 1755; *see also* Clarkson and Magos 2006, PML 35, at Fig. 6 (diagram representing steady state).

[345] "Paresthesia" is defined as an abnormal touch sensation, such as burning or tingling. DORLAND'S at 1371.

[346] Onset of paresthesia occurred, on average, at 40 mg of exposure, although paresthesia occurred at doses as low as 25 mg of methylmercury. Threshold doses for ataxia, dysarthria, deafness, and death were 55, 90, 170, and 200 mg of Hg, respectively. F. Bakir, et al., *Methylmercury poisoning in Iraq*, SCIENCE 181(96): 230-41, 238 (1973) ["Bakir"], filed as PML 178.

exposure to levels of from 90-125 µg/Kg per day for 100 or more days produced clinical symptoms of mercury intoxication, including ataxia, incoordination and weakness, and sensory disorders. Central nervous system damage–characterized by loss of sensation in hands, feet, and paresthesia around the mouth; ataxia; slurred speech; diminution of vision; and loss of hearing–was common, with extremity numbness and paresthesia as the first symptoms noted. Severe poisoning resulted in blindness, coma, and death. Bakir, PML 178, at 230, 236.

Autopsies of adult methylmercury victims showed damage restricted to focal areas of the brain and included cerebellar cortical atrophy involving the granule cell layer of the neocerebellum. Purkinje cells in the same area were largely spared. Clarkson and Magos 2006, PML 35, at 631.

The symptoms of ethylmercury poisoning in the China seed rice cases[347] observed in over 10% of the patients were (in order of most frequent symptom): weakness, loss of appetite, dizziness, nausea, abdominal pain and diarrhea, fever, numbness of extremities, paresthesia, ataxia, vomiting, thirst, unsteady gait, tinnitus, headache, insomnia, fatigue and sleepiness, heart palpitation, inability to walk, polyuria, and chest pain. *See* Zhang, PML 232, at Table I. Mild exposure cases were estimated to have ingested 0.5-1.0 mg/Kg body weight. Zhang, PML 232, at 253.

e. Fetal and Neonatal Exposures.

Elemental mercury inhaled during pregnancy reaches the fetal brain through a circuitous route, passing from the mother's lungs to her blood, crossing the placenta, and then passing through the fetus' liver, where some of the elemental mercury is oxidized. For this reason, after inhalation of mercury vapor, fetal brain levels of mercury are lower than maternal brain levels. Clarkson 2007, PML 622, at 3. The opposite effect occurs with regard to methylmercury. Brain levels in newborns may be as much as five times higher than those of the mother, based on animal studies.[348] Clarkson and Magos 2006, PML 35, at 627; *see also* Tr. at 2436.

Both cord blood and maternal hair have been used to measure the infant's prenatal exposure to methylmercury. Cord blood measures the mercury level at the time of delivery, whereas maternal hair levels can be used to measure mercury levels

[347] *See* J. Zhang, *Clinical Observations in Ethyl Mercury Chloride Poisoning*, AM. J. INDUST. MED. 5: 251-58 (1984) ["Zhang"], filed as PML 232.

[348] Doctor Rodier helped determine why fetuses are more sensitive to methylmercury ingestion than their mothers. Methylmercury causes arrest of cells in the process of dividing (called mitosis) at a point called starry metaphase. Infant brains have many cells at this point, but adult brains have very few. *See* Tr. at 2914-15.

over the course of the pregnancy.[349] Clarkson and Magos 2006, PML 35, at 627, 629.

Maternal exposures to ethylmercury occur primarily through vaccines administered during pregnancy, and through use of other pharmaceuticals, and are not a significant source of exposure. *See* Tr. at 364-65. More detailed information on fetal mercury exposure is contained in Section B.5 below.

f. Comparing Toxicokinetics of Ethylmercury and Methylmercury.

Clarkson and Magos summarized the toxicokinetics of the two substances, saying: "Methyl- and ethylmercury differ sharply in the patterns of tissue deposition and in the rate of metabolism to inorganic mercury. These large differences in disposition and metabolism indicate that the data on methylmercury are not a suitable reference for risk assessment for thimerosal." Clarkson and Magos 2006, PML 35, at 647. They also concluded that equivalent amounts of ethylmercury present a lesser risk to health than from methylmercury. Clarkson and Magos 2006, PML 35, at 652.

With regard to methylmercury, "[t]he peak value . . . appears to be the determinant of toxic damage." PML 35 at 633. In contrast, although acute high levels of ethylmercury have been documented to cause high brain levels of inorganic mercury and neurological symptoms, when the ethylmercury was excreted, the victims recovered from the neurological manifestations. Tr. at 3018. As is the case with methylmercury, most ethylmercury excretion occurs through the feces. Clarkson and Magos 2006, PML 35, at 647.

B. Significant Studies of Mercury Toxicity.

1. Introduction.

Petitioners' causation theories were based on mercury's interactions with brain tissue. Petitioners' experts relied heavily on a series of adult monkey studies involving methylmercury and on an infant monkey study performed using both TCVs and methylmercury for their contention that inorganic mercury deposits in the brain are a cause of autism. Additionally, petitioners' experts also relied on murine and rat studies and *in vitro* studies of mercury's effects on cell lines.

Respondent's experts discussed the same studies, explaining why they were not relevant for the positions for which they were cited and why the conclusions petitioners drew from them were not supported by the studies. They emphasized the importance of examining the doses that caused the observed effects, in comparison to TCV doses and

[349] A study of brain mercury levels in infants who died of natural causes within a few weeks of birth found that both maternal blood and maternal scalp hair correlated with infant brain levels of mercury. Clarkson and Magos 2006, PML 35, at 629.

the levels of other common mercury exposures. Additionally, Dr. Brent discussed several studies involving post-mortem human brain analyses and compared those results to those found in the adult monkey studies.

When human data are unavailable, primate studies are the closest to human studies in terms of mercury toxicokinetics. Doctor Aposhian testified that neonatal mice are also a good model for mercury's toxicokinetics in humans.[350] Tr. at 186-87.

2. Adult Primate Studies.

In the early to mid-1990s, a team of researchers from the University of Washington conducted a study of methylmercury toxicokinetics involving adult female monkeys. At least five papers were produced from this study, which reported on the metabolization of methylmercury and its subclinical effects and disposition in the brain. Throughout the testimony, these studies were variously referred to as the "adult monkey studies," "the adult primate studies," or by the name of one of the two primary authors, Vahter or Charleston. The two Vahter studies[351] measured species of mercury in the blood and brain. The Charleston studies[352] focused on mercury's effects at the cellular level in the brain.

The study design for both sets of papers involved five test groups of monkeys and one control group. Four groups of monkeys were given oral daily doses of

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[350] Doctor Aposhian testified that rat studies may not be good models because rat hemoglobin binds more mercury, resulting in less mercury reaching the brain than in humans, primates, or neonatal mice. Tr. at 188, Pet. Tr. Ex. 2, slide 53 (citing Clarkson 1997 and 2002). A careful search of the scientific and medical exhibits filed did not disclose either of these references. One 2002 article by Clarkson was filed (T. Clarkson, *The Three Modern Faces of Mercury*, ENVTL. HEALTH PERSP. 110(1):11-23 (2002), filed as PML 182) but it did not stand for the proposition for which Dr. Aposhian cited it. There were no 1997 articles by Clarkson filed by either party.

[351] *See* Vahter 1994, PML 60; Vahter, et al., *Demethylation of Methyl Mercury in Different Brain Sites of Macaca fascicularis Monkeys during Long-Term Subclinical Methyl Mercury Exposure*, TOXICOL. & APPLIED PHARMACOL. 134: 273-84 (1995)["Vahter 1995"], filed as PML 64.

[352] J. Charleston, et al., *Increases in the Number of Reactive Glia in the Visual Cortex of Macaca fascicularis Following Subclinical Long-Term Methyl Mercury Exposure*, TOXICOL. & APPLIED PHARMACOL. 129: 196-206 (1994) ["Charleston 1994"], filed as PML 33; J. Charleston, et al., *Autometallographic Determination of Inorganic Mercury Distribution in the Cortex of the Calcarine Sulcus of the Monkey* Macaca fascicularis *Following Long-Term Subclinical Exposure to Methylmercury and Mercuric Chloride*, TOXICOL. APPLIED PHARMACOL. 132: 325-33 (1995) ["Charleston 1995"], filed as PML 32; J. Charleston, et al., *Changes in the Number of Astrocytes and Microglia in the Thalamus of the Monkey* Macaca fascicularis *Following Long-Term Subclinical Methylmercury Exposure*, NEUROTOXICOL. 17(1): 127-38 (1996) ["Charleston 1996"], filed as PML116. Doctor Burbacher, whose infant primate study is discussed below, was the senior researcher on all five adult primate papers.

methylmercury at 50 µg/Kg of body weight.[353] One group was dosed for six months, one for 12 months, and one for 18 months; after the conclusion of the mercury dosing, the monkeys were sacrificed. A fourth group (called the "clearance group") was dosed for 12 months, and then allowed six months without any mercury dosing as a clearance period before sacrifice. The fifth group of monkeys received continuous IV infusion of mercury chloride (a form of inorganic mercury) at 200 µg mercury/Kg of body weight for three months. *See, e.g.*, Vahter 1994, PML 60, at 222.

a. The Vahter Studies.

In normal weight monkeys[354] exposed to methylmercury, the steady state of total mercury[355] in the blood (1.1 µg/g) was reached after about four months of daily doses. Tr. at 162. In contrast, in the control monkeys, the total blood mercury concentration was about 0.01 µg/g. Vahter 1994, PML 60, at 224. The half-time in blood was 23 days, with variations between 13-30 days. *Id*. at 226.

Not surprisingly, concentration of methylmercury in the brain increased based on the length of exposure. The average concentration of methylmercury in the occipital pole and thalamus was about 3 µg/g at six months and 4.5 µg/g at 12-18 months of exposure. Vahter 1994, PML 60, at abstract.

The accumulation of inorganic mercury in the brain and conclusions regarding its source constituted the most significant findings in the study. In the monkeys directly exposed to inorganic mercury, blood levels of 0.6 µg/g of inorganic mercury produced inorganic mercury brain levels of about 0.1 µg/g. Vahter 1994, PML 60, at abstract. However, exposure to methylmercury produced increasingly higher levels of inorganic mercury in the brain over time. Brain concentrations of methylmercury reached steady state at 12 months, but the level of inorganic mercury increased during the entire exposure period. Inorganic mercury constituted about 9% of total mercury in the brain

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[353] Doctor Brent called the 50 µg/Kg dose very high. Tr. at 1932. In comparison to the average daily intake of methylmercury in humans (3.5 µg per day in total, not per Kg of body weight, according to *Toxicological Profile for Mercury*, RML 6, at 10), his characterization was correct. The 50 µg dose for the adult monkey studies was selected in order to examine mercury levels in body tissues that were insufficient to cause weight loss, renal toxicity, or neurological problems, symptoms that had been observed in another study of long-term exposure of primates to daily doses of 70 µg/Kg body weight. That study had also found focal damage to cortical regions of the brain (including neuronal loss and degeneration, increased reactive and hypertrophic astrocytes, and microgliosis). Vahter 1995, PML 64, at 282. The levels of exposure in the adult primate study were designed to examine methlymercury's effects on the brain in the absence of clinical symptoms. Charleston 1996, PML 116, at 128. No clinical effects were observed in any of the groups. *Id.* at 130.

[354] Apparently, methylmercury does not mobilize to fat tissue. In heavier monkeys, a dose based on body weight resulted in higher blood total mercury levels (2.2 µg/g) and higher brain total mercury levels (7-22 µg/g) than those of normal weight monkeys. Vahter 1994, PML 60, at 225-26.

[355] Total mercury levels include all species of mercury present.

at 6-12 months, 18% at 18 months, and 74% at six months after termination of exposure.

Mean Brain Inorganic Mercury Measurements[356]

(In µg/g)

	Occipital Pole	Thalamus
Controls	0.002	0.008
6 Month Exposure	0.289	0.388
12 Month Exposure	0.308	0.608
18 Month Exposure	0.519	1.291
Clearance Group	0.214	0.616
Inorganic Mercury Group	0.106	(not provided)

The elimination half-time of inorganic mercury was on the order of years. *See* Vahter 1994, PML 60, at 224; Tr. at 162.

There was no correlation between inorganic mercury levels in the blood and in the brain. Blood inorganic mercury levels reached a steady state at 0.08 µg/g after four months of exposure, but brain levels of inorganic mercury increased over time to more than 30 times higher at six months of exposure and more than 60 times higher at 18 months. Vahter 1995, PML 64, at 280. The increasing amount of inorganic mercury indicated that organic mercury was demethylating in the brain. This conclusion was buttressed by the fact that the monkeys that received inorganic mercury had brain levels of inorganic mercury at 15-35% of the levels found in the monkeys who received only organic mercury, and by the findings in the clearance group that the amount of inorganic mercury continued to increase afer the mercury dosing ended. Vahter 1995, PML 64, at 273.

b. The Charleston Studies.

The Charleston studies examined where the mercury collected in the brain and its effects on brain cells. The first two Charleston papers (PML 33 and PML 32) focused on the cortex of the calcarine sulcus, a probable target for mercury because of elevated damage seen in this area after high levels of methylmercury exposure in adult humans

[356] Data on the occipital pole measurements were taken from Charleston 1994, PML 33, Table 4; data on the thalamus measurements were taken from Charleston 1996, PML 116, Table 1.

and prenatally exposed infants.[357] Charleston 1994, PML 33, at 196; Tr. at 1964-65.

These first two papers reported reactive glia[358] in increased numbers in every treatment group, including those receiving inorganic mercury. Charleston 1995, PML 32, at 329. Because the inorganic mercury group and the clearance group both had low levels of methylmercury and elevated levels of inorganic mercury, the authors concluded that inorganic mercury was responsible for the increase in reactive glia. Charleston 1994, PML 33, at 203.

There were no significant changes in cell numbers of astrocytes or neurons. Charleston 1994, PML 33, at abstract. There was no degradation in the structure of the neurons, nor any of the chronic changes in glial cells commonly observed after high level mercury exposure. Charleston 1994, PML 33, at 198.

The researchers found inorganic mercury deposits across all layers of the cortex in the methylmercury-exposed monkeys, with astrocytes and microglia accumulating high concentrations as compared to all other types of brain cells, and concentrations increasing with the length of mercury dosing. Charleston 1995, PML 32, at 326, 328-29.

The authors attributed the mercury deposits in reactive glia to phagocytosis, which may have represented an effort to protect the neurons and other central nervous system cells. Charleston 1994, PML 33, at 203; s*ee also* Charleston 1995, PML 32, at 329, 331 (suggesting that microglia were accumulating the mercury as a protective mechanism, particularly given that the number of glia increased over the course of the study). They could not determine what type of cellular debris the activated microglia were phagocytizing. As none of the other cell types were decreased after mercury exposure; the authors suggested that they might be dead astrocytes because dead astrocytes would be replaced. Charleston 1994, PML 33, at 203. Another possibility was that the reactive glia were collecting mercury from the extracellular fluid. Charleston 1994, PML 33, at 204. There was no observed increase in glial fiber acidic protein [“GFAP”] (Charleston 1994, PML 33, at 204), which suggests the lack of

[357] Doctor Brent explained that the calcarine sulcus controls visual fields, and constriction of visual fields is a common effect of mercury intoxication. Tr. at 1964-65.

[358] The study could not determine the precise type of reactive glia, but suggested that the increased reactive glia represented activated microglia rather than reactive microglia. Charleston 1994, PML 33, at 203. Microglia are phagocytes, and, once activated by the presence of a threat, may accumulate their mercury burden in the context of engulfing damaged or dead astrocytes containing mercury compounds or by removing mercury from the extracellular fluid. Charleston 1995, PML 32, at 331. The authors interpreted the increase in microglia to represent activated microglia, carrying out such phagocytic functions as removal of dead astrocytes. Charleston 1996, PML 116, at 134.

gliosis.[359]

The authors theorized that when the amount of mercury increased beyond the protective capacity of the astrocytes and microglia, mercury would begin to accumulate in the neurons. Charleston 1995, PML 32, at 331. The results were as predicted, but only in the 18-month exposure group. Neurons in the groups exposed to methylmercury for six and 12 months and the clearance group contained little mercury. As exposure time lengthened, neuronal mercury concentrations increased. Charleston 1995, PML 32, at 326.

The third Charleston paper focused on the thalamus. Mercury exposure caused no significant changes in the number of neurons or most other cell types, but there was a significant decline in astrocyte numbers in both the group exposed for six months and in the clearance group. Charleston 1996, PML 116, at abstract. The number of microglia increased in the 18-month exposure group and in the clearance group. There were no chronic changes in the glial cells, such as hypertrophic astrocytes. Charleston 1996, PML 116, at 130.

As in the two studies looking at the calcarine sulcus, more inorganic mercury was found in astrocytes and microglia than in any other cell types. However, the Charleston 1996 study found a significant relationship between the concentration of inorganic mercury in the tissue and the changes in microglia. Charleston 1996, PML 116, at 130, 135. The neurons and other cells had very limited deposits of inorganic mercury, particularly in the six-month, 12-month, and clearance groups. There were minor deposits of inorganic mercury found in the neurons of the 18-month exposure group. Charleston 1996, PML 116, at 130-31.

There was no gross damage to brain tissue nor any apparent degradation of neuronal structures. Charleston 1996, PML 116, at 130. The histological staining of the neurons did not demonstrate any significant damage to them. The lack of neuronal damage was compatible with the lack of any clinically apparent neurologic symptoms. Charleston 1996, PML 116, at 133.

The proposed explanation for the decline in the number of astrocytes in the six-month exposure group, but not in the 12-and 18-month exposure groups, was that, over time, the astrocytes were proliferating in response to the mercury exposure. Because of the small sample size, it was also possible that the study had insufficient power to

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[359] GFAP stain reacts only with astroglial cells, and stains more readily during gliosis. It will not stain neurons or other types of glial cells. Tr. at 2879-80. Several authors of the Vahter and Charleston studies commented on the lack of GFAP in the adult monkey studies as correlating with the lack of an increase in the number of astrocytes. *See* N. Mottet, et al., *Metabolism of Methylmercury in the Brain and Its Toxicological Significance*, METAL IONS BIOL. SYST. 34: 371-403, 380 (1997) ["Mottet"], filed as PML 197. Doctors Vahter and Charleston were co-authors on this paper and Dr. Mottet was a co-author of the adult primate studies.

detect a significant decline in the astrocytic population in the groups exposed for longer periods. Charleston 1996, PML 116, at 133. Loss of astrocytes may impact on their ability to carry out supporting functions for neurons, and thus may affect central nervous system performance. However, there was no loss of neurons observed. Charleston 1996, PML 116, at 134.

The authors speculated that continued accumulation of inorganic mercury in the thalamus might eventually lead to the loss of more astrocytes, which could affect the neuron population through an excitotoxic effect. This long-term exposure effect might have a different mode of damage than that associated with acute high level exposure. Charleston 1996, PML 116, at 135. The authors suggested that the thalamus might be more at risk than the neocortex because the thalamus tends to accumulate more inorganic mercury than other areas of the brain. Charleston 1996, PML 116, at 136. The authors also noted that an increase in reactive astrocytes is common after high-dose mercury exposure. They commented that an increased number of microglia could interfere with neuronal recovery after injury. Charleston 1996, PML 116, at 134.

c. Commentary on the Adult Primate Study.

Doctor Aposhian testified about two primary points drawn from the adult primate studies. First, inorganic mercury may be responsible for causing changes in astrocytes and activation of microglia.[360] Second, the loss of astrocytes and the increase in activated microglia might affect the functionality and survivability of neurons in the thalamus after methylmercury exposure. Tr. at 202-03; Pet. Tr. Ex. 2, slides 66-67. I note, however, that astrocyte levels showed an absolute level of decline only in the thalamus. The decline in the calcarine sulcus in the six-month exposure group was not found in the longer exposure groups, suggesting that any destroyed astrocytes were being replaced. *See* Charleston 1996, PML 116, at 133.

Doctor Brent agreed that inorganic mercury was likely responsible for the changes in cellular structure found in the adult primates. Tr. at 1888-89. However, he did not find the adult primate studies relevant to the question of whether mercury exposure could cause autism. Tr. at 1890-91.

His primary concern had to do with the doses of mercury received by the adult

[360] However, in their 2006 summary article, PML 35, Clarkson and Magos pointed out that the increase in reactive microglia in the occipital pole could not be correlated with brain levels of either inorganic mercury or methylmercury. Thus, they concluded that it was impossible to determine if the inorganic mercury was the cause or the consequence of the increased activity of the microglia because glial cells might be converting the organic mercury to inorganic mercury as a mode of defense. The 1996 Charleston paper, PML 116, did not report on any monkeys who receive inorganic mercury, but the 1994 paper, PML 33, did. *See* PML 35 at 634 (recording that the highest increase in microglia was found in the monkeys who received inorganic mercury, and that this group had the lowest levels of inorganic mercury and total mercury).

monkeys, as compared to human exposure to mercury. Tr. at 1932. The monkeys received a dose of 50 µg/Kg of body weight per day. A similar dose in an adult human weighing 70 kilograms, or approximately 155 pounds, would involve the administration of 3500 µg of mercury per day. Based on an average human intake of methylmercury of 11,000 µg annually, the adult monkeys received the equivalent of the average human yearly exposure in three days. They continued to receive the same level of mercury for periods of six, 12, or 18 months. Tr. at 1935-36. Doctor Brent noted the principle of dose-response, pointing out that at high enough doses of mercury or other substances, neurotoxicity would be expected. Tr. at 1938.

A second point was the Charleston 1996 thalamus study, PML 116, demonstrated astrocytic death, and thus a neurotoxic result, but the monkeys did not display any clinical signs of neurotoxicity. Tr. at 1932. This suggested that, even at these high levels of exposure, methylmercury did not produce clinically-apparent neurotoxic effects. *See* Charleston 1996, PML 116, at 133.

Further, he pointed out that if microglial activation continued because of the presence of inorganic mercury, then nearly everyone would have increases in microglial activation over a lifetime as more mercury is ingested and converted to persistent inorganic mercury in the brain. Tr. at 1968. Even at the levels of mercury used in the adult primate studies, no decline in astrocyte numbers in the calcarine sulcus was noted. Tr. at 1964-65.

Finally, two of the three papers reported findings from the calcarine sulcus, where mercury is known to accumulate. One of the common effects of mercury intoxication is a constriction of visual fields, which are controlled by the calcarine sulcus, but such constriction is not found in ASD. Tr. at 1964-65. Doctor Brent testified that the cellular findings in the calcarine sulcus supported his conclusion that the adult monkey studies were unrelated to toxic effects of mercury as a cause of autism, but were related to known effects of mercury in the brain. Tr. at 1890-91.

3. Infant Primate Study.

The Burbacher infant primate study, PML 26, was a logical follow-on to the adult primate study. Although there were some similarities in the two study designs, there were also significant differences that affect the conclusions that the expert witnesses drew from this study. Because this is a primate study measuring mercury levels in the brain after doses of the two species of mercury to which human infants are exposed, it provides the most data available about what may happen in human brains after TCV and other mercury exposure.

a. Study Design.

The Burbacher study involved the same type of monkey, Macaca fascicularis, involved in the adult primate studies. Forty-one infant monkeys were divided among

three exposure groups at birth. Burbacher, PML 26, at 1016. One group was given vaccines typically administered to human infants, with doses of 20 µg/Kg of ethylmercury (in thimerosal) through injections[361] at zero, seven, 14, and 21 days of age, for a total of 80 µg/Kg. A second group received 20 µg/Kg of methylmercury orally at the same ages.[362] *Id.* A third group of monkeys served as controls and did not receive any mercury.[363] Burbacher, PML 26, at 1016.

Unlike the adult monkey study, the infant monkey study was much more limited in the dose schedule (periodic versus daily doses), the type of examinations conducted (blood and brain mercury levels, similar to the Vahter studies rather than the Charleston cellular studies),[364] and the time frame over which the doses were received (a few weeks versus up to 18 months). The time frame allowed for "clearance" (the time between the final dose of mercury on Day 21 and the date of sacrifice) also differed substantially.

As Dr. Brent testified, the purpose of the Burbacher study was to do a pharmacokinetic analysis of what happens when mercury is administered to infant primates, rather than looking at any effect of TCVs on the brain. Tr. at 1807, 1859. Although the Burbacher paper indicated that the dose levels were chosen "based on the range of estimated doses received by human infants receiving vaccines during the first 6 months of life" (PML 26 at 1016), the study did not mirror human infant dosing.[365]

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[361] The injections contained the same vaccines received at comparable life stages by human infants, but the thimerosal levels were altered by mixing thimerosal with thimerosal-free vaccines to achieve the 20 µg/Kg body weight dose. Burbacher, PML 26, at 1016.

[362] The different methods of administration were chosen based on how humans are exposed to the two types of mercury (ethylmercury through TCVs by injection and methylmercury through diet). Tr. at 1816.

[363] The study reported weight gain for the control infants (PML 26 at 1017), but did not contain any data on mercury levels in the blood or brain tissue of the control group monkeys. This raises an issue about one of Dr. Brent's assumptions in his supplemental report, that of a "baseline" mercury level. Res. Ex. EE at 5. This issue is discussed more fully in Section VI.C., below.

[364] During the general causation hearing, petitioners' counsel suggested that cellular level studies of the brains of these infant monkeys, similar to those conducted on the adult primates detailed in the Charleston papers, were pending. *See* Tr. at 38. The Burbacher paper indicated that half brain samples were studied, but did not indicate what was done with the other half. Burbacher, PML 26, at 1016. As of the date the evidentiary record in this case was closed, no such study was filed, nor have there been any requests to reopen the record to file one.

[365] Human infants would have received one dose of a TCV (hepatitis B vaccine) administered at birth or shortly thereafter, followed by a second dose of TCVs (hepatitis B; diphtheria, pertussis, and tetanus ["DTP"]; and Haemophilus influenzae type b ["Hib"] vaccines) at two months; a third dose of TCVs (DTP and Hib) at four months, and a fourth dose of TCVs at six months (DTP, hepatitis B, and Hib). *See* CDC Childhood Immunization Schedules. The infant monkeys received one dose of hepatitis B at birth, followed by hepatitis B, DTP, and Hib at seven days, another dose of DTP and Hib at 14 days, and a

The amounts of mercury received differed, and the time frame between vaccinations was shorter. Based on half-time of ethylmercury in both monkeys and human infants, human infants would generally clear the ethylmercury from their bloodstream by the time of the next dose. In the infant monkeys, the compressed dosing schedule (designed to coincide with human developmental stages at vaccine administration), meant less clearance time and some accumulation of mercury in the blood, although the amount accumulated was less than that of the methylmercury-exposed infant monkeys. Tr. at 1807-08, 1817.

The total dose per kilogram of body weight received by the infant monkeys was significantly less than that received by the adult monkeys. Over the period in which mercury was administered (birth to 21 days of age), the infant monkeys received a total of 80 µg/Kg of either ethylmercury or methylmercury. *See* Burbacher, PML 26, at 1016. In contrast, the adult monkeys received 1050 µg/Kg of methylmercury over the same period (50 µg/Kg/day x 21 days = 1050 µg/Kg). *See* Vahter 1994, PML 60, at 222.

Blood was drawn prior to any mercury exposure, and drawn again at two, four and seven days after the initial and subsequent exposures. The monkeys were sacrificed between two and 28 days after the final mercury exposure, with blood drawn before sacrifice.[366] Burbacher, PML 26, at 1016. After sacrifice, brain mercury levels were measured. *Id*. at 1016-17.

There was little disagreement between the parties' experts about what the Burbacher study found. However, there was a great deal of disagreement about what the study meant.

b. Study Findings.

There were no significant differences in weight gain among the three groups, suggesting that there were no clinical effects from the mercury administration. Burbacher, PML 26, at 1017-18. This was also true at the much higher levels of exposure in the adult primate study. Vahter 1994, PML 60, at 223.

(1) Methylmercury-Dosed Monkeys.

In the methylmercury-exposed infant monkeys, the highest blood levels of total mercury were recorded two days after administration of the fourth dose. There was

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fourth dose (DTP, hepatitis B, and Hib) at 21 days. See Burbacher, PML 26, at Table 1; Tr. at 1808.

[366] The study referred to the period between final mercury exposure and sacrifice as the "washout" period. In the adult monkey papers, the "clearance group" performed a similar function, albeit over a longer period.

progressive accumulation of mercury in the blood, rising from between 8-18 ng/mL[367] two days after the first dose to between 30-46 ng/mL two days after the fourth dose. Burbacher, PML 26, at 1018. The half-time of mercury in the blood was about 21 days, which is consistent with the blood half-time of the adult monkeys in the Vahter study. *Id.* The authors found no differences in methylmercury's systemic distribution kinetics between adult and infant monkeys. *Id*.

In the methylmercury-exposed monkeys, brain levels of total mercury were between 1.7 to 3 times higher than the levels in the blood. The half-time of total mercury in the brain was about 60 days, which was longer than that of the adult monkeys (37 days) in the Vahter studies. Burbacher, PML 26, at 1018. The highest levels of total mercury in the brain were over 100 ng/g,[368] observed at about four days after the last dose. *See* Burbacher, PML 26, at 1018, Figure 3. Most of this was organic mercury; only about 6-10% was inorganic mercury. In half of the methylmercury-dosed monkeys sacrificed, the concentration of inorganic mercury was below the detection threshold of the test used to measure it.

These figures were consistent with the adult monkey measurements at the same points reported by Vahter. Burbacher, PML 26, at 1018-19. The Vahter studies indicated that the ultimate disposition of the methylmercury left in the infant brains would involve conversion of substantial amounts to inorganic mercury. In the Vahter studies, the metabolization of methylmercury to inorganic mercury in the brain continued long after the last dose was administered, with 9% inorganic mercury at six months of exposure, an amount that climbed to 74% inorganic mercury six months after termination of exposure. Vahter 1994, PML 60, at abstract. A similar conversion would have occurred with the methylmercury in the infant monkey brains if there had been a longer period before sacrifice. *See* Tr. at 1815, 1873-75, 1911; Res. Ex. EE, at 3.

(2) Thimerosal-Dosed Monkeys.

Thimerosal-dosed monkeys had blood levels of total mercury of 6-14 ng/mL two days after the initial exposure, levels which were similar to blood levels in premature infants receiving 12.5 µg of ethylmercury from their initial hepatitis B vaccine. Burbacher, PML 26, at 1019 (citing Stajich[369]). Blood concentrations of mercury in the

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[367] Note that mercury was administered in micrograms (µg), but the body measurement levels were in nanograms (ng), a measurement level 1000 times smaller than micrograms. Burbacher, PML 26, at 1016, 1019.

[368] There was no statistical difference between the brain level of methylmercury in the monkeys sacrificed on the first day and that of those sacrificed 28 days later. This indicated that the methylmercury was not being eliminated; it was being slowly converted to inorganic mercury. Tr. at 1912.

[369] G. Stajich, et al., *Iatrogenic exposure to mercury after hepatitis B vaccination in preterm infants*, PEDIATRICS 136(5): 679-81 (2000) ["Stajich"], filed as PML 249. This comparison required converting the 7.36 µg/L mean mercury level for preterm infants in the Stajich study to the ng/mL level

thimerosal group declined rapidly between doses with minimal accumulation in the blood, unlike the methylmercury-dosed infant monkeys. Half-times in the blood followed a biphasic model of an initial half-time of 2.1 days, and a terminal half-time of 8.6 days. *Id*. Blood clearance rates were about 5.4 times higher for ethylmercury than for methylmercury. *Id*.

The half-time for total mercury in the brain was 24.2 days, significantly shorter than the brain half-time for the methylmercury-dosed monkeys. There was also a significant decrease in the organic mercury in the brain over the washout period, a half-time of about 14.2 days. However, there was more inorganic mercury in the brains of the thimerosal-exposed monkeys. Between 21% and 86% of the brain mercury in the thimerosal-exposed monkeys was inorganic, at levels of about 16 ng/mL (the equivalent of 0.016 µg/mL). Burbacher, PML 26, at 1019.

Twenty-eight days after the last administration of mercury, the level of organic mercury remaining in the brain was more than ten times higher in the methylmercury-dosed monkeys. However, the level of inorganic mercury was about three to four times higher in the thimerosal-dosed monkeys. *Compare* Figure 7 (thimerosal-dosed) *with* Figure 4 (methylmercury-dosed). Burbacher, PML 26, at 1018-19. Levels of both types of mercury were very low; the graphs at the two figures represent amounts in nanograms, or parts per billion. *Id*.; Tr. at 1813.

In analyzing and summarizing their results, the authors noted that mercury is cleared from the body faster after the administration of thimerosal than after administration of methylmercury. Peak blood concentrations in the monkeys receiving methylmercury were nearly three times higher than those who received thimerosal. The brain concentration of total mercury was three to four times lower in the thimerosal-exposed monkeys than in the methylmercury-exposed monkeys, and the half-time for total mercury in the brain was much shorter (24 days vs. 60 days) in the thimerosal-exposed infant monkeys. Burbacher, PML 26, at 1020.

However, they also concluded that applying the methylmercury brain-to-blood ratio would not accurately predict brain levels in thimerosal exposure. Inorganic mercury levels in the brain (and the kidney) were twice as high in the thimerosal-exposed monkeys, at least over the period in which brain concentrations were measured. The authors noted that in the adult monkeys exposed to methylmercury, inorganic mercury levels continued to rise as methylmercury levels declined and cleared. Burbacher, PML 26, 1020. Thus, as Dr. Brent testified, the ultimate amount of inorganic mercury in the brains of the methylmercury-dosed monkeys would have increased over time. *See* Tr. at 1911-12.

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used in the Burbacher study. A 7.36 µg/L level converts to 7.36 ng/mL, which was then compared to the 6-16 ng/mL level found in the infant monkeys.

c. Commentary on the Burbacher Study.

In their initial expert reports, their hearing testimony, and their supplemental reports filed after the Theory 2 hearings concluded, Drs. Aposhian and Brent disagreed on several points. On the whole, I find Dr. Brent's interpretations of the study to be more reliable and correctly reflective of the study's findings than those of Dr. Aposhian, who sometimes misstated them.[370] Two significant areas of disagreement emerged: (1) whether the doses of ethylmercury via thimerosal in the Burbacher study were the equivalent of doses a human infant might receive through the first six months of TCVs; and (2) how much inorganic mercury in the brain would ultimately be produced by the administration of four 20 µg/Kg doses of ethylmercury versus how much would be produced from the same doses of methylmercury. In answering these questions, both Drs. Aposhian and Brent made reference not only to the Burbacher findings, but also to the Vahter and Charleston adult primate studies and other studies discussed below. Because the resolution of the second issue (how much inorganic mercury in the brain would be produced from TCVs versus that of dietary and other exposures to methylmercury) depends on studies in addition to the adult and infant primate studies, I defer discussing the second issue until I discuss the additional studies.[371]

Regarding differences in the dose levels of ethylmercury received by Burbacher's infant monkeys versus the dose received by human infants in early vaccinations, Dr. Brent's assertions were correct. His testimony that the higher amounts given to the infant monkeys were necessary to ensure that mercury levels would not be below the

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[370] See, *e.g.*, Dr. Aposhian's testimony that more methylmercury than ethylmercury is excreted from the brain and that methylmercury is "removed more rapidly from the brain, so that the amount of mercuric mercury formed from a given dose of methyl mercury is less than, the percentage is less than the conversion of ethyl mercury to mercuric." Tr. at 398. He also stated that "methyl mercury is removed from the brain faster than ethyl mercury is removed from the brain," again citing to the Burbacher study, PML 26. Tr. at 398. However, that study actually found that three to four times more total brain mercury was produced from the same dose of methylmercury as from ethylmercury in thimerosal, and that total mercury was cleared from the brain more rapidly after ethylmercury exposure than after methylmercury exposure. Burbacher, PML 26, at 1020. Inorganic mercury levels were higher after ethylmercury exposure during the time frame of the study, but Burbacher noted that the Vahter and Charleston adult monkey studies indicated that demethylation of the methylmercury continued for months after exposure ended. In the Burbacher study, the infant monkeys were sacrificed between two and 28 days after their last exposure, too short a time for the inorganic mercury from methylmercury exposure to peak. Burbacher, PML 26, at 1016, 1020. Part of Dr. Aposhian's supplemental report involved calculations indicating why he believed that methylmercury would ultimately produce less inorganic mercury than similar doses of ethylmercury. *See* Pet. Ex. 21 at 3. Based on Dr. Brent's supplemental report and my own careful reading of the infant and adult monkey studies, I am convinced that Dr. Aposhian's calculations of the amount of inorganic mercury that would ultimately have been produced were incorrect. *See* Res. Ex. EE at 1-3.

[371] Both supplemental expert reports (Supplemental Report of Dr. Aposhian, Pet. Ex. 21; Supplemental Report of Dr. Brent, Res. Ex. EE) contain a series of calculations based on assumptions or conclusions drawn from the adult monkey studies, the Burbacher studies, and several other studies. The calculations are complex, and criticisms of both sets of calculations cannot be readily understood without reference to the studies discussed below, particularly the human autopsy studies.

detection limits (*see* Tr. at 1808-09) was buttressed by the remarks of Dr. Polly Sager at the February 9, 2004 meeting of the Immunization Safety Review Committee, RML 436.[372]

Doctors Brent and Aposhian were in agreement that human infants who received TCVs according to the infant vaccination schedule would have received 187.5 µg of ethylmercury by six months of age.[373] *See* Pet. Ex. 21 at 11-12 (Dr. Aposhian's supplemental report) and Tr. at 1862 (testimony of Dr. Brent). In comparison, the infant monkeys received a total of 80 µg/Kg (four injections x 20 µg/Kg ethylmercury per injection), a fact that does not seem reasonably in dispute. *See* Burbacher, PML 26, at 1016. However, there is an important distinction between these two amounts. The first amount (187.5 µg) represents a total amount (without regard to infant weight) administered over a period of six months; the second figure represents an amount per kilogram of body weight administered over a period of 21 days.

A direct comparison between the two figures cannot be made without converting the 187.5 µg figure into a dose per kilogram amount. Doctor Brent performed a quick calculation at the hearing based on a body weight of a six-month-old child of roughly 8 kilograms, testifying that this would result in a typical infant receiving a 24 µg/Kg exposure (calculated by dividing 187.5 µg by 8 kilograms). Therefore, Dr. Brent concluded that the 24 µg/Kg figure is less than 1/3 of the dose received by the infant monkeys in the Burbacher study.[374] Even with extremely small infants, exposure would

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[372] P. Sager, National Institute of Allergy and Infectious Diseases, *Thimerosal Exposure from Vaccines and Ethylmercury Accumulation in Non-human Primates* (Feb 9, 2004), filed as RML 436. Although this information does not appear in the Burbacher paper, Dr. Brent identified his source for the data as an oral presentation from the preliminary data from the Burbacher study to the IOM in 2004. Tr. at 1809. An audio version of this oral presentation was filed as RML 436; Dr. Brent read a portion of the presentation into the record. The Burbacher study was submitted for publication in 2004, but not accepted until April, 2005, and not published until August, 2005. PML 26 at 1015. The preliminary data from the Burbacher study was furnished to the IOM for its report on TCVs and autism in 2004. *See* IOM 2004 Report, RML 255, at 135; Tr. at 1809.

[373] The focus on six months of age reflects the evidence that the brain changes in autistic individuals occur prenatally or, as petitioners asserted, in the first few months after birth. Thus, the TCV exposure by six months of age was the focus of most of the evidence, even though thimerosal exposure continued in vaccines administered later in infancy.

[374] This impromptu calculation underestimated the mercury per kilogram received by the human infants because some of the TCVs would have been administered in early infancy, when the infants would have weighed three to four kilograms rather than eight. I do not think this was a deliberate underestimation because the calculations were performed "on the spot" in response to questions during his testimony.

Using Dr. Aposhian's table of mercury content per vaccine and timing for vaccine administration (*see* Pet. Ex. 21 at 4) and using the median infant weights rounded off to the lowest whole number (*see* Pet. Ex. 1, p. 81 (Colin Dwyer's weight chart from his pediatric records)), at the time vaccines are normally recommended, I have refined Dr. Brent's rough calculations. Assuming an average infant weight of three

not approach the 80 µg/kilogram level administered to the infant monkeys. Tr. at 1862-63, 1966-67.

An additional factor that bears mention is the time frame over which the divided doses were administered. In order to simulate the effects on infant brains at similar levels of development, the infant monkeys were dosed on a more compressed schedule than that of human infants. They received four doses over 21 days, rather than over a period of six months. The Burbacher study noted that the compressed dosing schedule for the monkeys meant that there would not be complete clearance of one dose of thimerosal from the blood before the next dose was administered. This would result in higher peak blood levels of ethylmercury in the infant monkeys than in infant humans, even if the doses of ethylmercury received were the same.

The primary significance of the Burbacher study is the amount of inorganic mercury produced in the brains of the infant monkeys from the doses of organic mercury received compared to inorganic mercury levels in the brains of the adult primates, and the conclusions the parties drew therefrom. Those conclusions are discussed below, after consideration of the rat and murine studies and some human autopsy data.

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kilograms at birth, four kilograms at one month, five kilograms at two months, six kilograms at four months, and eight kilograms at six months of age, I roughly calculated that human infants would have received about 33 µg/Kg (compared to Dr. Brent's calculation of 24 µg/Kg). This is about 2.5 times less than the 80 µg/Kg dose the infant monkeys received. The calculations Dr. Brent performed were based on the aggregate of mercury in vaccines, divided by the infant's weight at six months. My calculations were similarly performed, but were based on median infant weight and mercury content at the time the TCVs would have been received. *Cf. Precision Pine & Timber, Inc. v. United States*, No. 2008-5092, 2010 WL 569733, at * 13-15 (Fed. Cir. Feb. 19, 2010) (affirming the trial court's recalculation of damages based on its construction of an alternative harvesting schedule not proposed by either party).

4. Rat and Murine Studies.

Two rat[375] and two mouse[376] studies discussed during the testimony were not particularly informative on the issue of organic and inorganic mercury's effects on the brains of human infants. In general, the studies used extraordinarily high doses of mercury and methods of administration unrelated to human exposure. One of the Magos 1985 article's more relevant findings was ignored by Dr. Aposhian in his direct testimony and in his slides. Magos noted:

> In spite of the higher inorganic mercury concentration in the brain of ethylmercury- than in the brain of methylmercury-treated rats, the granular layer damage in the cerebellum was widespread only in the methylmercury-treated rats. Thus inorganic mercury or dealkylation cannot be responsible for granular layer damage in alkylmercury intoxication. Moreover, histochemistry demonstrated no inorganic mercury deposits in the granular layer.

Magos 1985, PML 175, at 260 (emphasis added).

5. Human Exposure Studies.

a. Accidental Poisoning Data.

The primary studies of mercury's effects in accidental poisoning involved

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[375] Magos 1985, PML 175; P. Gallagher, et al., *Identity of Ultrastructural Effects of Mercuric Chloride and Methyl Mercury After Intracerebral Injection*, TOXICOL. 23: 261-66 (1982) ["Gallagher"], filed as PML 588. The Gallagher study involved direct injection of very high doses of either mercury chloride (inorganic mercury) or methylmercury into the brains of living rats, resulting in neuronal necrosis. Tr. at 205-06. Enough mercury was injected directly into the brain to produce clinically observable effects in the first six hours after injection and death in some rats within 24 hours. Gallagher, PML 588, at 262-63. Thus, the results of this experiment are not informative of human exposure, where organic mercury is metabolized to inorganic mercury within brain cells or extracellular fluid.

[376] Harry, PML 296; G. Zareba, et al., *Thimerosal distribution and metabolism in neonatal mice: comparison with methyl mercury*, J. APPL. TOXICOL.(electronic publication with no further citation provided) (2007) ["Zareba"], filed as PML 557. The Harry study, PML 296, measured the tissue distribution of a number of mercury compounds administered to neonatal mice. Both ethylmercury and thimerosal produced significantly less mercury in the brain than methylmercury. Harry, PML 296, at 187-88. This study demonstrated that methylmercury produced the highest brain levels of mercury, but some mercury from all sources reached the brain. Tr. at 1806-07. Brain levels were less than one percent of the total mercury administered. Tr. at 1881. The Zareba study involved the administration of thimerosal or methylmercury to neonatal mice by injection. Because methylmercury is not injected in humans, the toxicokinetic findings from this study regarding methylmercury cannot be readily extrapolated to human exposure. Nevertheless, the Zareba study also found that brain levels of inorganic mercury were about the same for both the thimerosal and the methylmercury-exposed groups. Tr. at 192-93; Zareba, PML 557, at 4-5.

ingestion of food products contaminated with high levels of methylmercury.[377] In the Minamata Bay disaster in Japan, children exposed prenatally to high levels of methylmercury developed a condition similar to cerebral palsy. Harada, RML 226, at 8; K. Eto, *Minamata disease*, NEUROPATH. 20: S14-19, S15 (2000), filed as RML 133. In autopsies of infants exposed prenatally to methylmercury who died shortly after birth, extensive disruption of the cellular structure of the brain was observed, with effects in the entire brain. Clarkson and Magos 2006, PML 35, at 635. In the Iraq disaster, similar effects were observed, and the infants prenatally exposed had higher concentrations of methylmercury in their blood than did their mothers. Bakir, PML 178, at 239. The studies of the Minamata and Iraqi disasters did not address speciation of mercury in the brain or the cellular level effects of prenatal or early infancy exposure to low levels of methylmercury.

Postnatal exposure showed a different pattern of brain damage. In autopsies of postnatal victims from the Minamata Bay disaster, lesions were observed in both the cerebral cortex and the cerebellar cortex. Harada, RML 226, at 18-19. In an autopsy performed on a mercury poisoning victim who worked at a fungicide plant, the damage was restricted to specific areas of the brain: the granule cell layer of the neocerebellum, responsible for the ataxia observed in victims, and cortical atrophy around the calcarine fissures, responsible for the constriction of visual fields. Clarkson and Magos 2006, PML 35, at 631.

The Zhang study, PML 232, of accidental ethylmercury poisoning in China involved oral ingestion of ethylmercury-contaminated rice, and did not focus on any prenatal or early infancy exposures.

b. Lifestyle Studies.

Three series of studies involving populations with high consumption of food containing methylmercury were filed: the Faroe Islands studies;[378] the Seychelles

[377] *See* M. Harada, *Minamata Disease: Methylmercury Poisoning in Japan Caused by Environmental Pollution*, CRIT. REV. TOXICOL. 25(1): 1-24, (1995) ["Harada"], filed as RML 226; Bakir, PML 178.

[378] *See* P. Grandjean, et al., *Cognitive Deficit in 7 Year-Old Children with Prenatal Exposure to Methylmercury*, NEUROTOXICOL. & TERATOL. 19(6): 417-28 (1997), filed as PML 176; P. Grandjean, et al., *Methylmercury Exposure Biomarkers as Indicators of Neurotoxicity in Children Aged 7 Years*, AM. J. EPIDEMIOL. 150(3): 301-05 (1999) ["Grandjean 1999"], filed as PML 180 [together "Faroe Islands"].

Islands studies;[379] and the New Zealand studies.[380] In terms of the adverse effects observed, the Faroe Islands study found very subtle, subclinical deficits in memory and language in children who were otherwise normal.[381] The deficits were associated with higher maternal consumption of whale meat and blubber. *See* Meyers, PML 241, at 1691. The Seychelles Islands studies did not find similar effects from high fish consumption.[382] *E.g.*, Meyers, PML 241, at 1692; Clarkson and Magos 2006, PML 35, at 642. The New Zealand study also found subtle effects associated with higher maternal hair levels, but confounding factors such as socioeconomic status and ethnic background produced similar results. *See* Clarkson and Magos 2006, PML 35, at 637, 643.

Doctor Rutter commented on the Seychelles Islands, Faroe Islands, and New Zealand studies, testifying that there is "some suggestive evidence that there may be slight cognitive sequelae with these intermediate levels" and that most commentators agreed with him. Tr. at 3295-96. However, none of the studies identified autism as one of the sequelae. Tr. at 3296.

Because these studies involved methylmercury ingestion by mothers during pregnancy, and there is insufficient information to establish a correlation with ethylmercury's effects, these studies are not informative of any effects of postnatal administration of TCVs. However, because exposure occurred during pregnancy, when the fetal brain is even more vulnerable than the postnatal brain, they suggest that low level methylmercury exposure during that particularly vulnerable period does not cause ASD.

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[379] *See* G. Myers, et al., *Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study*, LANCET 361: 1686-92 (2003) ["Meyers"], filed as PML 241; P. Davidson, et al., *Effects of Prenatal and Postnatal Methylmercury Exposure From Fish Consumption on Neurodevelopment: Outcomes at 66 Months of Age in the Seychelles Child Development Study*, JAMA 280(8): 701-07 (1998), filed as RML 105 [together "Seychelles Islands"].

[380] *See* T. Kjellström, et al., *Physical and Mental Development of Children with Prenatal Exposure to Mercury from Fish Stage 1: Preliminary Tests at Age 4,* NATIONAL SWEDISH ENVIRONMENTAL PROTECTION BOARD REPORT 3080 (1986), filed as PML 214; T. Kjellström, et al., *Physical and Mental Development of Children with Prenatal Exposure to Mercury from Fish Stage 2: Interviews and Psychological Tests at Age 6*, NATIONAL SWEDISH ENVIRONMENTAL PROTECTION BOARD REPORT 3642 (1989), filed as PML 215 [together "New Zealand"].

[381] The Grandjean 1999 study, PML 180, examined which biomarkers of mercury were associated with these subtle deficiencies. Cord blood mercury was the best predictor, suggesting that it is a prenatal effect of high maternal methylmercury exposure that produces the subtle differences found. *See* PML 180 at 303.

[382] The whale meat and blubber consumed by the Faroe Islanders contained higher levels of mercury than the fish meals consumed in the Seychelles, but the Seychellois ate seafood more often than the Faroe Islanders ate whale products. One suggestion for the different results from the two studies is that micronutrients present in the fish offset any effects of mercury. Meyers, PML 241, at 1691.

c. Autopsy Studies.

(1) Adult Brains.

A study of mercury accumulation in human brains, based on autopsy findings in individuals from Denmark and Greenland, was published in 1999.[383] The autopsies of 17 Greenlanders showed large individual variations in total brain mercury levels, with mean individual concentrations ranging from 59 µg/Kg to 4782 µg/Kg.[384] Pedersen, PML 603, at 100. The authors attributed the high variation to differences in lifestyle, noting that some Greenlanders eat traditional Arctic food (marine mammals) high in methylmercury, while others eat imported food. The two individuals with the highest concentrations of mercury were both hunters. Pedersen, PML 603, at 101,104-05. In spite of their high brain levels of mercury, there were no signs of methylmercury poisoning. Pedersen, PML 603, at 106-07.

There was a high correlation between the age of the individual at death and the concentration of mercury in the brain, indicating continued accumulation of mercury in the brain over a lifetime. The highest concentrations of total mercury were found in the cerebellum, with a median concentration of 492 µg/Kg. Pedersen, PML 603, at 100. Speciation of the mercury disclosed that between 1-60% was organic, with a median organic mercury level of 32%. Pedersen, PML 603, at 102.

In contrast, the Danes autopsied showed total mercury ranging from 1.2 to 11.8 µg/Kg, with very small variations among the 12 brains studied. There was no correlation of mercury levels with age. Pedersen, PML 603, at 100-01.

Autometallography studies were performed showing that the inorganic mercury was primarily located in glial cells. Inorganic mercury was found in neurons only in the two Greenlanders who had the highest total mercury levels. Pedersen, PML 603, at 103. In the adult monkey studies, a similar effect was found, with mercury primarily found in astrocytes and microglia, and in neurons only in those exposed to the highest total mercury levels. Pedersen, PML 603, at 106; Charleston 1996, PML 116, at 130-31.

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[383] M. Pedersen, et al., *Mercury Accumulations in Brains from Populations Exposed to High and Low Dietary Levels of Methyl Mercury: Concentration, chemical form and distribution of mercury in brain samples from autopsies*, INT'L J. CIRCUMPOLAR HEALTH 58(2): 96-107 (1999) ["Pedersen"], filed as PML 603.

[384] By way of comparison, the mean adult monkey brain total mercury levels in the Charleston studies varied from 3282 µg/Kg in the six-month exposure group to 4839 µg/Kg in the 18-month exposure group. These figures are taken from the occipital pole, which had lower levels of total mercury than the thalamus. Charleston 1994, PML 33, at Table 4. The data in the table were converted from µg/g to µg/Kg by multiplying by 1000 (there are 1000 grams per kilogram). Of note, the Charleston figures represent a mean calculated from the same site in several brains; the reported figures in the Pedersen study are means calculated from samples throughout an individual's brain.

(2) Infant Brains.

Doctor Brent discussed one of the most significant studies filed, one involving the effects of normal and high maternal dietary methlymercury on infant brains.[385] Thirty-two neonatal brains from Seychelles Islands infants were preserved on autopsy and analyzed. The findings were compared to those of 12 infants from the Rochester, NY, area who had died from causes not directly affecting the nervous system. Reference samples from infants who had died in the Iraqi grain disaster also provided comparisons. Lapham, RML 294, at abstract.

There were no abnormalities in cerebral or cerebellar cortical organization and the neurons appeared normal in the Seychellois infants. In 22 of the 32 brains, variable numbers of reactive astrocytes were found in the cerebral white matter, and, in 24 of the brains, there were increased numbers of reactive microglia in cerebral white matter. Lapham, RML 294, at 691. The Rochester brains, which contained much less mercury, had similar findings. Lapham, RML 294, at 692.

Total mercury levels in the Seychelles brains demonstrated variability among the brains and within different regions of the same brains. The mercury values were well above those of the Rochester brains, with values in the Seychelles brains generally between 50-250 ppb (nanograms per gram) and the Rochester brains generally less than 50 ppb.[386] Lapham, RML 294, at 694. The highest brain mercury concentrations were found in the cerebellum, basal ganglia, thalamus, pons, and medulla. Lapham, RML 294, at 696. There was no correlation between mercury levels and the degree or type of histological changes (the reactive microglia and astrocytes) observed. Lapham, RML 294, at 697.

A comparison of the gross anatomy of the Seychelles brains to reference samples from the Iraqi grain disaster did not disclose similarities.[387] The Iraq brains also showed "exuberant reactive gliosis in the white matter as evidenced by numerous plump astrocytes," demonstrating a scarring response to injury, likely caused by the

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[385] L. Lapham, et al., *An Analysis of Autopsy Brain Tissue From Infants Prenatally Exposed to Methylmercury*, NEUROTOXICOL. 16(4): 689-704 (1995) ["Lapham"], filed as RML 294.

[386] One Rochester brain contained total mercury levels similar to those in the Seychelles brains. Lapham, RML 294, at 696.

[387] The Iraqi infants' brains exhibited a simplified gyral pattern, with fewer and shallower sulci, a short frontal lobe, and reduced volume of white matter. The Iraqi infants' brains demonstrated derangement in the laminar pattern of the cerebral cortex, including disorganization and a lack of definition in the normal layers, with disorientation of cortical neurons and abnormal location of neurons in the cerebrum and cerebellum. The changes in the Iraqi infants' brains were indicative of disordered prenatal development in the second and third month of gestation involving faulty neuronal migration. Lapham, RML 294, at 697-98. This disordered development is a fundamental characteristic of methylmercury exposure in the prenatal period. Lapham, RML 294, at 699.

methylmercury exposure. Lapham, RML 294, at 699. Evidence of a low-grade destructive process in the form of variable numbers of reactive plump astrocytes and increased microglia in the white matter was found in the Seychelles brains. However, this could not be correlated to mercury content, unlike in the Iraqi infants' brains. Lapham, RML 294, at 699.

In comparison of mercury levels detected in other studies of humans and animals, the authors noted that toxic effects of mercury have been shown in brain levels above 1,000 ppb. In the Seychelles brains, the highest levels were all under 300 ppb. In the Rochester reference brains (and in reports from Germany), the levels were under 50 ppb. The highest level in one of the Iraqi brains was 13,700 ppb. Lapham, RML 294, at 700. The study measured both inorganic and total mercury levels, but did not report the inorganic mercury levels separately. *See id*. at 691, 694, 700.

d. TCV Studies.

Although there were no autopsy studies involving human brains and high ethylmercury exposure, several studies examined the effect of TCVs on blood mercury levels.

(1) The Pichichero Studies.

The two Pichichero studies[388] examined the metabolism of TCVs in human infants. The 2002 study measured concentrations of mercury in blood, urine, and feces of 40 full-term infants up to six months of age who received TCVs, as compared to 21 control infants who received mercury-free vaccines.[389] Most of the thimerosal eliminated was through feces. Pichichero 2002, PML 223, at abstract. Mercury was undetectable in the urine samples from most of the infants studied. *Id*. at 1739.

The authors noted that none of the infants had levels of mercury that exceeded those at which neurological effects had been observed.[390] Pichichero 2002, PML 223, at 1740. Doctor Aposhian noted that the blood mercury samples had a broad range, with an almost ten-fold variation between the lowest level and the highest. Tr. at 178. Since the study did not measure baseline levels, it is impossible to determine whether

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[388] Pichichero 2002, PML 223. A subsequent study with Pichichero as the lead author was filed as PML 497 and as RML 379: M. Pichichero, et al., *Mercury Levels in Newborns and Infants After Receipt of Thimerosal-Containing Vaccines*, PEDIATRICS 121(2): e208-14 (2008) ["Pichichero 2008"].

[389] Doctor Aposhian criticized the small sample size in the Pichichero 2002 study, noting that, based on the incidence of ASD, it was unlikely any of the children studied had an ASD. *See* Tr. at 177-78, 182, 185.

[390] This may have been a reference to the Faroe Islands studies, which are commonly cited as evidence of the lowest level of observed effects, but the filed copy of the article does not contain the endnotes indicating which studies were referenced.

this variation was based on the vaccines (or response to vaccines) or based on higher prenatal exposure.

The Pichichero 2008 study involved a larger sample of 216 TCV-exposed infants in three age cohorts: newborns, two-month-olds, and six-month-olds from Argentina, where TCVs were still used. Newborns received vaccines which contained either 12.5 µg or 32.5 µg of ethylmercury. The newborns all had cord blood samples taken before vaccination, and were randomly assigned to have samples of blood, urine, and feces taken at various intervals after vaccination. The two-month-olds received vaccines containing 37.5-57.5 µg of ethylmercury for a cumulative dose of 50-90 µg. The six-month-olds received vaccines containing 37.5-57.5 µg of ethylmercury for a cumulative dose of 112.5-162.5 µg of ethylmercury. Both older groups had blood, urine, and feces samples collected before and after vaccinations, with infants randomly assigned to collection intervals similar to those of the newborns. Pichichero 2008, PML 497, at e209.

Not surprisingly, the highest mercury concentrations were found in the blood shortly after vaccination: at 12 hours in the newborn group and at 24 hours in the two- and six-month groups. The highest detected level was 8.0 ng/mL in a newborn 12 hours after vaccination. Pichichero 2008, PML 497, at e210-11. Inorganic mercury was found in all stool samples, but very little mercury was detected in urine. Pre-vaccination blood samples found levels of mercury ranging from 0.3-5.0 ng/mL, with one newborn testing at 2.6 ng/mL before vaccination. The mercury in 23 post-vaccination blood samples was speciated, with methylmercury levels ranging from 1-50% of the total organic mercury detected. Because the vaccines were also tested for the type of mercury, with only ethylmercury detected, the presence of methylmercury in the blood samples indicated that mercury from sources other than thimerosal contributed to the total amount of mercury found. Pichichero 2008, PML 497, at e211. Pre-vaccination levels of blood mercury were about the same in six-month olds and two-month olds, indicating that TCVs did not cause an accumulation of mercury in the blood. Pichichero 2008, PML 497, at e213.

Doctor Aposhian's comments on the Pichichero 2008 study included the eight-fold variation in mercury levels among the children in the same group, noting that it demonstrated that not all children process mercury as fast as others. He suggested that this represented a difference in how they metabolized mercury, which could be genetically determined. Tr. at 179. He did not explain how this variation would differ from the bell curve of expected responses to drugs or toxins, much less that it constituted evidence of hypersusceptibility. Nor did he explain how very small all the measurements of mercury were.

Because the blood samples in the 2008 study were taken at specific time intervals and the limit of detection was lower, the 2008 study results were more precise and accurate than those from the 2002 study. Pichichero 2008, PML 497, at e209.

Doctor Aposhian called the 2008 Pichichero paper "flawed" because it measured mercury excretion in "normal children." Tr. at 182; Pet. Tr. Ex. 2, slide 49. Of course, at the ages of the children studied (from newborn to six months of age), it would be impossible to determine whether a particular child was autistic. As the effects on blood mercury levels from infant vaccinations can only be measured in infants too young to be classified as autistic, the use of "normal children" can hardly be considered to be a flaw.

Doctor Aposhian's criticism that the study did not provide any information about how much mercury stayed in the brain or other tissues was accurate (Tr. at 182-83; Pet. Tr. Ex. 2, slide 49), but brain biopsies of living children cannot be performed for ethical reasons and thus no study of living children would provide that data. Tr. at 184-85. The authors were not attempting to determine the tissue burden of mercury, only the effect of ethylmercury on blood mercury levels.

Doctor Aposhian cited to a website comment critical of the Pichichero 2008 study made by a Dr. Robert Indech,[391] filed as PML 651, commenting that the reduction in blood mercury levels reported in the Pichichero 2008 paper did not measure whether any mercury was excreted.[392] Other studies, however, have examined how much ethylmercury is excreted in feces, and have determined that a substantial proportion of the ethylmercury from TCVs is excreted in feces. *E.g.*, Clarkson 2002, PML 182, at 16. The Pichichero 2008 researchers examined stool and urine samples, determining that mercury was present, but they did not quantify excretion through feces. Pichichero 2008, PML 497, at e213-14. The Pichichero 2002 study reported the amount of mercury in fecal samples submitted at the time of the post-vaccination blood draws. Mean mercury levels in the spot samples were 82 ng/g in the two-month-old infants and 58 ng/g in the six-month-old infants. Pichichero 2002, PML 223, at 1738. Compared to the blood mercury levels measured, the fecal measurements represented a significant elimination of mercury.

The Pichichero 2008 paper may not have answered all the questions Dr. Aposhian would have liked (or have given answers that he hoped to see), but his conclusion that it is "flawed" is not supported by his testimony.

(2) The Stajich Study, PML 249.

This study compared blood mercury levels in 15 preterm and five term infants after one hepatitis B vaccination. Baseline mercury levels were obtained, with mean blood mercury levels of .04 µg/L in the term infants and .54 µg/L in the preterm

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[391] The website comment was filed as PML 651. Doctor Indech did not identify whether his title reflected a medical degree or any other relevant discipline. His letter was part of an open, on-line forum for peer review comments made post-publication. Comments in this process are not themselves peer reviewed before publication.

[392] Petitioners cited to the same website comment in their post-hearing brief at 22.

infants.[393] PML 249 at 680 (Figure). Blood mercury levels were measured again 48-72 hours after vaccination. Term infant mean blood mercury levels were 2.24 µg/L and mean levels in the preterm infants were 7.36 µg/L. Mean birth weights of the infants were significantly different as well, with the preterm at a mean of approximately .75 kilograms and the term infants at a mean of 3.6 kilograms. *See* PML 249 at 680.

In a 2003 paper[394] that compared a number of studies of thimerosal, Dr. Magos commented that the preterm infants in the Stajich study received, on average, a 4.8-fold higher dose per body weight of mercury than the term infants received, but their blood concentrations after vaccination were only 3.3-fold higher. Based on this, Dr. Magos concluded that the preterm infants actually "handled the ethylmercury load more efficiently than term infants did." Magos 2003, PML 564, at 266. He concluded, based in large measure on the Stajich and Pichichero 2002 studies as compared to earlier work on adults, that mercury clears from the infant body faster than from the adult body. Magos 2003, PML 564, at 268.

C. The Supplemental Reports.

Petitioners filed a supplemental expert report by Dr. Aposhian (Pet. Ex. 21) on April 2, 2009, some nine months after the specific causation hearing in Colin's case, and over 10 months after the general causation hearing concluded. Respondent filed a supplemental expert report by Dr. Brent on May 8, 2009.[395]

Most of Dr. Aposhian's report concerned a complex series of calculations designed to show that TCV-level doses of ethylmercury could produce brain levels of inorganic mercury[396] closely related to those found in the adult primates in the Vahter and Charleston studies. Pet. Ex. 21 at 2-5. The remainder of his supplemental report largely reiterated matters addressed during his testimony concerning the evidence for a

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[393] Although this difference seems large, the authors determined that it was not statistically significant. Stajich, PML 249, at 680-81.

[394] L. Magos, *Neurotoxic Character of Thimerosal and the Allometric Extrapolation of Adult Clearance Half-time to Infants*, J. APPLIED TOXICOL. 23: 263-69 (2003) ["Magos 2003"], filed as PML 564.

[395] These reports may have been filed earlier in the other two Theory 2 cases; I note that the signature page of Dr. Aposhian's report (Pet. Ex. 21 at 7) is dated 7/8/2008.

[396] Doctor Aposhian had also calculated probable brain levels in his initial report. PML 711 at 13-14. Those calculations were based on brain-to-blood ratios, a mechanism for estimating brain mercury levels from blood mercury levels. However, this method produces valid results only when the blood mercury levels have reached steady state (Clarkson and Magos 2006, PML 35, at 646; Cernichiari, RML 72, at 1018), something that will not occur based on administration of TCVs at two-month intervals. *See* Pichichero 2008, PML 497, at e211 (observing that blood mercury levels drop to baseline between TCV injections in human infants).

mercury efflux disorder in children with ASD.[397] Pet. Ex. 21 at 6.

Doctor Brent pulled no punches in his review of Dr. Aposhian's supplemental report, calling it "replete with incorrect statements, poorly researched science, incorrect calculations, and, hence, invalid conclusions." Res. Ex. EE at 1.

Citing the Burbacher, Stajich, and Pichichero 2002 and 2008 studies, Dr. Aposhian attempted to show that vaccine level doses of ethylmercury would produce an average brain inorganic mercury level of 43.7 ng/g. *See* Pet. Ex. 21 at 3-4. In converting blood ethylmercury levels to brain mercury levels, Dr. Aposhian used a conversion factor of 6.0 for brain-to-blood mercury levels derived from Magos 1987, PML 666.[398] He then determined that 34% of the total mercury in the brain would be converted to inorganic mercury, thus deriving the 43.7 ng/g level. Pet. Ex. 21 at 4.

Alternatively, using the highest blood concentrations of ethylmercury from the Pichichero 2008 study, and applying the same brain-to-blood conversion factor of 6.0 and the same 34% conversion factor for total mercury to inorganic mercury, Dr. Aposhian calculated a brain inorganic mercury level of 44.7 ng/g. Pet. Ex. 21 at 5.

Doctor Aposhian then compared both calculated figures to a 60 ng/g level that the Vahter 1994 paper indicated would cause brain neuroinflammation,[399] and

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[397] He prefaced his rebuttal to Dr. Brent's testimony by indicating that new studies had been published since May, 2008. However, there were only two studies discussed that were published in 2008 or later, and, although Dr. Aposhian referred to them by PML numbers (PML 667 and PML 670), the studies themselves were never filed. I decline to place much weight on Dr. Aposhian's recitation of these studies' findings or conclusions.

[398] A copy of PML 666 was never filed.

[399] As the Vahter 1994 study, PML 60, did not measure neuroinflammation, Dr. Aposhian's derivation of this figure requires referencing both the Vahter 1994 paper and the Charleston 1994 paper, PML 33. The Vahter study, PML 60, reported total mercury and inorganic mercury levels for individual monkeys, not mean levels. PML 60 at Table 2. Figure 6 from the Vahter 1994 study, PML 60, shows mean brain levels in a bar graph, but none of those amounts convert to 60 ng/g. One monkey exposed to inorganic mercury had a 60 ng/g (reported as 0.06 µg/g in Table 2, PML 60) level of inorganic mercury in her brain. However, a conclusion regarding "neuroinflammation" in this monkey's brain cannot be drawn because the Charleston 1994 paper, PML 33, reported group results for reactive glia, not results for individual monkeys. The group's inorganic mercury level was 0.106 µg/g. *See* PML 33, Table 4.

Because the increase in reactive glia was reported at a group level, the appropriate reference point for determining the mercury level provoking the increase is the group's mean. Converting the reported 0.106 figure from µg/g to ng/g involves multiplying by 1000 (1 µg = 1000 ng), resulting in the lowest mean level of inorganic mercury at more than 100 ng/g. *See* Charleston 1994, PML 33, Table 4 (level of inorganic mercury in the inorganic mercury group). Based on Table 4, PML 33, one cannot conclude, as Dr. Aposhian did, that 60 ng/g of inorganic brain mercury produces neuroinflammation.

I note that the Charleston 1996 study, PML 116, did not mention the inorganic mercury group at

concluded that TCV levels of ethylmercury would produce sufficient inorganic mercury for adverse effects on infant brains. Pet. Ex. 21 at 3, 5.

With regard to ethylmercury's conversion to inorganic mercury in the infant monkeys' brains, the two witnesses came to similar conclusions. Doctor Aposhian initially calculated that, based on the amounts of ethylmercury and inorganic mercury in the brain at the end of the washout period, the infant monkeys would have approximately 19 ng/g of inorganic mercury in the brain. Pet. Ex. 21 at 3. Doctor Brent calculated that the amount would not be above 20 ng/g.[400] Res. Ex. EE at 4.

However, that is where the agreement between the two witnesses ended. Doctor Brent reiterated his earlier testimony that the infant monkeys would have received 3.3 times the amount of ethylmercury received by human infants.[401] Res. Ex. EE at 5. For the reasons indicated in note 374, I do not completely accept Dr. Brent's calculations. Instead, I conclude that the Burbacher infant monkeys received approximately 2.5-3 times more ethylmercury than human infants received through six months of age.

Doctor Brent's next set of calculations used the baseline mercury data to compute that the amount of inorganic mercury in the brains of the infant monkeys that could be attributed to TCVs was only 4 ng/g (brain concentration of 20 ng/g as measured minus 16 ng/g at baseline = 4 ng/g). Res. Ex. EE at 5. He then applied his

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all. I also note that the Charleston 1994 study also reported that the group of monkeys that received inorganic mercury was the only group to experience edema. PML 33, at 202.

[400] Doctor Brent also referred to a baseline of inorganic mercury in the brains of the infant monkeys of 16 ng/g, using data from the Vahter adult control monkeys from the same facility as the Burbacher infant monkeys. Res. Ex. EE at 5. I did not find the figure that Dr. Brent attributed to the Vahter 1994 study, PML 60. The Vahter 1994 paper did not report mean mercury levels for controls, only individual levels for each monkey, and a mean calculated from the individual total mercury levels is not 16 ng/g. *See* PML 60, Table 2.

Baseline data for the occipital pole of the control adult monkeys appeared in the Charleston 1994 study, PML 33, at Table 4. The inorganic mercury level for the control monkeys was 0.002 µg/g, and the total mercury level was 0.008 µg/g. Converting this data to ng/g involves multiplying the measured mercury by 1000, resulting in 2 ng/g for inorganic mercury and 8 ng/g for total mercury in the control monkeys (1000 ng=1 µg). Because I cannot determine where Dr. Brent derived his data, and because of a concern that adult baselines might be different from infant baselines, I removed the baseline data from all of Dr. Brent's calculations. As this would result in higher amounts of inorganic mercury in the brain attributable to TCVs, petitioners benefit from the removal of the baseline mercury levels Dr. Brent used.

[401] He slightly refined the earlier off-the-cuff calculations he made during his testimony in this portion of his supplemental report (noting that female infants at six months of age would weigh slightly over seven kilograms, versus eight kilograms for males). He divided the weight at six months of age into the total mercury received (187.5 µg divided by 8 kilograms = 23 µg/Kg). However, he did not correct for the fact that some vaccines would have been administered at the lower body weights of birth, one month, two months, and four months of age. By my calculations, *see supra* note 374, the human infants would have been closer to 33 µg/Kg.

correction factor of 3.3, accounting for the lower human infant exposure, to the 4 ng/g level in the infant monkeys (4 divided by 3.3), resulting in a 1.2 ng/g contribution of TCVs to human inorganic brain mercury levels. Res. Ex. EE at 5.

In my own calculation, if I consider baseline mercury levels to be zero, and if I apply the 2.5 correction factor for lower human exposure, I calculate a TCV contribution of approximately 8 ng/g (20 ng/g divided by 2.5 = 8 ng/g). Because there is undoubtedly some level of inorganic mercury in the brains of human neonates (*see* Lapham, RML 294, Table 2),[402] this calculation likely overestimates the TCV contribution to brain mercury levels.[403] I note that 8 ng/g is more than seven times lower than 60 ng/g which Dr. Aposhian associated with neuroinflammation, and more than 25 times lower than the lowest mean level of inorganic mercury reported in the methylmercury-dosed adult monkeys. *See* Charleston 1994, PML 33, at Table 4.

I have no difficulty in accepting the remainder of Dr. Brent's calculations, and concur with his criticisms of Dr. Aposhian's calculations. He indicated that Dr. Aposhian's application of an old brain-to-blood ratio of 6 in humans was incorrect, for a number of reasons. The ratio was not only based on outdated, incorrect information (*see* Res. Ex. EE at 5-6), it was based on methylmercury, not ethylmercury. One of the strongest contributions of the Burbacher study was hard evidence that methylmercury's kinetics cannot be extrapolated to ethylmercury's. Res. Ex. EE at 6 (point 1). The Vahter 1994 study established that the monkey brain-to-blood ratio of 2.6 that Dr. Aposhian used was also wrong. Res. Ex. EE at 6 (point 3); *see also* Vahter 1994, PML 60, at 226 (indicating the ratio is 3.2 at 6 months and 5.1 at 12-18 months). Brain-to-blood ratios are valid only when blood levels reach a steady state, something that does not happen with episodic vaccinations. *See* Res. Ex. EE at 10.

Doctor Brent convincingly explained why Dr. Aposhian's calculations of probable brain mercury levels from the blood data in the Pichichero 2002 study were flawed. *See*

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[402] In the autopsy data from infants who were three days of age or younger at the time of death, total brain mercury levels ranged from below the limits of detection to as high as 38 ng/g in the infants born in Rochester, NY. *See* RML 294, Table 2.

[403] Another study, not referenced by either party, examined the concentrations of total mercury in the occipital lobe of the brain of human fetuses and infants up to three months of age. *See* E. Lutz, et al., *Concentrations of Mercury, Cadmium and Lead in Brain and Kidney of Second Trimester Fetuses and Infants*, J. TRACE ELEM. MED. BIOL. 10: 61-67 (1996) ["Lutz"], filed as PML 198. Doctor Vahter was the senior researcher on this study. The study found mean levels of total mercury of 5 µg/Kg in the fetal brains (Lutz, PML 198, at Table 4), which converts to 5 ng/g. Thus, Dr. Brent was correct in determining that infant brains are likely to contain a baseline amount of mercury, but his estimates of the amount were probably too high (16 ng/g estimated by Dr. Brent, versus the 5 ng/g level found in the Lutz study). I note that the Lutz study figures are lower than those from the same brain region reported for the control infants in the Lapham study, but not by much. Aside from one control brain with much higher levels than any of the others studied (Lapham, RML 294, at 696 and Table 2), the total mercury in the occipital lobe of the brains from infants three days old or younger ranged from amounts below the limit of detection (which varied from sample to sample) to 38 ng/g. Lapham, RML 294 at Table 2.

Res. Ex. EE at 8-12. In addition to the calculation and assumption errors he noted, the infant autopsy study (Lapham, RML 294) found infant brain mercury levels in a chronically mercury-exposed population far lower than Dr. Aposhian's formula would indicate. *See* Res. Ex. EE at 11-12.

D. Doctor Aposhian's Opinion Regarding Mercury Causation of ASDs.

1. Overview.

As indicated above, Dr. Aposhian also offered his own opinion on mercury causation of autism. Although I have concluded that he lacked the qualifications to proffer an opinion on ASD causation, I have, nevertheless, elected to discuss his opinion. His report and testimony[404] presented "six pillars" (points) upon which his opinion rested. *See* Tr. at 420. These six points are: (1) the Adams 2007 study, PML 138;[405] (2) the hair studies by Holmes, PML 237,[406] and Hu, PML 16;[407] (3) the Bradstreet chelation study, PML 244;[408] (4) the efficacy of chelation as a treatment for autism (PML 9);[409] (5) the Hornig study, PML 15;[410] and (6) the Courchesne 2005 paper, PML 104. Doctor Brent methodically dissected the studies upon which five of the six pillars were based.[411] He also noted that these studies did not differentiate between children with early onset and regressive autism, referring to petitioners' hypothesis that mercury was causal of regressive autism. Tr. at 1833-46; Supp. Report of Dr. Brent, Res. Ex. EE, at 8. Of note, of the studies upon which Dr. Aposhian relied, only the Holmes study differentiated children with regressive autism from those with early onset

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[404] A similar hypothesis of mercury causation of autism was presented by Dr. Aposhian in the Theory 1 cases. My conclusions here are based solely on the Theory 2 evidence.

[405] J. Adams and J. Romdalvic, *Mercury, Lead, and Zinc in Baby Teeth of Children with Autism Versus Controls,* J. TOXICOL. ENVTL. HEALTH, PART A 70: 1046-51 (2007) ["Adams"], filed as PML 138.

[406] A. Holmes, et al., *Reduced Levels of Mercury in First Baby Haircuts of Autistic Children*, INT'L J. TOXICOL. 22: 277-85 (2003) ["Holmes"], filed as PML 237.

[407] L. Hu, et al., *Neutron Activation Analysis of Hair Samples for the Identification of Autism*, Poster Presentation: Transactions Am. Nuclear Soc. (2003) ["Hu"], filed as PML 16.

[408] J. Bradstreet, et al., *A Case-Control Study of Mercury Burden in Children with Autistic Spectrum Disorders*, J. AM. PHYSICIANS & SURGEONS 8(3): 76-79 (2003) ["Bradstreet"], filed as PML 244.

[409] Autism Research Institute, *Treatment Options for Mercury/Metal Toxicity in Autism and Related Developmental Disabilities: Consensus Position Paper* (2005) ["ARI Monograph"], filed as PML 9.

[410] M. Hornig, et al., *Neurotoxic effects of postnatal thimerosal are mouse strain dependent,* MOL. PSYCHIATRY 1-13 (2004) ["Hornig"], filed as PML 15.

[411] Doctor Brent declined to address the Courchesne 2005 paper, PML 104, as the paper's subject matter was outside his area of expertise. Tr. at 1833, 1958. However, other witnesses addressed that paper.

or typical autism.[412] Thus, the findings from these studies, even if valid, would relate to most children with autism, not merely to those with regressive or "clearly regressive" autism.

2. Doctor Aposhian's Six Points.

a. Higher Levels of Mercury in Baby Teeth As Evidence of a Higher Body Burden of Mercury.

The Adams 2007 study, PML 138, measured levels of three heavy metals in baby teeth of 16 children with autism and 11 control children.[413] The mean level of mercury in the teeth of children with autism was 0.15 µg/g; the level in controls was 0.07 µg/g.[414] Adams, PML 138, at 1048-49. Based on these findings, Dr. Aposhian concluded that autistic children have a higher body burden of mercury.[415] Tr. at 420-21. However, he did not know if the mercury level in teeth had any correlation with blood mercury levels or brain inorganic mercury levels. Tr. at 425-26.

Doctor Brent pointed out a number of problems with reliance on the Adams 2007 study. Doctor Aposhian conceded that two of Dr. Brent's criticisms were correct, referring to the small number of participants and the failure to match carefully the control children to the case children by gender. Tr. at 422-24, 1836. Only 45% of the control children were male, compared to 81% of the children with ASD. Adams 2007, PML 138, at 1047. There is some evidence that males and females process mercury differently. *See* Tr. at 424,1836; *see also* Woods 2007,[416] PML 428 (showing gender differences in mercury retention).

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[412] Holmes, PML 237, at 280-81 and Table 3. Holmes reported the highest hair mercury levels in the children with regression, who were less severely affected by autism. However, the validity of the levels of mercury reported and the statistical methods used were criticized by Dr. Brent, as discussed below, and thus I do not find the Holmes study's results of much value.

[413] Lead levels in children with autism were a mean of 0.38 with controls showing 0.29. Zinc levels were roughly the same in both case and control children. Adams, PML 138, at 1048-49.

[414] The species of mercury present in the teeth in the Adams study was not determined. Tr. at 425; *see* Adams, PML 138, at 1049.

[415] Doctor Brent pointed out that tooth mercury has not been correlated with body burden of mercury. Tr. at 1836. The only article Dr. Aposhian could reference for such a correlation was one demonstrating that lead in teeth was reflective of body burden of lead, by "Needleman." Tr. at 421. No article by Needleman was filed by petitioners. However, the Tvinnereim study, (*see* H. Tvinnereim, et al., *Heavy metals in human primary teeth: some factors influencing the metal concentrations*, SCI. TOTAL ENVTL. 255: 21-27 (2000) ["Tvinnereim"], filed as RML 488) indicated that teeth may be reflective of metal levels during early life. Tvinnereim, RML 488, at 21-22.

[416] J. Woods, et al., *The Contribution of Dental Amalgam to Urinary Mercury Excretion in Children,* ENVTL. HEALTH PERSPECT. 115(10): 1527-31 (2007) ["Woods 2007"], filed as PML 428.

The mercury levels found in both groups of children in the Adams 2007 study were much lower than those found in the larger Tvinnereim study, RML 488.[417] Tr. at 1835, 1837. Also, the Adams 2007 study failed to control for the type of tooth. The Tvinnereim study established that molars had significantly higher mercury levels than other types of teeth.[418] RML 488, at 23-24. There was no control for pica[419] or for the amount of lead in the teeth, both potential confounders, in the Adams 2007 study. Tr. at 1837. Doctor Brent also pointed out errors in statistical analysis performed by the authors of the Adams 2007 study. Tr. at 1836; Res. Tr. Ex. 4, slide 23.

b. Lower Mercury Levels in Hair as Evidence of Impaired Mercury Excretion.

Doctor Aposhian relied on two hair studies, Holmes, PML 237, and Hu, PML 16, for his contention that children with autism do not excrete mercury as well as children without it. Tr. at 219-20. The Holmes study, which measured only hair mercury levels, found that hair from first baby haircuts of autistic children contained less mercury than that of control children, with the mean level in the autistic group of 0.47 ppm and the mean level in the control group of 3.63 ppm. Tr. at 426; Holmes, PML 237, at 280. According to Dr. Aposhian, the Hu study (referred to by Dr. Aposhian as the "study from the MIT Group") was "confirmation of the Holmes study."[420] Tr. at 428.

Doctor Aposhian acknowledged that only a very small percentage of mercury is excreted through hair. Tr. at 427. He also agreed that diet and chelation would affect the levels of mercury found in hair, and that neither the Holmes nor the Hu study controlled for diet. Tr. at 428-29. However, the strongest evidence undercutting Dr. Aposhian's reliance on Holmes and Hu was that five subsequent studies attempted to

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[417] The Tvinnereim study examined 1271 primary teeth without fillings and demonstrated that the heavy metal content, including mercury, in teeth was affected by the number of caries, the type of tooth, and the amount of lead present. Tvinnereim, RML 488, at 22-24; Res. Tr. Ex. 4, slide 21; Tr. at 1834-35. The mean mercury content of the 554 teeth tested for the presence of mercury was 0.267 µg/g, with a maximum level of 5.293 µg/g and a minimum level of 0.004 µg/g found. Table 2 of that study reflected that teeth with caries had higher levels of mercury than teeth without caries, and the type of tooth affected the level of mercury found. Tvinnereim, RML 488, at 23-24. Mercury levels were affected by lead levels. *Id.* at 24.

[418] Doctor Aposhian was unaware that mercury levels varied depending on the type of tooth tested. Tr. at 424.

[419] Pica involves the ingestion of non-food substances, and children with autism are disproportionately afflicted with pica. Pica can increase levels of heavy metals. Tr. at 1837. *See also* DORLAND'S at 1436.

[420] The Hu study was simply an abstract, which looked at hair mercury levels in only three autistic individuals. Tr. at 1839. Two of the three were undergoing chelation and on a seafood-free diet. The one individual not undergoing chelation had a hair mercury concentration typical of that of the U.S. population. Tr. at 1839-40.

duplicate the Holmes data, but were all unable to do so.[421] These other studies constituted strong evidence of erroneous results in the Holmes study. Tr. at 1840.

A very large study[422] of hair mercury levels among U.S. children showed a mean mercury level of 0.22 parts per million. NHANES, RML 333, at Table 1. Based on this result, both the autistic and control children in the Holmes study had high levels of hair mercury, with the control children having mercury levels almost 15 times higher than the mean U.S. level. Tr. at 1838-39.

The Adams 2006 study, RML 2,[423] found no significant differences in hair mercury levels between children with autism and control children. Adams 2006, RML 2, at 204. Doctor Aposhian offered no comment on this study, and appeared unaware of it. Tr. at 432-33.

The Adams 2006 study's authors commented:

> Overall, it appears that the children with autism do not have major differences in their levels of toxic metals compared to controls. Because mercury toxicity has been suggested as a cause of autism, it is worthwhile to note that the autistic children in this study had levels that were very similar to those of the typical children.

Adams 2006, RML 2, at 204.[424]

Three other studies all failed to duplicate Holmes' results. The Ip study, RML

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[421] In their supplemental expert reports, both Drs. Aposhian and Brent discussed an additional 2008 study by Adams (cited as PML 667) of mercury levels in hair. Pet. Ex. 21 at 6; Res. Ex. EE at 12-13. Because the study was not filed (*see supra* note 397) and the experts differed in their interpretations of the study's findings, I have placed no reliance on it.

[422] M. McDowell, et al., *Hair Mercury Levels in U.S. Children and Women of Childbearing Age: Reference Range Data from NHANES 1999-2000*, ENVTL. HEALTH PERSPECT. 112(11):1165-71 (2004) ["NHANES"], filed as RML 333.

[423] J. Adams, et al., *Analyses of Toxic Metals and Essential Minerals in the Hair of Arizona Children with Autism and Associated Conditions, and Their Mothers*, BIOLOGICAL TRACE ELEMENT RES. 110: 193-209 (2006) ["Adams 2006"], filed as RML 2. The lead author appears to be the same person as the lead author on the Adams 2007 teeth study, PML 138, as both are listed with initials "J.B." and both list Arizona State University as their academic affiliation.

[424] The authors stated that their results were not necessarily inconsistent with Holmes, if the Holmes data reflected a temporary inability to excrete mercury in young infants, perhaps based on a higher use of oral antibiotics (citing to Rowland, PML 187). Adams 2006, RML 2, at 204.

257,[425] did not find a significant difference in hair mercury levels between autistics and non-autistics. Tr. at 429-30. The Kern study, RML 274,[426] also failed to replicate Holmes' results regarding hair mercury levels in children with autism. This study found lower levels of arsenic, cadmium, and lead in the hair of autistic children, but did not find differences in hair mercury in such children to be statistically significant. Kern, RML 274, at abstract. Fido and Al-Saad, RML 138,[427] found higher levels of mercury, lead, and uranium in hair samples in autistics than they did in controls. RML 138 at 293. They noted that "the fetus can inherit heavy metals during pregnancy and these metals can remain in the body tissue for years." *Id*. at 295. Doctor Aposhian was reluctant to put much reliance on the Fido and Al-Saad study, but agreed that its results were the opposite of those from the Holmes study. Tr. at 431-32.

c. Chelation Mobilizes More Mercury in ASD Subjects.

The Bradstreet study found that autistic children excreted substantially more mercury than control children when both were administered succimer (also known as DMSA[428]) for three days. Tr. at 433; Bradstreet, PML 244, at 77. Fifty-five children with autism were matched for age, sex, and vaccination status with eight, non-randomly selected controls. Mean urinary mercury excretion after three days of chelation was 6.42 µg/g of creatinine for the ASD children and only 1.08 µg/g of creatinine for the control children. Bradstreet, PML 244, at 76-77. No pre-chelation levels were

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[425] P. Ip, et al., *Mercury Exposure in Children with Autistic Spectrum Disorder: Case-Control Study*, J. CHILD NEUROL. 19(6): 431-34 (2004) ["Ip"], filed as RML 257. The Ip study's findings with regard to differences in blood mercury levels were challenged in a paper by DeSoto. M. De Soto & R. Hitlan, *Blood Levels of Mercury Are Related to Diagnosis of Autism: A Reanalysis of an Important Data Set*, J. CHILD NEUROL. 22(11): 1308-11 (2007) ["DeSoto"], filed as PML 423. However, DeSoto's reanalysis of the Ip findings with regard to hair mercury levels implied that there were no defects in that analysis. Doctor Aposhian stopped short of agreeing with this statement (*see* Tr. at 431), but the DeSoto article itself clearly so states. *See* DeSoto, PML 423, at 1309.

[426] J. Kern, et al., *Sulfhydryl-Reactive Metals in Autism*, J. TOXICOL. & ENVTL. HEALTH 70: 715-21 (2007) ["Kern"], filed as RML 274.

[427] A. Fido and S. Al-Saad, *Toxic trace elements in the hair of children with autism*, AUTISM 9(3): 290-98 (2005) ["Fido and Al-Saad"], filed as RML 138.

[428] DMSA is dimercaptosuccinic acid, a water-soluble and relatively non-toxic chelating agent. Tr. at 433-34. A chelating agent mobilizes metals. DMSA is FDA-approved for the treatment of children with elevated blood lead levels, but is used off-label to treat mercury or arsenic intoxication because it has proven safe for administration to children. Tr. at 434. DMSA will chelate mercuric mercury, but it mobilizes methylmercury as well. When children are chelated to remove mercury, it is likely that both organic and inorganic mercury are excreted in urine. Tr. at 440-41. The majority of the mercury comes from the kidney, but some comes from other tissues. Tr. at 441. Studies by Dr. Aposhian performed on animals exposed to mercury vapor (elemental mercury) demonstrated that DMSA does not remove mercury from the brain. Tr. at 442.

determined for either group.[429] Tr. at 1843. The authors could not determine whether the higher mercury excretion levels in the ASD children were the result of higher mercury intake or a reduced ability to excrete it without chelation. Bradstreet, PML 244, at 79.

Doctor Brent had a number of criticisms of the Bradstreet study. He noted that the failure to control for diet was a potential confounder and that the control children were typically developing children brought to Dr. Bradstreet's practice based on parental concerns about mercury toxicity. Tr. at 1841-42. Based on the data reported, Dr. Brent attempted to verify that the results were statistically significant, and was unable to do so. Tr. at 1842. He also noted that the range of values produced was huge and overlapping, as reflected on Table 1. PML 244 at 77. The mercury concentrations in the case children varied from zero to nearly 59 µg/g, and the control children's mercury levels varied from zero to 6 µg/g. *Id.*; Tr. at 1842. This range is simply too large from which to draw any conclusions. The urinary mercury levels in the majority of the case children were consistent with those of anyone who is chelated. Tr. at 1843. The study also failed to verify that the chelator was actually administered per the study protocol, and it failed to exclude children who had prior chelation, which may have skewed results. Tr. at 1843.

Doctor Brent also challenged the study's conclusion about "body burden" of mercury, commenting that chelation primarily mobilizes mercury stored in the kidney, and thus conclusions about body burden were overbroad. Tr. at 1843. Doctor Brent criticized the standards of the journal in which the Bradstreet study appeared, noting that studies published in it were not peer reviewed and the journal was not indexed. He also noted that the editor of the journal was associated with SafeMinds.[430] Tr. at 1840-41, 1843-44.

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[429] The failure to ascertain pre-chelation levels of urinary mercury is contrary to standard practice. Doctor Aposhian has performed a number of chelation studies and has published between five and ten peer reviewed articles on chelation. Tr. at 434. Although some of his earlier studies may not have involved pre- and post-chelation measurements, in his later studies, he insisted on obtaining both measurements. Tr. at 435. The Bradstreet study did not take pre-chelation measurements and did not control for diet, which could affect mercury levels. Tr. at 436. However, in his supplemental report, Pet. Ex. 21 at 6, Dr. Aposhian appeared to excuse Dr. Bradstreet's failure to take a baseline test because of the difficulty in obtaining urine specimens from children with ASD. Doctor Brent called this excuse paradoxical because of the apparent ease with which post-challenge urine samples were obtained by Dr. Bradstreet and other researchers. Res. Ex. EE at 13-14.

[430] The SafeMinds website describes it as a group "founded to investigate and raise awareness of the risks to infants and children of exposure to mercury from medical products, including thimerosal in vaccines." SafeMinds (Sensible Action for Ending Mercury-Induced Neurological Disorders) website, http://www.safeminds.org/ (last visited Feb. 20, 2010); *see also* J. Baker, PML 599, at 250-51 (describing SafeMinds as an advocacy organization created by a group of "self-designated 'Mercury Moms'").

Most significantly, the Soden study, RML 458,[431] which was published in a peer reviewed journal, attempted to duplicate the Bradstreet study, while correcting for some of the defects noted in it.[432] The Soden study found no evidence that the autistic subjects had excess levels of mercury or other heavy metals. RML 458 at 479. Only one of the autistic children[433] had a post-chelation urinary mercury level above the limits of detection[434] and none of the typically developing control children did. Because of the small number of control subjects, no statistically significant comparison could be made. RML 458 at 479.

d. Chelation Improves Autism's Symptoms.

Doctor Aposhian's fourth point was based on the 2005 Autism Research Institute Monograph, PML 9.[435] He testified that he relied on this monograph as well as "what parents told me at these think-tank meetings...."[436] He acknowledged that there were

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[431] S. Soden, et al., *24-Hour provoked urine excretion test for heavy metals in children with autism and typically developing controls, a pilot study*, CLIN. TOXICOL. 45: 476-81 (2007) ["Soden"], filed as RML 458.

[432] To correct for flaws noted in the Bradstreet study, dietary restrictions were imposed, pre-chelation (baseline) urine levels were measured, diagnoses of autism were confirmed, and those with previous chelation were excluded. RML 458 at 477-78.

[433] This child was placed on a fish-free diet for one month, then chelated again. The post-chelation urinary mercury declined significantly in the second challenge. Soden, RML 458, at 479.

[434] The limit of detection was 1 µg per 24 hour-urine collection. Soden, RML 458, at Table 1.

[435] This monograph included the disclaimer that it was not intended as medical advice and stated that it represented the consensus opinion of the listed contributors, which include James B. Adams, Ph.D, the lead author of the Adams 2007 paper filed as PML 138; Mark Geier, M.D., Ph.D, who was listed as a petitioners' expert witness; Boyd Haley, Ph.D, listed as a petitioners' expert witness; Elizabeth Mumper, M.D., an expert witness for petitioners; Richard Deth, Ph.D., an expert witness for petitioners; and S. Jill James, Ph.D., the author of several articles filed by petitioners and relied upon by them during presentation of their case. Petitioners' Initial Disclosure of Experts, OAP Master File, filed Feb. 14, 2006 (listing Drs. Adams, Geier, Haley, Mumper, and Deth as petitioners' experts). The monograph included in bold type the following statement: "Overall, our consensus position is that removal of mercury and other toxic metals is one of the most beneficial treatments for autism and related disorders." PML 9 at 5. The only study cited in the monograph to support this claim of improvement after chelation is one by A. Holmes, who presented research results at a meeting, but apparently never published the results. PML 9 at 13, reference 15.

[436] Doctor Mumper also mentioned "think tank" meetings. *See, e.g.*, Tr. at 1193. They appear to be *ad hoc*, rather than standing, groups. Doctor Aposhian described them as "by invitation only" meetings of 20-100 people talking about autism. Tr. at 406-07. The guest list at one he attended involved parents of autistic children, scientists, and physicians. He also indicated that ARI hosted think tanks about twice annually. Tr. at 407; *see also* Tr. at 1199-1200, 1217 (Dr. Mumper discussing ARI-hosted and other "think tank" meetings).

"shortcomings" in relying on parental views,[437] rather than controlled clinical trials. Tr. at 437. He also noted that the ARI Monograph had never been published in a journal. Tr. at 438. He was unaware of any peer reviewed study demonstrating that chelation improved the neurological manifestations of autism. Tr. at 438. The ARI Monograph also indicated that chelating agents did not remove inorganic mercury from the brain. PML 9 at 10, 14; Tr. at 442.[438]

In spite of the lack of efficacy of the most common chelating agents in removing inorganic mercury from the brain, Dr. Aposhian nevertheless relied upon the reported success of chelation in improving the symptoms of autism.[439] He explained that the removal of mercury from other places in the body would have an effect on enzyme levels in other tissues, but did not explain why that would be significant. He agreed that chelation would not reduce the brain damage that he contended inorganic mercury caused. Tr. at 443. He could not otherwise explain how chelation therapy could improve neurologic function in children with ASD, although their purported improvement was one of the points upon which his opinion regarding mercury causation rested. Tr. at 444-45.

Doctor Deth testified that because autistic individuals have oxidative stress throughout their bodies, the chelation of peripheral mercury in tissues outside the brain "can have useful effects by restoring normal metabolism and normal redox state peripherally, helping peripheral cells to work better. And as a result, the beneficial peripheral metabolism can affect [the] brain."[440] Tr. at 579-80. The effect could be reducing the inflammatory cytokines in the blood that contribute to neuroinflammation, or it could be the result of increased availability of specific amino acids affected by mercury. Tr. at 580. Doctor Deth did not identify whether his opinion was theoretical only, or whether it was based on evidence that chelation improved ASD symptoms. Additionally, his views on chelation were shaped by his theory that TCV levels of mercury cause a chronic state of oxidative stress throughout the body, and thus did not

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[437] Respondent's experts noted more than "shortcomings." On cross-examination, Dr. Rutter testified about a number of substances that were, anecdotally, effective in treating autism, but, when tested in a scientific study, were not efficacious. They included fenfluoramine and secretin. Tr. at 3342-43; *see also* Tr. at 3703-04 (anecdotal reports about secretin's efficacy contrasted with results from blinded studies showing no difference in efficacy from placebo).

[438] Doctor Aposhian indicated that he was currently involved in a study of a chelating agent called D-Penicillamine, which decreased both organic and inorganic brain. Tr. at 442-43 (the transcript reflects the testimony as referring to "Depenicillamine"). According to Dr. Aposhian, the paper was being prepared for publication at the time of the general causation hearing, but it was never filed by petitioners.

[439] Doctors Deth and Mumper supported Dr. Aposhian's claim that chelation was effective therapy in autism, in spite of its inability to remove mercury from the brain. Tr. at 580, 1598-99.

[440] The "redox state" of the body refers to the body's oxidative stress level. Doctor Deth's assertions regarding mercury's effects on oxidative status are discussed in Section VII, below.

rely on brain mercury levels exclusively. Doctor Deth's theory of system-wide, mercury-induced oxidative stress was severely undercut by contrary testimony from experts with far superior credentials. *See* Section VII below.

Doctor Mumper also testified that chelation was beneficial in treating some children with ASD. Tr. at 1216. Her preferred method of chelation was to use substances other than chelating agents to help the body excrete mercury.[441] Tr. at 1336. She recognized that no controlled studies had been performed and indicated that she was working with NIH to develop one. Tr. at 1199, 1336-37, 1599.

Doctor Brent summed up his criticism of Dr. Aposhian's fourth point in testifying: "I couldn't find a single study in the peer-reviewed medical literature or scientific literature that demonstrates that chelation therapy is beneficial in autism." Tr. at 1845. Doctor Fombonne concurred. Tr. at 3702-03. He noted that no professional body recommends chelation as a treatment for autism. Tr. at 3703. *See also* Tr. at 2398, 2453 (Dr. Rust concurring that chelation was not effective).

e. Genetic Susceptibility to Mercury.[442]

Doctor Aposhian asserted that children with ASD were hypersusceptible[443] to mercury, stating that "in some specifically susceptible subset of infants who received mercury-containing vaccines on the U.S. vaccination schedule in place from roughly 1991 to 2003, the ethylmercury probably caused the symptoms of autism in many of them." PML 711 at 24. He testified that "many people accept the idea that there's a genetic predisposition to mercury toxicity, I think the effects of mercury, and there are a number of papers that prove that now." Tr. at 276. He specifically referred to the Hornig study, PML 15, in his report. PML 711 at 25. Elsewhere in his report, he relied on acrodynia, commonly known as Pink Disease, as evidence of hypersusceptibility. PML 711 at 19-20. In testimony, he mentioned the "Woods study," apparently referring to PML 45,[444] as evidence of a polymorphism[445] in some individuals occupationally

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[441] Some of her testimony about her chelation practices was unclear. At one point, she testified that she tended not to use it in her practice (Tr. at 1556) and, at another point, indicated that she did chelate children in her clinic but preferred to use "natural chelators," rather than DMSA (Tr. at 1598).

[442] In his report (PML 711 at 25), Dr. Aposhian's fifth point mentioned only the susceptibility of genetically altered mice to mercury, citing the Hornig study (PML 15). A genetic susceptibility in mice to mercury, with mercury producing autism-like symptoms, would be relevant to Dr. Aposhian's assertions that children with ASD are hypersusceptible to mercury's effects. Thus, this section discusses the Hornig study, as well as evidence not addressed elsewhere, regarding the purported hypersusceptibility.

[443] He did not define what he meant by "hypersusceptible."

[444] *See* J. Woods, et al., *The association between genetic polymorphisms of coproporphyrinogen oxidase and an atypicial porphyrinogenic response to mercury exposure in humans,* TOXICOL. & APPL. PHARMACOL. 206: 113-120 (2005) ["Woods 2005"], filed as PML 45. Porphyrins are compounds involved

exposed to mercury. Tr. at 213, 230-31.

For reasons that have more to do with epidemiology than biology or pharmacology, petitioners postulated a small group of children with ASD who are unusually sensitive to the effects of mercury or unable to excrete it properly. As indicated in Section V, a number of epidemiological studies have failed to find any evidence that thimerosal exposure plays any role in the development of autism.[446] However, because epidemiological studies may be unable to rule out the effect of TCVs on a small, "hypersusceptible" group of children, petitioners have argued that there must be such a group. However, acrodynia, polymorphisms affecting porphyrin excretion, and Dr. Hornig's mice all fail to demonstrate the existence of hypersusceptibilty to mercury.[447]

Although Dr. Aposhian's report referenced "Pink Disease"[448] and the urinary porphyrin studies by Woods[449] as additional evidence of the existence of a mercury efflux disorder, neither was discussed at any length during his testimony. *See* Tr. at 141, 160 (Pink Disease) and 213, 230-31 (porphyrin polymorphisms). With regard to Pink Disease, the unavailability of evidence regarding the doses of teething powders

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in the biosynthesis of heme and are excreted in urine. *See* DORLAND'S at 1488-89 (porphyrin and porphyrinogen). Doctor Woods, who was identified as an expert witness for petitioners (*see* PSC's Unopposed Motion for Leave to Designate Additional Expert Witness Dr. James Woods, Ph.D., OAP Master File, filed Aug. 8, 2007), but who was not called, conducted several studies to determine if urinary porphyrins could be used as biomarkers for mercury in occupationally-exposed workers, primarily dentists. He noted that about 12-16% of these individuals had an atypical excretion pattern. *See* Woods 2005, PML 45, at 114. I note that this pattern did not involve mercury excretion; it involved porphyrin excretion. It did not assert that such individuals were "hypersusceptible" to mercury.

[445] Polymorphisms are variations of genes that are sufficiently common in populations that they cannot be considered mutations. *See* DORLAND'S at 1481; Tr. at 619-20.

[446] Parker, RML 368. This literature survey examined 12 studies of the relationship of thimerosal to autism. The authors concluded that there is no reliable evidence of a link between TCVs and autism and that the pharmacodynamics of ethylmercury make such an association unlikely.

[447] Petitioners also argued that the "wide variations" in blood mercury levels in humans after administration of mercury indicate a hypersusceptibility. Pet. Post-Hearing Br. at 21 (citing Pichichero 2008, PML 497). They failed to adduce any evidence that these variations are anything more than a typical dose-response relationship. I note that similar "wide variations" have been found in primate studies. *See, e.g.*, Vahter 1994, PML 60, at 226 (noting large variations in blood half time in individual monkeys, and reports of similar variations in human subjects); Burbacher, PML 26, at 1018-19 (reporting a two-fold variation in blood mercury levels after methylmercury ingestion and similar variation in the thimerosal-exposed monkeys).

[448] *See* A. Dally, *The Rise and Fall of Pink Disease*, SOC'Y SOC. HIST. MED. 10(2): 291-304 (1997), filed as PML 184.

[449] *See* Woods 2005, PML 45. This study identified polymorphisms on the CPOX gene. Woods2005, PML 45, at 119.

used on the children who developed symptoms effectively precludes any conclusions regarding a supposed "hypersusceptibility." With regard to Woods' findings that 15% of dentists occupationally exposed to mercury exhibit an unusual porphyrin excretion pattern (*see* PML 45 at abstract), the Rose study, PML 430,[450] indicates that the polymorphisms associated with this pattern are not present in greater numbers of children with autism.

Doctor Aposhian did not address the Hornig study, PML 15, during his direct examination. His testimony about the study on cross examination could hardly be considered a ringing endorsement of the study's findings. When asked if he still relied upon it, he commented: "That's a very difficult question now, because some people have claimed that they can't repeat it." Tr. at 449. He added that, at the present, he had "no firm opinion" on the study's findings. Tr. at 449.

Doctor Brent testified that the Hornig study's findings were non-replicable by other investigators. Tr. at 1845-46; Res. Ex. EE at 14. Because Dr. Aposhian's reliance on the Hornig study at the hearing was lukewarm at best, but Dr. Deth placed greater reliance on it, further discussion of the study and respondent's criticisms of it are postponed to Section VII below.

In his supplemental opinion, Dr. Aposhian noted that the Laurente study, PML 668,[451] supported the Hornig study's findings. Pet. Ex. 21, at 6. In his supplemental report, Dr. Brent also commented on the Laurente study, noting that the dosing schedule was such that the study animals (hamsters) were administered toxic doses of mercury as evidenced by the 50% weight disparity between the treated hamsters and the controls. Weight loss is a symptom of mercury toxicity. Thus, he did not find it informative on the effects of vaccine doses of mercury on human infants. Res. Ex. EE at 14.

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[450] This group of researchers built on Woods' work to examine the role the CPOX polymorphisms might play in the response of children with autism to heavy metals. The authors indicated that lead and mercury, among other substances, inhibited the role of the CPOX gene, and suspecting that CPOX polymorphisms might play a role in the susceptibility to heavy metal toxicity in neurodevelopment, the study investigated the prevalence of the CPOX polymorphisms in children with ASD. PML 430 at 86. However, the study was "negative for both of the CPOX polymorphisms," indicating that autistic children were less likely to have the polymorphisms associated with atypical urinary porphyrin excretion patterns. PML 430 at 90.

[451] J. Laurente, et al., *Neurotoxic effects of thimerosal at vaccines* [sic] *doses on the encephalon and development in 7 days-old hamsters*, AN. FAC. MED. LIMA 68(3): 222-37 (2007) ["Laurente"], filed as PML 668. This study was initially identified as Pet. Tr. Ex. 11. I note that, with the exception of the senior researcher (a professor in the department of medicine and a member of the internal medicine department at a hospital in Lima, Peru), all the authors were medical students. Aside from any other criticisms of this study, it suffers from some of the same defects in design as the Burbacher infant monkey study. Although it attempted to duplicate the vaccine-level doses of thimerosal, the mercury was injected at two-day, not two-month, intervals, allowing little or no time for the elimination of the first dose before the second and third doses were administered. PML 668 at Table 1.

f. Postnatal Loss of Brain Cells in Autism.

Doctor Aposhian's sixth point posits that autistic children experience a postnatal loss of brain cells, particularly in the cerebellum. Report of Dr. Aposhian, PML 711, at 25. Tr. at 450-51. Doctor Aposhian could not recall the details of the study he cited in support of this point (Tr. at 450-51), but his report reflected that it was the Courchesne study, filed as PML 104, at 584. *See* PML 711 at 25.

Doctor Kemper noted that Dr. Aposhian misread or misinterpreted the Courchesne 2005 paper. Tr. at 2834. The specific neurons reported as decreased in those with autism were Purkinje neurons. PML 104 at 584. These are precisely the neurons reported as decreased in most of the neuropathology studies and which are likely a prenatal loss. *See* Tr. at 2835; *see also* Section IV.G.3.b. Mercury exposure spares Purkinje cells. *E.g.*, Clarkson and Magos 2006, PML 35, at 631.

3. Evaluation of Dr. Aposhian's Causation Opinion.

In his summary, Dr. Brent addressed five of the six points on which Dr. Aposhian's theory of mercury causation of autism rested.[452] He noted that none of the four studies (Adams tooth study, Holmes hair study, Bradstreet chelation study, and Hornig mice study) upon which Dr. Aposhian primarily relied could be replicated, and that the benefits of chelation in treating autism had not been substantiated in any peer reviewed study. *See* Tr. at 1846. Even if mercury is responsible for causing ASD, Dr. Aposhian himself acknowledged the ubiquity of non-vaccine mercury exposure, testifying that humans are exposed to approximately 6-10 µg of mercury vapor from dental amalgams per day, and retain most of the methylmercury to which they are exposed through food, about 6-20 µg per day.[453] Tr. at 461-62.

The Courchesne 2005 paper likewise provided no real support for Dr. Aposhian's causation opinion. This paper summarized findings from many diverse studies and speculated on their implications for autism's causes and treatments, but the comments on cell loss merely reiterated the neuropathology findings. The authors did not attribute such cell loss to postnatal toxic exposures.

E. Factual Conclusions Regarding Mercury.

Doctor Brent referred to a scientific methodology for determining if a given substance was responsible for a particular toxic effect, in which four questions must be

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[452] He specifically declined to address the Courchesne 2005 paper, PML 104, because it was outside his area of expertise. Tr. at 1958.

[453] Doctor Aposhian took his data about methylmercury ingestion primarily from *Toxicological Effects of Methylmercury*, PML 228. Tr. at 460. However, the data did not include any separate table for exposures of children from birth to age three. Tr. at 462.

answered: (1) to what chemical was the patient exposed; (2) how much of the substance was involved; (3) what conditions is the chemical known to cause; and (4) did this exposure cause the condition from which the patient suffers? (a reformulation of Dr. Brent's testimony at 1798-99; and Res. Tr. Ex. 4, slide 3). Essentially, this methodology asks: what, how much, can it, and did it?

Applying Dr. Brent's methodology, I conclude that it is undisputed that human beings are born with some amount of mercury present in their brains. Throughout the first year of life, U.S. children have additional mercury exposure from diet, environment (air and water), and, prior to the removal of most TCVs from the U.S. market, TCVs. Mercury exposure continues throughout life, and some portion of the mercury to which human beings are exposed adds to brain mercury levels.

Petitioners have contended that inorganic mercury in the brain is responsible for at least some cases of ASD. However, the amount of inorganic mercury produced in the brains of infants who received TCVs is extremely low. Doctor Aposhian's calculations of the contribution of TCVs to brain inorganic mercury levels were incorrect, but even if I use his figures, TCVs produced far less than the amount of inorganic mercury in the brain that produced inflammatory responses in adult primates. The actual TCV contribution was undoubtedly much smaller than Dr. Aposhian postulated.

The evidence is clear that ethylmercury, in sufficient doses, is neurotoxic. The brain levels at which toxic effects have been observed are not well-established for ethylmercury, but total brain mercury levels associated with toxic effects are thousands of times higher than the levels produced by TCVs, and hundreds of times higher than baseline measurements in autopsies of human neonates.

Through a series of accidental poisonings, toxicologists have determined the neurotoxic effects from prenatal and early postnatal mercury exposure. Those effects are not ASDs. Through sophisticated tests administered to children in populations exposed pre- and postnatally to levels insufficient to produce toxicity, but sufficient to produce measurable cognitive effects, effects of lower dose exposure have been described. Once again, those effects are not ASDs.

The levels of inorganic and total brain mercury at which widespread evidence of neuroinflammation was observed in the adult monkeys were far higher than the levels found in human neonates (baseline exposure) plus any amount attributable to vaccines. Even in the adult primates, the cellular changes in the brain produced no observable neurological effects after months of daily exposure. Every two days, the adult primates received approximately as much mercury as is contained in all the mercury in the first six months of TCVs, calculated at a dose per kilogram.

Methylmercury has an affinity for certain areas of the brain. The brain areas most affected by mercury are not the areas affected in ASD patients. The brain cells most vulnerable to mercury's effects are largely unaffected in ASD patients.

Conversely, the loss of Purkinje cells is the most consistent pathological finding in the ASD autopsy studies, but mercury exposure spares Purkinje cells while damaging others. The neurological symptoms caused by mercury exposure do not resemble ASD's symptoms and behaviors.

The evidence that some individuals are hypersusceptible to mercury's effects is singularly unconvincing. There is no reliable evidence that mercury levels in children with ASD, with or without regression, differ from those in the general population. There is no reliable evidence that children with ASD respond differently to mercury than neurotypical children do. The studies upon which Dr. Aposhian relied were, in general, poorly performed, and in all cases, their results either had not been or could not be duplicated.

Through Dr. Aposhian, petitioners attempted to demonstrate mercury's probable causal role in ASD. Similarly, through Dr. Aposhian, petitioners attempted to demonstrate that vaccine levels of TCVs, alone or in combination with other sources of mercury exposure, would produce brain levels of mercury sufficient to provoke oxidative stress, oxidative injury, and neuroinflammation. The evidence presented by Dr. Aposhian failed to do either.

Section VII. The Disruption of Sulfur Metabolism Hypotheses.

A. Overview.

Petitioners identified Dr. Deth's three major contributions to the general causation case as: (1) describing the biochemical process by which mercury can create an oxidative environment in the brain; (2) describing the biochemical processes involved in neuroinflammation; and (3) identifying "genetic and epigenetic differences between individuals" to explain why TCVs produce autistic symptoms in only a small number of those exposed to TCVs. Pet. Post-Hearing Br. at 44. This section examines the evidence underlying Dr. Deth's opinion that "the most critical problem in autism" involves maintaining a normal "redox"[454] status in cells (Tr. at 505) and attempts to explain the complex aspects of cellular metabolism involved in the "biochemical processes" to which petitioners' brief referred. It also examines the evidence regarding Dr. Deth's assertions that children with autism have an impaired ability to handle oxidative stress.

Although Dr. Doctor Deth opined on a relationship among autism, mercury, oxidative stress, and cellular metabolism, his qualifications as an expert in several of

[454] "Redox" refers to the balance between reduction and oxidation in cells (Tr. at 2170), concepts explained in more detail below.

these areas were lacking.[455] The effects of oxidative stress were central to his causation hypothesis, but Dr. Deth's only publication on oxidative stress was a review article[456] which set forth much of the same hypothesis regarding the relationship between mercury, oxidative stress, and autism presented in his testimony. His research into the effects of mercury began four or five years prior to his testimony but, as of the May 2008 hearing, he had published only one peer reviewed article on mercury.[457] Tr. at 599-600. He had conducted no research on autism. He has a Ph.D. in pharmacology, teaches at Northeastern University, and maintains his own laboratory there, but his research efforts have focused, not on neurotoxicology, neuropharmacology, autism, or sulfur metabolism,[458] but rather on hypertension and cardiovascular problems. *See* Tr. at 495; *see also* PML 712.

Arrayed against Dr. Deth were five witnesses, including a medical doctor with a specialty in clinical pharmacology (Dr. Roberts, Tr. at 2154-55); a pharmacologist with specialties in environmental toxicology and molecular neuroscience and a research focus on neurodegenerative diseases (Dr. Johnson, Tr. at 2198-99); a neuropharmacologist with a research focus on dopamine receptors (Dr. Mailman, Tr. at 1975, 1977); a molecular biochemist with a research focus in molecular toxicology, sulfur metabolism, and oxidative stress (Dr. Jones, Tr. at 2692-93, 2696-98); and Dr. Brent, a medical toxicologist, who treats adults and children for metal toxicity (Tr. at 1782, 1792). Each of respondent's experts offered relatively brief testimony[459] focused on specific (and different) aspects of Dr. Deth's hypothesis, with their testimony carefully restricted to their own areas of expertise. Each had impeccable academic and research credentials in the areas in which they opined. Taken individually and as a whole, respondent's witnesses were far more qualified than Dr. Deth to opine on the matters in issue. This became very apparent as they pointed out deficiencies in his understanding of the subcellular processes involved in his hypothesis, as well as deficiencies in his own experimental work.

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[455] At least one court, albeit one that applies the *Frye* standard rather than *Daubert*, has excluded Dr. Deth's testimony on the thimerosal-autism hypothesis. *See Blackwell v. Wyeth*, 971 A.2d 235, 265, 268 (Md. 2009) (affirming trial judge's ruling that Dr. Deth's opinions were not reliable).

[456] Deth, PML 563. He acknowledged that this was his only publication on oxidative stress. Tr. at 598.

[457] M. Waly, et al., *Activation of methionine synthase by insulin-like growth factor -1 and dopamine: a target for neurodevelopmental toxins and thimerosal*, MOL. PSYCHIAT. 9: 358-70 (2004) ["Waly"], filed as PML 257. Doctor Deth was listed as the senior researcher. He testified that the Waly article was rejected by three journals before the fourth agreed to publish it. Tr. at 3967-68. Doctor Deth has also published a monograph, which was not peer reviewed, and not filed as evidence. Tr. at 600-01.

[458] "Sulfur metabolism" refers to that part of the body's metabolic processes involving sulfur-containing compounds.

[459] Doctor Brent's overall testimony on mercury toxicology was not brief, but he addressed only certain aspects of Dr. Deth's hypothesis pertaining to mercury's effects.

Summarizing Dr. Deth's opinions on the causal role of mercury in autism is difficult. Not only were the biochemical processes allegedly affected very complex, his explanations of those processes lacked coherence. He opined that very small amounts of mercury had a scattershot effect on a number of biochemical processes, inducing systemic metabolic abnormalities and oxidative stress. PML 713 at 2. He also opined that these metabolic abnormalities resulted in interference with neuronal functioning in attention and cognition, causing the major symptoms of autism. *Id.* at 2, 4.

His entire hypothesis rested on a speculative "genetic susceptibility"[460] to environmental toxins, such as heavy metals in general, and mercury in particular. He asserted that children with autism have polymorphisms–variations in genes that are not considered mutations--that render them more sensitive to mercury's effects by impairing their ability to eliminate ethylmercury, maintain normal oxidative and methylation balance, and maintain synchronization in neuronal signaling. PML 713 at 2.

The scientific studies upon which he relied provided, at best, only tangential support for his hypothesis. His own research, most of which was unpublished, unduplicated, or mentioned for the first time during the Theory 2 general causation hearing, was poorly performed and scientifically implausible. Based on *in vitro* effects of mercury on "neuronal cells,"[461] he claimed that mercury had the same effects on human brain cells. PML 713 at 2; *see also* Tr. at 2204 (Dr. Johnson's summary of Dr. Deth's testimony).

In addition to his own unpublished research,[462] Dr. Deth relied heavily on his one article on mercury, the Waly study, PML 257. Tr. 3967-68. He relied on two studies

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[460] Although it is widely recognized that ASD has a strong genetic basis (*see, e.g.*, Bailey 1995, PML 90), there is virtually no evidence that those with ASD have any genetic susceptibilities or sensitivities to any particular chemicals or toxins not also present in similar proportions of typically developing children.

[461] The cells used in Dr. Deth's unpublished work were actually neuroblastoma cells from a tumor that had originated, not in the brain, but elsewhere in the body. Tr. at 2204-09. This is a common cell line used in research, but peculiarities of this cell line rendered many of Dr. Deth's conclusions highly questionable. *See* discussion at Section VII.C.3.b., *infra*.

[462] Petitioners intimated that Dr. Deth's inability to complete and publish his research was hampered by governmental efforts to suppress research funding into the role of TCVs in autism causation. *See* Tr. at 588; Pet. Post-Hearing Br. at 8. Considerable testimony was devoted to the NIH process for approving research proposals. Tr. at 415-06, 587-89, 656-60, 2203-04. However, there was a dearth of evidence that Dr. Deth's research proposals were turned down due to any malign governmental action. Doctor Johnson was part of the NIH study section that reviewed a grant proposal submitted by Dr. Deth in 2003. His recollection was that Dr. Deth's hypothesis was weak, the preliminary data did not support it, and the proposed experiment was poorly designed. Doctor Johnson convincingly testified that research proposals are evaluated solely on their scientific merit by a group of subject matter experts, not NIH employees. Tr. at 2203-04.

conducted by Dr. S. Jill James,[463] calling them the strongest evidence in support of his hypothesis. Tr. at 583-84. He also claimed that the "strongest evidence" in favor of his hypothesis derived from his own unpublished work on post-mortem brain samples from individuals with ASD. Tr. at 582-83.

Perhaps his most extravagant claim involved the quantity of mercury required to induce the claimed effects. He claimed the ability to detect the effects of mercury on cells at levels 100-1000 times lower than levels used by other researchers. *See* Tr. at 2223-24. He testified that mercury, in amounts at or well below the amounts contained in TCVs, could induce some individuals to enter into and remain in a state of oxidative stress. *See* Tr. at 514-15, 622-23.

In the course of the hearing, nearly every premise of his causation theory, other than that of the ubiquity of mercury exposure in children (with or without autism), was seriously undermined, where not completely demolished. Mercury, and a number of other heavy metals, can affect cellular metabolism, but Dr. Deth's assertions that mercury does so in the manner and at the levels of exposure postulated and with the effects claimed were not scientifically supported. His assertion that oxidative stress in children with autism is causal of their autism was pure speculation.

Some background information on oxidative stress and sulfur metabolism follows, and primarily focuses on the amino acids and processes that are implicated in Dr. Deth's hypothesis and experiments. Thereafter, I discuss the studies upon which Dr. Deth relied and the criticisms of them.

B. Background Information.

1. Oxidative Stress.

a. Physical Chemistry of Oxidation.

Molecules are composed of atoms of one or more elements. Tr. at 2167. Oxidation is the removal of one electron from an atom's outer ring, leaving behind an unpaired electron. Tr. at 2167. An oxidated atom (or the molecule of which it is a part) is referred to as a "free radical." Tr. at 2168. Free radicals are unstable and highly

[463] Doctor Deth identified the two James studies upon which he primarily relied as S. James, et al., *Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism*, AM. J. CLIN. NUTR. 80: 1611-17 (2004) ["James 2004"], filed as PML 5; and S. James, et al., *Metabolic Endophenotype and Related Genotypes are Associated with Oxidative Stress in Children with Autism*, AM. J. MED. GENET. PART B 141B: 947-56 (2006) ["James 2006"], filed as PML 49. Tr. at 583-84. Two additional research papers co-authored by Dr. James were filed as exhibits: James 2005, PML 7; and S. James, et al., *Cellular and mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism*, FASEB J. 23: 1-10 (2009) (epublished) ["James 2009"], filed as PML 760. Her book chapter, S. James, *Oxidative Stress and the Metabolic Pathology of Autism*, *in* AUTISM: CURRENT THEORIES AND EVIDENCE (A. Zimmerman ed., 2008), was filed as PML 705.

reactive; they try to capture electrons from other molecules to restore their stability and balance. Tr. at 2168. If a free radical encounters a lipid[464] containing a hydrogen atom, it will extract the hydrogen atom from the lipid. The lipid then becomes a free radical with an unpaired electron. Tr. at 2168. The lipid radical will immediately react with oxygen in the body, but it will still have an unpaired electron, and thus remains a radical. If it oxidizes another lipid to restore its own balance, it creates yet another free radical lipid. Tr. at 2169; Res. Tr. Ex. 6, slide 5 (illustrating the chain reaction). This chain reaction process continues until it is terminated by an antioxidant molecule donating an electron, a process called reduction. Tr. at 2169. Antioxidant molecules can donate an electron without becoming highly reactive themselves, stopping the chain reaction. Tr. at 2169-70. The state of natural balance between oxidation and reduction (redox) is called homeostasis.[465] Tr. at 3900.

b. Sources of Free Radicals.

Free radicals are produced by the simple act of breathing, because about 1% of the air that we breathe is converted to hydrogen peroxide.[466] Tr. at 518-20, 2702-04. In the process of creating ATP molecules,[467] mitochondria, subcellular organelles present in every cell of the body, also release hydrogen peroxide. Tr. at 521. The innate immune system also produces ROS as a defense against invading microorganisms; microglial cells in the brain perform the same function and also release ROS. Tr. at 511-12; *see also* Tr. at 2191.

c. Oxidative Stress and Oxidative Damage.

There is a distinction among oxidative stress, oxidative damage, and oxidative damage with adverse consequences, although they are on the same continuum. Tr. at 2172, 2193, 2195-96. Oxidative stress is defined as an imbalance in the cell in favor of oxidation, and is a normal part of human metabolism. It can be the cause or the effect of an injury. Exposure to infectious agents, bruising, and exercise may all cause oxidative stress. In the brain, oxidative stress may be produced by a brain disease or by a traumatic brain injury. Oxidative stress is a normal part of human metabolism, and

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[464] A lipid is a polyunsaturated fatty acid. Res. Tr. Ex. 6, slide 5; DORLAND'S at 1055.

[465] DORLAND'S at 859.

[466] Hydrogen peroxide is one type of reactive oxygen, which are collectively referred to as "ROS"–reactive oxygen species. These ROS can attack and damage other cells, in addition to invading pathogens. Tr. at 521.

[467] "ATP" stands for adenosine triphosphate, the body's primary energy source. DORLAND'S at 30; Tr. at 2788. Although ATP can be produced in other ways, mitochondria act as energy factories and are the main source for ATP. Tr. at 530; *see also* PML 713, at 4.

the human body has evolved a battery of protective mechanisms to deal with it.[468] Tr. at 606, 614, 2170-71, 2174-75. Oxidative stress can be beneficial, because a modest degree of it upregulates antioxidant defenses, making them available to combat further oxidative activity. Tr. at 2170-72. Normally, the body senses when its redox status is altered, and responds to oxidation by synthesizing more antioxidant enzymes. Tr. at 2172-73. Some degree of oxidative damage is normal; runaway oxidative damage is not. Tr. at 2196. When oxidative stress is causal of an injury, it is referred to as pathological. *See, e.g.*, Tr. at 2761. Oxidative damage is found in neurodegenerative diseases occurring later in life, such as Alzheimer's and Parkinson's disorders, but the precise role oxidative damage plays in such disorders is not established. *See generally* Tr. at 523, 2174, 2189, 2493.

2. Sulfur Metabolism and Oxidation.

a. Natural Responses to Oxidative Stress.

The human body has evolved sophisticated mechanisms for dealing with both naturally occurring levels of oxidative stress and the increased oxidative stress produced by disease or injury. Tr. at 614, 2171-72, 2174-75. Glutathione ["GSH"], a small peptide present and synthesized in every cell of the body, is the body's primary antioxidant defense mechanism. Tr. at 2701-02, 2705. Thioredoxin molecules complement glutathione in protecting against oxidative stress (*see* Hansen, Pet. Tr. Ex. 6, at 138;[469] Tr. at 2761), but many other antioxidants also exist in the body. Tr. at 2761.

b. Glutathione.

Glutathione is a thiol, a sulfur-containing compound,[470] and the most abundant thiol in the body.[471] Tr. at 2699-2700. It is composed of three amino acids:

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[468] Doctor Deth conceded that the human body has numerous compensatory mechanisms for dealing with oxidative stress. Tr. at 614.

[469] J. Hansen, et al., *Differential oxidation of thioredoxin-1, thioredoxin-2, and glutathione by metal ions*, FREE RADICAL BIO. & MED. 40: 138-45 (2006) ["Hansen"], filed as Pet. Tr. Ex. 6. Doctor Jones was the senior researcher on this study.

[470] Sulfur is the fifth most abundant element in biological systems. Nearly all life on earth depends upon sulfur. Tr. at 2699. A thiol is often represented in scientific nomenclature as "-SH." *See* Rose, PML 430, at 90.

[471] Doctor Deth testified that the normal concentration of glutathione in a cell is 10 millimolar, which is roughly equivalent to the amount of sodium present in cells and bodily fluids. Tr. at 507-08. Doctor Jones offered more nuanced testimony, explaining that cellular concentrations of glutathione vary, based on the cell type. It is present at 10 millimolar in the liver and kidneys, but red blood cells and small intestine cells in a fasting state have much less, only 0.2 and 0.1 millimolar, respectively. Tr. at 2705.

glutamate,[472] cysteine, and glycine, with cysteine in the middle. Tr. at 506-07, 523-24. In a reduced state, the sulfur in a thiol has one hydrogen atom attached. Tr. at 504, 506. When two thiols both have their hydrogen atoms removed through oxidation, the sulfur atoms join together to create a disulfide, or an oxidized form of the thiol. Tr. at 506. When a glutathione ["GSH"] molecule is oxidized, it loses a hydrogen atom, becoming "GS." Two oxidized glutathione molecules will combine, creating oxidized disulfide glutathione ["GSSG"]. Tr. at 2176.

c. Cysteine.

One of Dr. Deth's experiments involved mercury's interference with cysteine transportation and production. Cells obtain cysteine from extracellular sources, with the cysteine transported across the cell membrane; they also obtain it intracellularly, through transsulfuration[473] of homocysteine.[474] Deth, PML 563, at 191; Tr. at 524. Cysteine's oxidized form is cystine. James 2005, PML 7, at 2. The cysteine component of glutathione contains the thiol group to which mercury[475] and other heavy metals bind when glutathione detoxifies heavy metals. James 2005, PML 7, at 2.

d. Glutathione's Functions.

Glutathione has three major detoxification functions within the human body as:

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[472] Glutamate is the substance Dr. Kinsbourne identified as responsible for brain overexcitation in his hypothesis, discussed in Section VIII below.

[473] There was a great deal of testimony, primarily from Dr. Deth, regarding the transsulfuration process by which glutathione and other amino acids are created. To summarize and simplify his complex and sometimes confusing testimony, I note that the transsulfuration pathway is an intracellular process in which homocysteine, an amino acid, is converted to cystathionine, which in turn is converted to cysteine, which is converted to glutathione. *See* James 2005, PML 7, at 2 and Fig. 1.

[474] A third source, protein catabolism, was not implicated by Dr. Deth's causation hypothesis. Deth, PML 563, at 192.

[475] There are two states for mercury, bound and free. Tr. at 3925. Free mercury, in the form of mercury ions, is the mercury available to form compounds; bound mercury has already formed a compound with another molecule or element. Mercury binds easily to sulfur compounds because the electrons in mercury's outer ring easily replace the hydrogen atoms in thiols, creating a strong bond called a mercaptan. Tr. at 499-501. However, virtually any heavy metal, not just mercury, will bond to any thiol. Tr. at 2709. Mercury preferentially binds to serum albumin, rather than the thiols present in red blood cells. *See* Clarkson and Magos 2006, PML 35, at 635. The toxicity of mercury may stem from its ability to form stable compounds with sulfur molecules. C. Carvalho, et al., *Inhibition of the Human Thioredoxin System: A Molecular Mechanism of Mercury Toxicity*, J. BIOL. CHEM. 283(18): 11913-23 (2008) ["Carvalho"], filed as Pet. Tr. Ex. 7, at 11913. The binding of mercury to a thiol permits methylmercury to pass the blood brain barrier and enter the brain. *See id.* at 11913.

(1) an anti-carcinogen;[476] (2) an antioxidant; and (3) a co-enzyme for metabolism.[477] Tr. at 2701-03; Res. Tr. Ex. 9, slide 3. Substantial testimony concerned glutathione's antioxidant role, which involves eliminating reactive chemicals, including ROS, as part of the body's primary defense against oxidative stress. Tr. at 504, 507, 2701-02. Glutathione eliminates most of the hydrogen peroxide produced in the body. Tr. at 2702-03; *see also* Res. Tr. Ex. 9, slide 4 (left center box).

There are natural variations in glutathione content,[478] and a large number of reactions in which glutathione is involved. These mechanisms have evolved to work despite fluctuations in glutathione content, and despite the simultaneous nature of these many reactions. Tr. at 2704-05.

e. Glutathione Production in the Brain.

Doctor Deth's hypothesis and experiments focus on oxidative stress in the brain, and the effect of mercury on glutathione, the primary antioxidant. Although most cells can manufacture cysteine, the precursor to glutathione, astrocytes and neurons cannot. Astrocytes are dependent on cysteine produced in the liver[479] for their synthesis of glutathione. Once produced, cysteine is circulated in the plasma, where it is oxidized to cystine. James 2005, PML 7, at 2 and Fig.1. Cystine is taken up by astrocytes, which convert it to glutathione. Tr. at 509. Astrocytes produce more glutathione than they need, and export the excess into the area around neurons.[480] In this extra-cellular environment, glutathione is converted back into cysteine, which is taken up into neurons by a transporter molecule. Neurons use the cysteine to make their own glutathione. Tr. at 509-10; *see also* James 2005, PML 7, at 2. Thus, astrocytes control the amount of

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[476] Glutathione is the most important anti-carcinogenic chemical in the body, forming part of numerous anti-carcinogenic compounds. Tr. at 2702-04; *see also* Res. Tr. Ex. 9, slide 4 (right side boxes).

[477] An example of glutathione's coenzymatic activity concerns the elimination of formaldehyde through a catalytic reaction. An extensive list of other coenzymatic uses for glutathione is provided on Res. Tr. Ex. 9, slide 4, in the center bottom box. Tr. at 2704.

[478] In a peer reviewed study performed by Dr. Jones' laboratory, the glutathione levels in the adults tested varied by 25-30%, depending on the time of day, producing changes in redox status (the GSH/GSSG ratio). Tr. at 2715-17. Doctor Jones did not identify the study by name or citation.

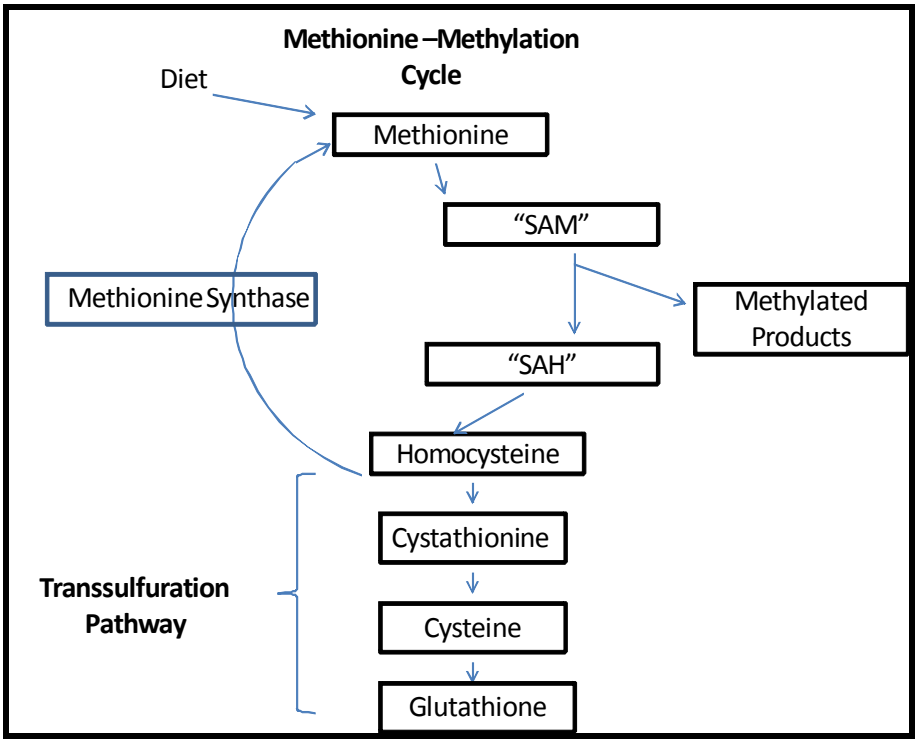
[479] This process involves the production of glutathione in the liver. Glutathione enters the bloodstream, where it breaks down into cysteine and cysteinylglycine. The cysteine is oxidized into cystine, and in that form passes the blood brain barrier. James 2005, PML 7, at 2; *see also* Tr. at 509 (Dr. Deth discussing this cycle in more detail); Pet. Tr. Ex. 3, slide 4.

[480] The process of taking up and exporting chemicals from a cell is accomplished through transporters or antiporters on the cell membrane. Transporters may be unique to a specific class of amino acids or other molecules. Antiporters exchange an amino acid outside the cell membrane for a different amino acid on the inside of a cell. *See generally* Tr. at 510-11, 547, 2749.

cysteine available to the neurons, and ultimately, the amount of glutathione that neurons can produce. Tr. at 510; *see also* James 2005, PML 7, at 2.

f. Homocysteine, the Methionine-Methylation Cycle, and the Transsulfuration Pathway.

Doctor Deth testified at some length about the transsulfuration pathway and the methionine-methylation cycle, and the pivotal role he believes that homocysteine plays in these two metabolic processes. The James 2005 paper, PML 7, at 12, contains a diagram of these two processes at Fig. 1; a simplified version follows:



(1) The Methionine-Methylation Cycle.

The methionine-methylation cycle begins with the sulfur-containing amino acid, methionine. All proteins, which constitute about 20% of the human body, contain methionine.[481] Tr. at 2699. Methionine is obtained either from dietary sources or as the result of recycling from homocysteine. *See* Tr. at 526, 2752-53.

Within the methylation cycle, methionine is activated by ATP to synthesize S-

[481] All proteins contain cysteine as well. Tr. at 2699.

adenosylmethionine ["SAM"].[482] SAM donates a methyl group to produce methylated products for DNA,[483] proteins, phospholipids,[484] and neurotransmitters.[485] James 2005, PML 7, at 2 and Fig. 1; James 2004, PML 5, at 1611-12. In the process of donating the methyl group, SAM is converted to S-adenosylhomocysteine ["SAH"]. SAH is thereafter synthesized into homocysteine. James 2005, PML 7, at 2 and Fig. 1; Tr. at 516, 525; Pet. Tr. Ex. 3, slide 8. Thereafter, homocysteine either enters the transsulfuration pathway or is remethylated by methionine synthase[486] as one source of methionine. James 2004, PML 5, at 1612.

(2) The Transsulfuration Pathway.

Homocysteine production begins with the amino acid methionine and other essential amino acids present in the diet. Tr. at 525. Once homocysteine is created, it may enter the transsulfuration pathway to make cystathionine, which is converted to cysteine, which is in turn converted to glutathione. Alternatively, homocysteine may be recycled into methionine via the action of methionine synthase. *See* James 2005, PML 7, at 2 and Fig. 1. This transsulfuration process is a one way street for homocysteine; if it enters the transsulfuration pathway, it is irreversibly removed from the methionine cycle. James 2006, PML 49, at 948. Doctor Deth testified that there are multiple mechanisms that control the flow of homocysteine toward or away from the transsulfuration pathway. Tr. at 571-72.

C. Doctor Deth's Views Regarding Mercury, Methylation, and Oxidative Stress.

1. Overview of Matters in Dispute.

The information regarding the transsulfuration pathway and methionine-methylation cycle presented above did not appear to be in dispute. However, Dr. Deth presented additional testimony about homocysteine, the transsulfuration pathway, and

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[482] SAM is also a sulfur-containing amino acid. Tr. at 515.

[483] Methylation of DNA is the process by which genes are turned on or off. The failure of a gene to be turned on ("expressed") during development can have significant consequences. Tr. at 516-17. This happens in conjunction with another set of proteins involved with DNA, called histones. DNA methylation and histone methylation are involved in gene silencing, or the epigenetic regulation of genes. Tr. at 517. Interference with DNA methylation as a result of problems with methionine synthase activity was part of the mechanism of injury Dr. Deth postulated as causal of ASD, discussed below. *See generally* Rodenhiser and Mann, PML 459 (explaining DNA and histone methylation).

[484] Phospholipids are phosphorus-containing lipids and are the major form of lipid in cell membranes. DORLAND'S at 1428.

[485] Neurotransmitters are methylated to terminate their activity. Tr. at 517-18.

[486] This involves the transfer of a methyl group from methylfolate (which is produced in an ancillary metabolic process) to homocysteine via methionine synthase. James 2004, PML 5, at 1611.

the methionine-methylation cycle that Dr. Jones testified was incorrect or for which there was insufficient evidence. I set forth Dr. Deth's views first, followed by Dr. Jones' criticisms of those views.

To summarize Dr. Deth's views, mercury depletes glutathione levels.[487] Decreased glutathione causes increased oxidative stress because there is less glutathione available to combat it. Oxidative stress turns off methionine synthase activity, resulting in the production of less methionine. PML 713 at 5. Lowered methionine levels result in reduced SAM production, which means there are fewer methylated products available for DNA methylation, which affects gene expression. Impairments in gene expression can produce autistic symptoms. PML 713 at 5-6.

Reduction in methionine synthase activity affects the D4 dopamine[488] receptor on neuronal cells, adversely affecting neuronal signaling ability, resulting in less synchronization for neuronal activity. According to Dr. Deth, the effect on dopamine receptor activity can produce autistic symptoms. PML 713 at 5.

Both the dopamine receptor effects and reduced gene expression would be enhanced in children with mercury hypersusceptibility because smaller levels of mercury would affect them more. Likewise, children with a genetic predisposition to oxidative stress would be more affected by additional increases in oxidative stress levels. Tr. at 3900-01.

In his report, his article on autism, methylation, and oxidative stress (PML 563), and in much of his testimony, Dr. Deth focused on how these purported effects of mercury on DNA methylation and dopamine receptors caused or contributed to ASD. However, in the more recent experiments, and in his rebuttal testimony, Dr. Deth appeared to shift his focus to the persistence of mercury in the brain. In addition to the effects on methylation activity, Dr. Deth opined that mercury blocked cysteine transporters, and thus affected the ability of neurons to acquire sufficient cysteine for production of the amount of glutathione needed. This effect was enhanced in human brains because neurons lacked the capability to use methionine synthase. As he explained, mercury in the brain stresses cells, affecting their redox status, but also

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[487] The fact that mercury binds to glutathione as part of the body's process for detoxifying mercury is not in dispute. *See* Clarkson and Magos 2006, PML 35, at 627 (discussing the binding of mercury to glutathione before elimination in the feces). Whether vaccine-level amounts of mercury can materially affect glutathione levels is addressed below.

[488] Dopamine is manufactured by nerve cells. About 80% of nerve cells use dopamine to communicate with other cells. Tr. at 1986. A dopamine nerve cell fires when electrically excited, releasing a small amount of dopamine. After release, the dopamine binds to proteins called dopamine receptors located on cell membranes. Tr. at 1987. There are two families of these receptors, the D1 family (consisting of the D1 and D5 receptors) and the D2 family (consisting of the D2, D3, and D4 receptors). Tr. at 1987-88.

interferes with the process by which normal redox status is restored. Tr. at 3916-17. Neurons with depleted glutathione levels cannot maintain homeostasis, resulting in a state of oxidative stress manifesting as the neuroinflammation described by the Vargas study, PML 69. Tr. at 571, 655. He equated inflammation to oxidative stress, representing evidence of oxidative injury. Tr. at 655, 3912-13.

Doctor Deth relied on the Waly study, as well as several unpublished experiments performed in his own laboratory to support the hypotheses he advanced. Additionally, he relied on his discovery concerning an extracellular methylation process involving a receptor for the neurotransmitter dopamine, and the purported inability of human neurons to use methionine synthase in their methionine-methylation cycle. Doctor Deth's views of dopamine receptor methylation and neuronal disabilities shaped much of his research and the conclusions he drew therefrom. Doctor Mailman, an expert on dopamine receptors, challenged this receptor "discovery" and both Drs. Jones and Brent testified that the methionine synthase deficiency was one peculiar to the neuroblastoma cells Dr. Deth used and was not a deficiency in human neurons.

These issues affected the reliability of the causation opinions he proffered. They also influence the weight I have accorded to Dr. Deth's laboratory's experiments and conclusions that he and his research team drew therefrom. Although Dr. Deth's testimony was superficially coherent, the defects pointed out by true experts revealed the critical flaws in Dr. Deth's presentation, and, ultimately established that his hypothesis of causation was not reliable.

2. Disputes Regarding Control of the Methionine-Methylation Cycle.

a. Doctor Deth's Assertions.

Doctor Deth explained that methionine synthase is extremely sensitive to oxidative stress.[489] Tr. at 535; PML 563 at 191. When oxidized, cobalamin stops the process by which methionine synthase converts homocysteine into methionine. Tr. at 540. Less methionine means less SAM is produced, leading eventually to lower production of homocysteine, and lower levels of glutathione. *See* Tr. at 541; Pet. Tr. Ex. 3, slide 15.

[489] The mechanism for this sensitivity involved a fairly convoluted explanation. Doctor Deth testified that methionine synthase has five distinct parts or "domains": homocysteine, methylfolate, cobalamin, SAM, and "CAP" domains. Tr. at 537-39; Pet. Tr. Ex. 3, slide 14. At the heart of the cobalamin domain is a cobalt atom. Homocysteine is converted to methionine by the methylfolate group transferring a methyl group to the cobalt atom through methionine synthase, creating methylcobalamin. Methylcobalamin then transfers the methyl group to homocysteine, which creates methionine. This cycle continues unless interrupted by oxidation. Tr. at 538-39. The portion of methionine synthase that is most easily oxidized is cobalamin's cobalt atom, which acts as an oxygen sensor. Tr. at 539. According to Dr. Deth, oxidized cobalamin stops methionine synthase from reacting with homocysteine because the methyl group cannot be transferred from methylfolate to oxidized cobalamin, and, thus, no methylcobalamin is created. The "CAP" domain limits oxidation of cobalamin, but it is not present in all cells. Tr. at 539-40.

When the redox environment improves, oxidized cobalamin is repaired by SAM, but glutathione is necessary to produce methylcobalamin,[490] the substance used by SAM to repair the oxidized cobalamin. *See* Tr. at 541; Pet. Tr. Ex. 3, slide 16. Doctor Deth called methylcobalamin synthesis "glutathione-dependent." Tr. at 541. According to Dr. Deth, glutathione ultimately controls the methionine-methylation cycle because it controls whether methionine synthase is turned on or off. Tr. at 557.

If methionine synthase is not present or is turned off, homocysteine is involved only in glutathione production, not the methionine cycle. Doctor Deth called this a "switch mechanism." Tr. at 526. When methionine synthase activity is inhibited by oxidative stress, methylation activity within the cell is inhibited, causing reduced methylation of homocysteine, phospholipids, and DNA. Decreased DNA methylation increases the expression of certain genes, including genes that promote DNA and glutathione synthesis. Deth, PML 563, at 193; Tr. at 534-35.

b. Doctor Jones' Views.

Doctor Jones disagreed with Dr. Deth's explanation about glutathione's role in regulating methionine synthase and thereby regulating the methionine-methylation cycle. He testified that the oxidative pathway is controlled by dietary methionine, not glutathione. Tr. at 2752-53. He also testified that Dr. Deth's hypothesis about glutathione's effect on methionine synthase was incorrect. Tr. at 2757.

As Dr. Jones noted, an essential part of Dr. Deth's hypothesis about mercury's effects is that glutathione determines which of the two pathways homocysteine takes. Tr. at 2752. According to Dr. Jones, the scientific literature[491] establishes that the degradative or oxidative pathway is actually controlled by the amount of dietary methionine. Tr. at 2752. If there is an excess amount of methionine in the diet, the system works to stimulate the degradative or oxidative pathway to degrade (get rid of) the excess methionine by transforming it into homocysteine and eventually glutathione. Tr. at 2753.

Another point established by the scientific literature is that SAM regulates two enzymes. One of these enzymes, not glutathione, determines whether homocysteine is degraded or recycled. Tr. at 2753-54. As summarized on Res. Tr. Ex. 9, slide 25, "the scientific evidence does not support regulation of trans[s]ulfuration in response to downstream effects of [glutathione], but rather to control by methionine and SAM."

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[490] Doctor Deth's slides and testimony used the terms methylcobalamin, vitamin B-12, and methyl B-12 interchangeably. For consistency, I use the term methylcobalamin.

[491] The Rodenhiser and Mann article, PML 459, at 343 supports Dr. Jones' position (the methyl groups used in DNA methylation "are acquired through the diet and are donated to DNA through the folate and methionine pathways").

c. Resolution.

I accept the testimony of Dr. Jones as correct. Not only did Dr. Jones possess far greater expertise than Dr. Deth in the areas of cellular methylation and oxidative stress, but also Dr. Jones' explanation of the control mechanism was, unlike Dr. Deth's, logical. Doctor Deth's explanation of how oxidative stress affects cellular metabolism had internal inconsistencies[492] and would result in the process winding down due to an insufficiency of homocysteine. Under his view of the process, lower glutathione levels caused by oxidative stress would reduce methionine levels, which would result in less homocysteine available to produce glutathione. Tr. at 535. This view may account for his statement that the effect of mercury is stoichiometric.[493] *See* Tr. at 3896.

However, the cycle does not wind down under conditions of oxidative stress because, as Dr. Jones pointed out, dietary sources of methionine inject methionine into the cycle at a point before the methylation process that produces, not only cellular methylation products via SAM, but homocysteine as well. Other reasons for rejecting his views of cellular metabolism are discussed below.

3. Doctor Deth's Assertions Regarding Dopamine Receptor Methylation and Human Neurons.

a. The D4 Receptor Methylation Hypothesis.

Doctor Deth testified that, in the course of his research involving cardiovascular systems, he discovered that the D4 receptor[494] for the neurotransmitter dopamine has its own methylation cycle.[495] Tr. at 528. All other methylation cycles occur inside the

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[492] On one hand, Dr. Deth asserted that oxidative stress triggers increased glutathione production, because homocysteine is diverted into transsulfuration because methionine synthase is turned off. Tr. at 535. On the other, he testified that "what we should expect to see during oxidative stress is [too] little glutathione, associated with [the] lower activity of the methylation pathways." Tr. at 537.

[493] He did not explain what he meant by this concept, which is defined as "the study of numerical relationships of chemical elements and compounds and the mathematical laws of chemical changes; the mathematics of chemistry." DORLAND'S at 1763.

[494] Receptors are proteins located on cell membranes that recognize and bind to certain chemicals. Tr. at 1987. Dopamine receptors recognize dopamine, as well as other chemicals. Tr. at 1997. However, dopamine will also bind to other receptors, including those for similar chemical families, such as serotonin or norepinephrine. Tr. at 1997. Not all cells have a D4-type dopamine receptor, but such receptors are present in most neuronal cells, and, in particular, in the "GABA-ergic" or inhibitory neurons. Tr. at 528-29. *See also* Tr. at 803 for testimony from Dr. Kinsbourne about GABA-ergic receptors, such as the D4 receptor.

[495] *See also* Waly, PML 257, at 359. All three of the studies cited in the Waly article for the proposition that a separate D4 dopamine receptor methylation cycle exists are studies from Dr. Deth's own laboratory. *See* Waly, PML 257, at 359, 368 n.15-17. Two of the three studies cited were filed as exhibits:

cell; this was the first instance ever found of extracellular regulation of methionine synthase. Waly, PML 257, at 365; *see also* Tr. at 527-28. Dopamine's role as a neurotransmitter suggested to him that interference with methylation activity in the D4 receptor might play a role in brain dysfunction because disruption of neurotransmitter functions would impact attention and awareness.[496] Tr. at 531-34. Determining why nature allows "this one receptor, and only this one dopamine receptor, to carry out a methylation activity" prompted his research. Tr. at 528.

Because methylation is necessary for dopamine receptors to synchronize the firing of neural networks in the brain (Tr. at 522), Dr. Deth hypothesized that disruptions of the methylation cycle by an environmental trigger would interfere with normal neuronal functioning.[497] The "environmental trigger" dovetailed neatly into Dr. Deth's hypothesis that the D4 receptor could be affected by oxidative stress caused by neurotoxins such as mercury. Deth, PML 563, at 193-94. He testified that impaired methylation results in "impaired attention, impaired gamma synchronization, as well as problems during development with inappropriate gene expression." Tr. at 535. He extrapolated from the connection between a D4 polymorphism and ADHD to suggest that a similar mechanism was responsible for autism.[498] *See* Tr. at 495.

Doctor Deth testified that the D4 receptor has a methionine molecule sticking out from the cell's surface. Dopamine reaching the D4 receptor activates this methionine molecule, causing it to give up its methyl group to the phospholipids on the cell membrane, making the membrane more fluid. Tr. at 527, 529, 531-32. In cells other than human neurons, methionine synthase is then reactivated by a methyl group from SAM. Tr. at 527-28; PML 713 at 5.

b. Defects in Human Neuronal Cells.

Based on research in his laboratory, Dr. Deth asserted that human neurons are

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A. Sharma, et al., *D4 dopamine receptor-mediated phospholipid methylation and its implications for mental illnesses such as schizophrenia*, MOL. PSYCHIATRY 4: 235-46 (1999) ["Sharma"], filed as PML 152; R. Zhao, et al., *Relationship between dopamine-stimulated phospholipid methylation and the single-carbon-folate pathway*, J. NEUROCHEM. 78: 788-96 (2001) ["Zhao"], filed as PML 151. The third study, which was not filed as an exhibit, also had Sharma as the primary author. Doctor Deth was listed as the senior researcher on the two articles filed.

[496] Sharma, PML 152, suggests such a role in mental illnesses.

[497] *See* T. Demiralp, et al., *DRD4 and DAT1 Polymorphisms Modulate Human Gamma Band Responses*, CEREBRAL CORTEX 17: 1007-19 (2007), filed as PML 143. This study found that a genetic variant in the D4 dopamine receptor is a risk factor for attention deficit hyperactivity disorder ["ADHD"], increasing the risk of ADHD by three to five times. Doctor Deth testified that the polymorphism, combined with an environmental risk factor or trigger, results in ADHD. Tr. at 532-34.

[498] However, the Deth paper, PML 563, at 194, noted that the polymorphism involved in ADHD is not increased in autism.

incapable of reactivating methionine through SAM's donation of a methyl group, and must rely on glutathione to reactivate methionine synthase through synthesis of methylcobalamin. Tr. at 541-42; *see also* Tr. at 528; PML 713. Thus, the availability of glutathione to reactivate methionine synthase affects all cellular methylation processes in the brain.

If Dr. Deth's assertion is accurate, the inability of human neurons to activate methionine synthase other than through glutathione would make brain methylation processes highly dependent on glutathione levels. However, Dr. Deth's laboratory supplied the only evidence that human neurons are incapable of reactivating methionine synthase, from experiments on rat brains and on "human neuronal cells." *See* Tr. at 541-42.

Although his experiments were conducted upon what he described as human neuronal cells, Dr. Deth actually used human neuroblastoma cells (SH-SY5Y cells). They were not human neurons (brain cells). Tr. at 2205-07, 3935-36; Waly, PML 257, at 359. The distinction is significant because the cells used have differences from human neurons that cast considerable doubt on whether his experimental results, even if valid, can be ascribed to effects on human neurons *in vitro*, much less *in vivo*. Defects in these neuroblastoma tumor cells also affect the assertion that neurons cannot reactivate methionine synthase.

c. The Waly Study, PML 257.

The Waly study examined the effects of insulin-like growth factor 1 ["IGF-1"][499] and dopamine on methionine synthase activity. Doctor Deth claimed the results supported his hypothesis concerning the dopamine receptor methylation cycle and defects in human neurons. *See* PML 713 at 5.

The first part of the study measured phospholipid methylation and DNA methylation activity in cultured cells at a basal rate.[500] The basal measurements were then compared to the activity after the cells were incubated with either dopamine or IGF-1. Tr. at 564-65; Waly, PML 257, at 359, 364. Dopamine stimulated an increase in folate-dependent phospholipid methylation. Waly, PML 257, at 360. To confirm the D4 receptor involvement in this process, cell membrane proteins were separated and radiolabeled. A single protein corresponding to the D4 receptor was identified using gel electrophoresis. *Id.* at 361. The authors therefore concluded that this stimulation reflected "D4 receptor-directed [methionine synthase] activity." Waly, PML 257, at 366.

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[499] Doctor Deth testified that this is a growth factor "which acts similar to other brain growth factors, neuronal growth factor, brain derived growth factor, and stimulates the signaling pathway that activates the cysteine uptake." Tr. at 565.

[500] "Basal rate" indicates measurements taken in the cellular culture with nothing added to the cells. *See* DORLAND'S at 202.

IGF-1 also stimulated an increase in folate-dependent phospholipid methylation. It increased methionine synthase activity by 212% over the basal level. Waly, PML 257, at 360. Similar effects on DNA methylation were observed, with a six-hour exposure to IGF-1 increasing DNA methylation by more than 100% and dopamine exposure increasing it by 41%. Waly, PML 257, at 364.

4. Problems with Dr. Deth's "Discoveries" and the Waly Study.

a. Dopamine Receptors and the Separate Methylation Cycle.

Doctor Mailman, an expert on dopamine receptors (*see* Tr. at 1977), identified a number of problems with Dr. Deth's assertions regarding dopamine, dopamine receptors, the postulated presence of an extracellular methylation cycle, and the Waly study. In general, he described it as a poor study and one he would not have recommended for publication. Tr. at 1999.

(1) No Evidence for Methionine Synthase at the D4 Receptor.

In summary, Dr. Mailman testified that the only data demonstrating that the D4 dopamine receptor has a separate methylation cycle came from Dr. Deth's laboratory and the papers containing that data did not include information sufficient to establish that the cycle actually exists. Tr. at 2029.

He testified that the D4 receptor does not contain methionine synthase nor any remnant of methionine synthase. Tr. at 2018. Also, there was no evidence that methionine synthase directly interacts with the D4 receptor, that methylation changes the physical properties of cell membranes, or that the type of methyl group transfers described by Dr. Deth actually happen at the D4 receptor. Tr. at 1990-91.

(2) Lack of Appropriate Experimental Controls.

Doctor Mailman described the Waly study as "poorly controlled, even by Dr. Deth's own standards."[501] Tr. at 2015. Dopamine will, at various concentrations, bind to any dopamine receptor, as well as to receptors for other neurotransmitters such as serotonin. The neuroblastoma cell line used has other receptors for dopamine and serotonin; thus the need to use antagonists[502] to block receptors other than the D4

[501] The reference to Dr. Deth's own standards stems from other research done by his laboratory that employed appropriate controls. Tr. at 1997; Res. Tr. Ex. 5, slide 23.

[502] "Antagonist" is used to describe a compound that binds to a receptor, blocking its action and preventing other drugs or compounds from turning it on. Tr. at 1996.

receptor should have been obvious.[503] Tr. at 1997. Also, the Waly study used an antagonist that is known to bind to more than a dozen different receptors as an experimental control, rather than using a more selective antagonist, as Dr. Deth's laboratory did in earlier work. The Waly study used only dopamine as an agonist[504] in examining effects, and used only one antagonist. Tr. at 1996-97. These failures markedly weaken the Waly study's conclusions. Tr. at 1997, 2014-16; Res. Tr. Ex. 5, slide 23. Doctor Johnson echoed Dr. Mailman's comments, noting that the study failed to use selective inhibitors to knock out or target the specific proteins being studied. *See* Tr. at 2220-21.

(3) The Biology of the D4 Dopamine Receptors.

The Waly study attempted to prove that the D4 receptor was responsible for phospholipid methylation. However, the researchers failed to determine which of several different forms of the D4 receptor were present in the cells studied. The antibodies they used in the process combine with several related proteins, making the conclusion that the gel electrophoresis actually measured activity in a D4 receptor highly suspect. Tr. at 1998; Res. Tr. Ex. 5, slide 24.

b. Neuroblastoma Cells, Human Neurons, and Methionine Synthase.

(1) Drawing Conclusions from Poor Experimental Design.

Doctor Mailman explained that an experimental model should be selected based on how it will produce information relevant to the questions being addressed by the study. Tr. at 1994. To adequately test Dr. Deth's hypothesis under appropriate scientific standards, the experiment should have been performed on cultured brain neurons. Tr. at 1995. The failure to do so further weakens Dr. Deth's conclusions. Tr. at 1995-96.

Doctor Johnson buttressed Dr. Mailman's critical comments about the use of neuroblastoma cells and the conclusions drawn from these cells' responses. Tr. at

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[503] Doctor Mailman also pointed out that Dr. Deth's hypothesis failed to account for the large number of signaling mechanisms involved with the D4 receptor and related receptors. Tr. at 1992. He noted that the receptors omitted from Dr. Deth's diagram of the D4 receptor interact with dozens of proteins, including what are called scaffolding proteins, signaling molecules, and other receptors. Tr. at 1991-92. In evaluating the effects of a single compound on a receptor, the researcher must consider all of these interactions. Doctor Deth did not do so. Tr. at 1992-93; *see also* Res. Tr. Ex. 5, slide 19 (reflecting the abundant variety of signaling mechanisms involved in the D4 receptor). Doctor Deth's study design did not account for the known interactions of the D4 receptors with other classes of receptors throughout the brain. *See* Tr. at 2001-02. If thimerosal were having an effect on the D4 receptor, it would affect a number of other pathways, and there is no evidence that it does. Tr. at 2001.

[504] Pharmacologists use the term "agonist" to describe a drug that binds to a receptor and turns it on. Tr. at 1996.

2219-20. Because the Waly researchers used a cell line derived from peripheral neuronal tumors, their results do not reflect what would happen in normal neurons. Tr. at 2219-20.

Doctor Mailman also criticized the study for using only one type of cell, thus limiting any conclusions to that cell type. Given that Dr. Deth's laboratory has used multiple cell lines in past studies, the researchers were clearly aware of the value of parallel studies. Tr. at 1995.

(2) Neurons and the Purported Methionine Synthase Deficiency.

Doctor Johnson, an expert on neurodegenerative diseases, pointed out that Dr. Deth's assertion that human neurons cannot use SAM to reactivate methionine synthase was based on his experiments with neuroblastoma cells. Those cells are mutated and do not have the same type of methionine synthase found in normal cells, including astrocytes and neurons. Tr. at 2219. As one of the principal purposes of the Waly study was to determine effects on methionine synthase activity, the use of cells with an abnormal form of methionine synthase presented a significant problem. Although the precise impact of the methionine synthase mutation on the Waly study's results cannot be determined, the mutation renders their results even less applicable to what happens *in vivo* than most *in vitro* studies. Tr. at 2219-20.

Doctor Brent buttressed Dr. Johnson's testimony that these neuroblastoma cells are defective in methionine synthase, unlike normal human neurons. Tr. at 1827-28. He testified that conclusions drawn from experiments on methionine synthase activity in neuroblastoma cell lines cannot be used to draw conclusions about human brains. Tr. at 1827-28.

c. Conclusion.

The discovery of an extracellular methylation cycle, when all other methylation cycles take place inside cells, is so highly unusual that it warrants independent confirmation. That confirmation is lacking. The assertion in the Waly study that the D4 receptor was the site of the methylation activity was based on gel electrophoresis, but a critical failure in that process was noted by Dr. Mailman. In view of Dr. Mailman's many publications on dopamine receptors, his testimony regarding them carries exceptional weight.

As Dr. Deth had not conducted studies on human brain cells, other than his unpublished work discussed below, his testimony that human neurons lack the ability to use SAM to reactivate methionine synthase lacks scientific support. He based his findings on experiments conducted on cells with a known methionine synthase mutation.

In summary, Dr. Deth and his colleagues designed an experiment around two

faulty premises: the existence of the only extracellular methylation cycle, and a purported defect in human neuronal cells . In view of these problems, and the other issues noted by Drs. Jones and Mailman, any conclusions drawn from the first part of the Waly study are so unreliable as to render its evidentiary value virtually nil.

D. Mercury's Effects on Cell Metabolism.

1. Overview.

Doctor Deth asserted that mercury would stress cells to a more oxidized level. Tr. at 3915-16. For mercury to cause neurological symptoms, it must be present in the brain. However, Dr. Deth was unable to state how much mercury in the brain would be necessary to cause effects on sulfur metabolism. Tr. at 622-23. He contended that small effects might be demonstrated from levels as low as 1 nM of mercury in the brain, but he "guess[ed] it would be the administration of equivalent concentrations that produce 30 nanomolar" as, based on the monkey studies, human brain levels are in that same range. Tr. at 624. Thus, he "would guess that in the range of 10 to 100 nanomolar, in that range, would be sufficient to cause a loss of function." He emphasized that this was not based on an experimental measurement. Tr. at 624-25. He acknowledged that most mercury in the brain would be chemically bonded to other molecules and, based on the strength of the bonds formed by mercury with many substances, these bonds would be unlikely to break. Only mercury in free form would be available to react with other cells, and that amount in the brain was unknown and likely to be low. Tr. at 625-27.

Most of Dr. Deth's opinions about how mercury affects cellular metabolism are derived from the second part of the Waly study and from a series of other experiments in his own laboratory. On May 13, 2008, during the Theory 2 general causation hearing, much of Dr. Deth's research was disclosed to the court and respondent for the first time.[505] Building on the findings of the Waly study, and using the same type of neuroblastoma cells,[506] Dr. Deth and his colleagues developed a series of experiments

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[505] Doctor Deth indicated that he had finished his research on methionine synthase in November, 2007, but he did not discuss any of it in his expert report. Tr. at 561, 649-51. Although his report was dated August 24, 2007, it was not filed in the Theory 2 cases (*Mead* and *King*), until March 20, 2008. The data on Pet. Tr. Ex. 3, slides 24, 26, 28, 31, 34, 35, and 37 were all available by November, 2007, at the latest. Tr. at 649-51. The data appearing on slide 36 only became available a few weeks prior to Dr. Deth's testimony. Tr. at 651-52. When recalled in rebuttal, Dr. Deth testified that he and his colleagues needed to be "more complete in our understanding of these changes in the sulfur metabolism that occur" and to develop "a more satisfying story" before submitting the research results for publication. Tr. at 3907. As of August 27, 2009, the date the evidentiary record was closed, no publication pertaining to these results had been filed, and, to date, there has been no request to reopen the evidentiary record.

[506] Doctor Deth again referred to these cells as "cultured human neuronal cells" in explaining his unpublished research results. Tr. 547. As the testimony of Drs. Mailman and Johnson clearly established, this was an incorrect characterization.

to determine how neurotoxins inhibit the activity of the dopamine methylation system. Using the data presented on slides 21-28, 31, 34, and 35-37 of Pet. Tr. Ex. 3, Dr. Deth described the experiments and their results.

These experiments included measurements of the effects of mercury on: (1) cysteine uptake; (2) glutathione and methylcobalamin levels and methionine synthase activity; and (3) phospholipid methylation in lymphoblasts.[507] He also presented more recent work involving comparisons of the amount of methionine synthase messenger RNA ["mRNA"] in brain tissue from autism patients to that of neurotypical controls.

In discussing a study's findings and the conclusions drawn by Dr. Deth therefrom, I have also included criticisms specific to that study in the same section. To avoid repetition, I have included respondent's experts' criticisms pertaining to more than one study in Section VII.E.

2. The Waly Study, Part 2.

The second part of the Waly study examined the inhibitory effects of ethanol and selected heavy metals on the stimulated activity of both phospholipid and DNA methylation. Doctor Deth characterized the experiments as investigating how "several neurodevelopmental toxins...interfere with this novel mode of regulation." Waly, PML 257, at 359, 363. He used the study's findings to conclude that very small amounts of mercury could disrupt the pertinent cellular metabolic processes, and thus contribute to oxidative stress. PML 713 at 5. The results reflected inhibitory effects from very small amounts of mercury and thimerosal.[508] Tr. at 564-65: Pet. Tr. Ex. 3, slide 30.

a. Findings.

The study found an IC_{50} effect[509] from 15 nM of mercury on IGF-1-stimulated folate-dependent phospholipid methylation. Waly, PML 257, at 363. It also found an IC_{50} effect from 1 nM of thimerosal on basal, IGF-1-stimulated, and dopamine-

[507] Lymphoblasts are cultured white blood cells. Tr. at 566.

[508] Ethanol and lead also had significant effects on methylation, although their effects were not as pronounced as those of mercury and thimerosal. Waly, PML 257, at 361, 363. A dose of 8.8mM (0.04%) of ethanol produced "one of the most highly ethanol-sensitive responses reported to date." *Id.* at 361. It is significant that the Waly study found effects of both ethanol and thimerosal at doses much lower than those reported by other laboratories. *See* Section VII.E.2. below.

[509] "IC" stands for "inhibitory concentration." An IC_{50} value for a substance represents the dose at which the substance inhibits 50% of the reaction being measured. *See* http://goldbook.iupac.org/I03036.html (last visited Feb. 22, 2010) (based on IUPAC, COMPENDIUM OF CHEMICAL TERMINOLOGY (2d ed. 1997)).

stimulated folate-dependent phospholipid methylation.[510] Thimerosal blocked folate-dependent radiolabeling of the D4 dopamine receptor. When divalent copper ions (CU2+) were added, thimerosal inhibition was reduced.[511] Waly, PML 257, at 363. Thimerosal and mercury each reduced methionine synthase activity to a nearly undetectable level and completely blocked the stimulatory effects of IGF-1 and dopamine. Waly, PML 257, at 363. The authors attributed these effects to an inhibition of methionine synthase activity. Waly, PML 257, at 363-64.

The authors commented that mercury levels of 15 nM, about half of what they called a "toxic exposure,"[512] had a potent inhibitory effect on IGF-1-stimulated methylation in cultured cells. Waly, PML 257, at 367. Noting that a single TCV "produces acute ethylmercury blood levels of 10-30 nM, and levels of 3.8-20.6 nM 3-20 days after vaccination (citing to Stajich, PML 249, for the acute exposure level,[513] and Pichichero 2002, PML 223, for the later blood levels[514]), they commented that potent thimerosal effects were observed in their experiment at a 1.0 nM dose. They concluded that thimerosal could, at concentrations well below the levels produced by a single vaccine, adversely affect methionine synthase activity. Waly, PML 257, at 367.

b. Conclusions.

In discussing their results, the authors stated:

Our studies also provide evidence that ethanol, heavy metals and the vaccine preservative thimerosal potently interfere with [methionine

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[510] This is an extremely small dose, a fact that figures significantly in the critical comments of respondent's experts, below.

[511] Divalent copper ions were added, along with the IGF-1, based on a paper showing that the signaling activity of IGF-1 was copper-dependent. Tr. at 565. This addition of copper, and the failure to add copper in one of the unpublished studies, figure in respondent's experts' criticisms.

[512] The authors asserted that the EPA had recommended a definition of "toxic exposure" to mercury as a blood level of 29 nM. Waly, PML 257, at 367. The document cited in the Waly paper for this statement about EPA recommendations was not filed as an exhibit in this case, and thus I cannot determine what was meant by a "toxic dose" or whether the EPA recommendation pertained to another species of mercury. Of course, a blood level of mercury is not equivalent to the dose administered.

[513] The Stajich study actually reported the range of blood mercury levels at 48-72 hours after vaccination. They ranged from 1.3-23.6 µg/L in the preterm infants and from 1.4-2.9 µg/L in the full-term infants. PML 249 at 680.

[514] The Pichichero 2002 study actually measured blood mercury levels in the two-month-old infants between three and 21 days after vaccination. *See* PML 223, Fig. 1. Mercury concentrations were below the detection limit in five of the 17 samples from this group. In the remaining 12 samples, blood mercury levels ranged from 4.5-20.55 nM. Only one of eight control samples had measurable mercury, 4.9 nM. PML 223, at 1738-39 (but note that at one point, the control's blood mercury level is reported as 4.65 nM, and at another as 4.9 nM (*compare* 1739 *with* table at 1738)).

> synthase] activation and impair folate-dependent methylation. Since each of these agents has been linked to developmental disorders, our findings suggest that impaired methylation, particularly impaired DNA methylation in response to growth factors, may be an important molecular mechanism leading to developmental disorders.

Waly, PML 257, at 365.

The paper concluded by once again setting forth Dr. Deth's theory: the rise in autism and ADHD could both be a "manifestation of vaccine-associated neurodevelopmental toxicity, since the D4 dopamine receptor is linked to ADHD," and the receptor's phospholipid methylation function is dependent upon methionine synthase.[515] Waly, PML 257, at 368.

3. The Effects of Thimerosal on Cysteine Uptake.

a. The Experimental Data.

Doctor Deth and his colleagues incubated neuroblastoma cells in various concentrations of thimerosal[516] for one hour and then measured the activity of the EAAT3 cysteine transporter[517] by the uptake of radioactive cysteine in the cells. Tr. at

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[515] The authors caveated their findings by noting that molecular events in tumor-derived cell lines might not resemble those in normal cells, and that cultured cells do not represent the complex *in vivo* environment, where other metal ions, redox status, and other factors could affect methylation. They noted that further study would be needed to "evaluate the possibility that vaccine components...may have contributed to the risk of autism, ADHD and other developmental disorders." Waly, PML 257, at 368.

[516] Doctor Mailman noted that this experiment involved the use of thimerosal, not ethylmercury. Tr. at 2012. *In vivo*, humans are injected with thimerosal, but the body rapidly metabolizes it to ethylmercury. It is ethylmercury that reaches the brain, not thimerosal. Once in the brain, ethylmercury is either excreted or converted to inorganic mercury. Tr. 2011-12. He called the use of thimerosal on the neuroblastoma cells a "cardinal defect," noting that Dr. Deth did not apply his understanding of the biochemical process to his own experiment. Tr. at 2012-13.

[517] Cysteine, like other amino acids, is transported across cell membranes by transporter proteins. Doctor Deth testified that in neurons, the transport is accomplished by the excitatory amino acid transporter-3 ["EAAT3"], which also transports glutamate, the primary excitatory amino acid. Tr. at 510-11, 547; Deth, PML 563, at 191. He intimated that this is the only cysteine transporter available in neurons (Tr. at 545), a point with which Dr. Jones disagreed. Tr. at 2748-49. Two studies indicate that Dr. Jones is correct. *See* L. Mutkus, et al., *Mercuric Chloride Inhibits the In Vitro Uptake of Glutamate in GLAST- and GLT-1--Transfected Mutant CHO-K1 Cells*, BIOLOGICAL TRACE ELEM. RES. 109: 267-80 (2006) ["Mutkus"], filed as PML 571. The study indicated that there are five glutamate transporter subtypes, with EAAT2 comprising about 1% of all brain protein and accounting for over 90% of glutamate uptake in the cerebral cortex and hippocampus. Although the article did not specifically state that these transporters also transport cysteine, it did indicate that cysteine residues were found in several of the transporters. PML 571 at 268. The Aschner 2000 article, PML 568, indicates that there are three EAAT transporters in neurons: EAAT3, EAAT4, and EAAT5. PML 568 at 201. It seems unlikely that the EAAT3 transporter is

547-48; Pet. Tr. Ex. 3, slide 21. They confirmed that they were measuring the activity of the EAAT3 transporter through the use of pharmacological inhibitors. Tr. at 547. As Dr. Deth described the effects, "exquisitely low concentrations" of thimerosal (nanomolar amounts) caused a two-thirds reduction in the uptake of cysteine. Tr. at 548, 3934. Thimerosal inhibited the uptake of cysteine as a function of its concentration (a dose-response effect). Tr. at 547. Doctor Deth compared the reduction of cysteine uptake from nanamolar amounts of thimerosal to the reductions produced by similar amounts of lead, arsenic, aluminum, and mercury (all metals with an affinity for thiols). Thimerosal showed the greatest effect. Tr. at 548-49; Pet. Tr. Ex. 3, slide 21.

Doctor Deth testified that 30 nM concentrations of thimerosal, a level that has been measured in plasma and which has been estimated to occur in the brain after vaccination, caused a two-thirds reduction in cysteine uptake.[518] Tr. at 548; Pet. Tr. Ex. 3, slide 21. Doctor Deth was relying on Dr. Aposhian's estimates of brain mercury concentrations in human infants as evidence that vaccines could produce a 30 nM level of mercury in the brain.[519] Tr. at 548.

b. Evidence of a "Cystathionine Block" in Human Brains.

Building on this unpublished data showing that mercury impeded cysteine uptake, Dr. Deth opined that the effects of mercury's interference with cysteine uptake would be greater in humans than in monkeys, in an apparent reference to the cellular effects of mercury found in the adult monkey brains (the Charleston studies). Tr. at 549-50. He based this opinion on a 1958 paper showing higher levels of cystathionine[520] in human brains than in monkey or other animal brains. Tr. at 543, 2225-27; Pet. Tr. Ex. 3, slide 17. From the difference in cystathionine levels in human versus animal brains, Dr. Deth concluded that there was a "block in human brains after the cystathionine that limits its ability to go all the way to cysteine and glutathione." Tr. at 543. He opined that this phenomenon makes human neuronal cells more dependent

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the only one of the three to transport cysteine, particularly in view of the continued, albeit reduced, cysteine uptake found in Dr. Deth's own experiments. *See* Tr. at 548.

[518] He indicated that a 30 nanomolar level of thimerosal was represented on his chart at a point between the 10^{-7} and10^{-8} entries.

[519] The estimate of 28.7 nM appeared in Dr. Aposhian's initial report. PML 711 at 14. In his supplemental report, Dr. Aposhian's calculations were performed using nanograms per gram. Regardless of the measurements used in his computations (molecular weight or weight), I do not consider Dr. Aposhian's estimates of brain mercury concentrations caused by TCV administration to be valid, as discussed in Section VI. Thus, Dr. Deth's assertion that a 30 nM level of mercury in the brain could be produced by TCV administration is likewise invalid.

[520] Cystathionine is the first of the two intermediate steps on the transsulfuration pathway between homocysteine at one end and glutathione on the other. Cysteine is the second intermediate step, falling between cystathionine and glutathione. Tr. at 543.

on the uptake of cysteine from outside the cell, primarily from the astrocytes, through their release of excess glutathione. Tr. at 544.

c. Conclusions Drawn by Dr. Deth from Cysteine Uptake Data.

Doctor Deth concluded that the effects of mercury on the neuronal cysteine and glutamate EAAT3 transporter would make human cells especially vulnerable to oxidative stress. When neurons are subjected to oxidative stress, they respond by taking up more cysteine to synthesize more glutathione. Deth, PML 563, at 191. If there is a block inside human brains at the cystathionine level, then taking up cysteine from extracellular sources becomes more critical to producing glutathione and maintaining a normal oxidative state. Because mercury interferes with this extracellular intake by its effects on the EAAT3 transporter, the neuronal ability to deal with oxidative stress would be significantly impaired. Tr. at 545, 547. According to Dr. Deth, his own work and studies involving mouse brains[521] demonstrate that the EAAT3 transporter is "absolutely critical for survival and normal function of neurons." Tr. at 545, 3933-34.

d. Criticisms Specific to the Cysteine Uptake Experiments.

(1) No Evidence for a Metabolic "Block."

The only support for Dr. Deth's conclusion that human brains have some type of metabolic block between cystathionine and cysteine is 1958 data. Even assuming that these data are accurate (an assumption challenged by Dr. Johnson (*see* Tr. at 2225-26)), Dr. Deth jumped from high cystathionine levels to the conclusion that there was a blocked metabolic process without any data that such a block actually exists. He did not rely on any measurements of lower cysteine and glutathione levels in human brains; he simply concluded that they must be low as a result of high cystathionine levels. It is equally likely that cysteine and glutathione levels are also higher in human brains. Tr. at 2225-26. Noninvasive measurements of brain glutathione levels by MRI are possible. *See* Tr. at 2700-01.

(2) Transport Mechanisms.

Doctor Deth relied upon an inhibition of cysteine transport through the EAAT3 transporter as a critical aspect of his hypothesis. According to Dr. Jones, Dr. Deth's hypothesis did not account for basic cell physiology. Cells constantly manufacture proteins, and to do so, they need all 20 amino acids. Tr. at 2748. All cells have multiple amino acid transporters and antiporters to keep them supplied with appropriate

[521] In mice, when the EAAT3 transporter is knocked out, there is a major decrease in glutathione levels, and the mice suffer neurodegenerative consequences. According to Dr. Deth, in mature neurons, the literature indicates that the EAAT3 transporter is the source for more than half of cysteine uptake. When this transporter is blocked, Dr. Deth's studies demonstrated that two-thirds of the uptake of cysteine was blocked. Tr. at 3934.

concentrations of all amino acids. Tr. at 2748-49. A high concentration of one amino acid in the cell will result in its transportation outside of the cell, while a second amino acid the cell needs is transported into the cell. Tr. at 2749.

Doctor Deth's own data on cysteine uptake in the presence of various concentrations of thimerosal illustrated this point: Over a very broad range of concentrations of thimerosal, there was little to no change in cysteine uptake, reflecting the presence of other cysteine transporters. Tr. at 2750. Based on similar experiments in other cells and other culture conditions, even the highest concentrations of thimerosal Dr. Deth used permitted enough cysteine to enter the neurons to allow them to synthesize sufficient glutathione and produce proteins. Tr. at 2750-51. Thimerosal may have inhibited cysteine transport in this cell line, but not sufficiently to support Dr. Deth's hypothesis of an ultimate effect on glutathione synthesis in the human brain. Tr. at 2751.

4. Effects of Thimerosal on Glutathione and Methylcobalamin Levels.

Doctor Deth's unpublished work also examined the effects of mercury and thimerosal on glutathione and methylcobalamin levels, and on measurements of methionine synthase activity.

a. Findings.

In this experiment, a one-hour incubation of human neuroblastoma cells in thimerosal at various low concentrations reduced glutathione levels, with reductions increasing as the dose increased.[522] Tr. at 553; Pet. Tr. Ex. 3, slide 24. A 30 nM concentration of thimerosal reduced glutathione levels by about two-thirds. A one hour pretreatment of neuroblastoma cells with a 100 nM concentration of thimerosal reduced methylcobalamin levels to almost zero. Tr. at 556. Measurements of methionine synthase activity after incubation of the cells in various concentrations of thimerosal demonstrated a complete loss of methionine synthase activity at very low doses of thimerosal in the presence of hydroxyl-B-12, and a substantially reduced activity level at higher levels of thimerosal in the presence of methylcobalamin.[523] Tr. at 559-60. *See* Pet. Tr. Ex. 3, slide 28 (chart in lower left corner illustrating the methionine synthase activity in the presence or absence of methylcobalamin). Inorganic mercury also had a potent effect, only slightly less than that of thimerosal. Tr. at 561.

b. Conclusions.

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[522] Referencing again the incorrect assumption that TCVs could produce a 30 nM brain mercury level, Dr. Deth noted that the 30 nM level effects were represented by the mark between the 10^{-7} and 10^{-8} levels on slide 24, Pet. Tr. Ex. 3. Tr. at 555.

[523] Doctor Deth explained the effect of having methylcobalamin as a co-factor was that glutathione did not have to reactivate methionine synthase because the methylcobalamin did. *See* Tr. at 558.

According to Dr. Deth, a reduction in glutathione levels would predict a reduction in the synthesis of methylcobalamin, precisely the result Dr. Deth obtained. Tr. at 556. He testified that, without methylcobalamin, methionine synthase would be effectively turned off in the brain and would remain turned off until normal oxidative status was regained. Without methionine synthase, the D4 receptor's methylation activity would be inhibited. Persistent inorganic mercury in the brain would perpetuate this effect, and if normal oxidative status were not regained, there would be a persistent loss of the role of the D4 dopamine receptor. Tr. at 557-58.

c. Criticisms of the Data and Conclusions.

(1) Timing is Everything.

Doctor Johnson explained that Dr. Deth's selection of a one-hour exposure period was calculated to demonstrate the maximum effect on glutathione levels. In studies of this nature, the standard practice would be to measure the effect of thimerosal (or ethylmercury or other heavy metals) over time. In response to exposure to a toxin, glutathione levels are initially reduced as the glutathione binds to the toxin. Reduced glutathione levels trigger the manufacture of more glutathione, restoring and eventually exceeding baseline levels. Tr. at 2229-30. It is this response to oxidizing agents that caused Dr. Johnson to comment that mild oxidative stress is actually good for the body. Tr. at 2229.

By picking a one-hour time frame, what Dr. Deth and his colleagues measured was a very acute depletion of cellular glutathione.[524] Tr. at 2229. At 24-48 hours after exposure, the basal level of glutathione may be doubled or even tripled over baseline, making the exposed cells more resistant to toxicity. By selecting only one time point to measure effects, Dr. Deth ignored the effect of dose over time. Tr. at 2230. What Dr. Deth's data represented is a preconditioning response, demonstrating that a little stress is good because it triggers compensatory mechanisms. *See* Tr. at 2230-31.

Doctor Jones concurred with Dr. Johnson's testimony, describing in more complex terms how the body reacts to lowered glutathione levels and what types of substances trigger these effects. *See* Tr. at 2739-43.

(2) Basal Levels of Glutathione.

Doctor Johnson testified that the basal levels of glutathione Dr. Deth reported in his unpublished work on SH-SY5Y neuroblastoma cells were inconsistent and wrong. On one slide, Dr. Deth reported a basal glutathione level of about 700 nM per milligram

[524] Doctor Johnson clearly identified Res. Tr. Ex. 7, slide 11, as containing hypothetical data to illustrate this well-known effect. Tr. at 2230.

of protein.[525] On another, he reported a basal level of over 1500 nM of glutathione per milligram of protein for the same cells.[526] Tr. at 2228.

In a number of other papers that measured glutathione levels in these same SH-SY5Y cells, Dr. Johnson found that the basal level of glutathione was reported as between 12 and 30 nM per milligram of protein. Tr. at 2228-29. He testified that the discrepancy between Dr. Deth's results and these other studies could simply be a calculation error, but it evinced a "careless nature" regarding evaluation and reporting of data. Tr. at 2229. Someone with familiarity with glutathione levels, the published literature, and these cells "would have noticed that these numbers are extremely high and far off base." Tr. at 2229.

Doctor Jones was also critical of Dr. Deth's report of thimerosal's effects on glutathione levels because the glutathione levels Dr. Deth reported did not make sense. Tr. at 2737. Liver cells contain the highest levels of glutathione in the body at approximately 10 millimoles of glutathione, but the graph appearing on Pet. Tr. Ex. 3, slide 24, reflects 750 nanomoles per milligram of protein, a figure that would require a level of 20 millimoles of glutathione in tissue.[527] There is no body tissue that contains glutathione at that level.[528] Tr. at 2738.

Doctor Deth responded to the criticisms by saying that he found conflicting reports in the literature concerning glutathione levels in the cells he used. He indicated that he would return to his lab and check the calculations.[529] Tr. at 3922. Nevertheless, he contended that thimerosal resulted in a 40% decrease in glutathione levels, reflecting thimerosal's interference with sulfur metabolism. Tr. at 3922.

5. Phospholipid Methylation in Lymphoblasts.

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[525] *See* Pet. Tr. Ex. 3, slide 24.

[526] *See* chart "f" on Pet. Tr. Ex. 3, slide 28.

[527] Doctor Jones computed the amount taking the amount of protein (20%) and the amount of water (70%) in mammalian tissue. For one milligram of protein, there would be 3.5 microliters of water, then converted the figures to milimolar concentrations. He testified that there would be about 750 nanomoles in about 3.7 microliters. Tr. at 2737.

[528] Doctor Deth's explanation was that Dr. Jones misunderstood the graph. He explained that his graph represented a 300 mole per milligram change in glutathione level based on a one nanomole change in the amount of thimerosal. He indicated that this was evidence of the "big multiplier" effect of thimerosal on regulatory proteins. Tr. at 3920-21. However, that is not what the slide indicated. The axis is clearly labeled as nanomoles of glutathione per milligram of protein, not as a change in the amount of glutathione. Pet. Tr. Ex. 3, slide 24. If the slide correctly reported the findings, there is something wrong with the data. If the slide, which is clear on its face, does not represent what the study found, this is simply one more reason to give little weight to Dr. Deth's unpublished work.

[529] No additional information was provided to the court.

Based on the findings of the Waly study regarding thimerosal's effects on phospholipid methylation in neuroblastoma cells, Dr. Deth's laboratory decided to measure the effect on lymphoblasts to determine the relative sensitivity of two cell types. Although affected by thimerosal, lymphoblast phospholipid methylation was about 10 times less sensitive than that of the neuroblastoma cells used in the Waly experiment. Tr. at 566; *see also* Pet. Tr. Ex. 3, slide 31. Doctor Deth attributed this effect to transsulfuration being less efficient in the "most vulnerable cells types," such as neurons. Tr. at 566-67.

6. Brain Tissue Studies.

Doctor Deth's laboratory received brain tissue samples from the Autism Tissue Program, which included "the same samples in most part used by Vargas, et al, [PML 69] in their study." Tr. at 568. He described the evidence from his laboratory's work with messenger RNA derived from these samples as the strongest evidence in favor of his hypothesis. Tr. at 582-83. Doctor Deth explained the rationale behind these studies, but his explanations were not coherent.

According to Dr. Deth, the availability of methionine synthase "depends upon its gene in the DNA, which is transcribed to...messenger RNA, which then gives rise to the final protein enzymes." Tr. at 567. Thus, methionine synthase activity can be regulated at the protein level. Tr. at 567. He attempted to explain this concept:

> For instance, the cofactor can be oxidized of B12, it can be exerted at the level of the messenger RNA, which can be, for example, determine (sic) how much messenger RNA is translated into protein. Or it can be at the gene level itself, how much original product from the gene is made into messenger RNA that is transcription. So we can see that nature can regulate the activity of methionine synthase in very short microseconds or millisecond waves, that's a level of the co-factor, or for days or hours at a time, depending upon which level of control is chosen.

Tr. at 567-68. Although there may be some transcription errors, this particular excerpt is more incoherent than most of Dr. Deth's testimony. It appeared that Dr. Deth was attempting to measure the quantity of mRNA present and available to code for the proteins that are a part of methionine synthase, and thus compare methionine synthase activity in the brains of those with ASD to control brains.

a. Findings.

Using PCR, Dr. Deth's laboratory amplified the mRNA samples and estimated the amount of mRNA available for methionine synthase in both individuals with autism

and controls.[530] Tr. at 569. Instead of using primer sets directed against the entire mRNA gene, the laboratory devised primer sets directed against each of the component proteins (domains) in methionine synthase. Tr. at 569-70. A comparison of the amounts of mRNA for the CAP and cobalamin domains in autistic brains versus controls is set forth on Pet. Tr. Ex. 3, slide 34. The amounts of mRNA for these two domains were significantly lower in the autism samples. Tr. at 570. The amount of mRNA for the CAP domain varied by age, with more differences between case samples and controls at younger ages, but less difference between the case and control samples in the older patients. Tr. at 572-73; Pet. Tr. Ex. 3, slide 36.

b. Conclusions.

To Dr. Deth, this suggested "the possibility that there is a relationship between lower levels of the messenger RNA of methionine synthase, and the presence of inflammation." However, he did not measure inflammation in the samples he tested. Tr. at 570-71. Reasoning very indirectly, he concluded that less mRNA meant less methionine synthase, which meant that homocysteine would be diverted to making glutathione, which fights oxidative stress.[531] Tr. at 571. Because methionine synthase is a sensor for oxidative stress, reduced methionine synthase would indicate the presence of oxidative stress in the brain, and would be evidence of an adaptive response to oxidative stress and neuroinflammation. Tr. at 571. The presence of both neuroinflammation and reduced methionine synthase suggested to him that the two outcomes are related. Tr. at 571. He interpreted the CAP domain findings as suggesting that the reduction in methionine synthase had a greater impact in the young. Tr. at 573.

c. Criticisms.

Doctor Johnson had significant concerns about the unpublished data pertaining to PCR testing in these brain samples. Tr. at 2235-37. He noted that the presentation did not include information that would be expected in a peer reviewed study before any scientific weight would be accorded the data. This included: (1) the number of samples analyzed; (2) the amount of RNA in the assay; (3) the standards for the PCR reaction; (4) the use of a housekeeping gene as a control;[532] and (5) the quality of the RNA. Tr. at 2235-37. Having experienced difficulties in obtaining reliable RNA samples from Down syndrome postmortem samples, Dr. Johnson was concerned about the RNA

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[530] On rebuttal, Dr. Deth testified that the mRNA in the samples was converted in the laboratory to complimentary DNA ["cDNA"] at a lab in Rome. The cDNA was then amplified. Doctor Deth's team measured the mRNA levels of methionine synthase. Tr. at 3905.

[531] This reflected Dr. Deth's view that methionine synthase controlled what happened to methionine and homocysteine, rather than dietary methionine levels. *See supra* Section VII.C.2.a.

[532] Doctor Deth testified on rebuttal that a housekeeping gene was used. Tr. at 3906.

quality in this case. Without RNA gels and analysis to determine that the RNA is good, running the assays is pointless. Tr. at 2237. Doctor Johnson found it impossible to get a sufficient yield of high-quality RNA from which to run PCR. Tr. at 2237.

The data presented in Dr. Deth's slides and testimony did not indicate how many samples were analyzed, or how the assay was run. Tr. at 2235. There is no indication of the RNA quality, and, according to Dr. Johnson, "if there's any RNA breakdown in the samples before you run this assay it can completely mess up what you're trying to interpret." Tr. at 2237.

In the Purcell study, PML 567,[533] researchers examined cerebellar tissue samples using high-density microarrays to measure gene expression.[534] The authors noted the difficulties of analyzing RNA from postmortem brains in terms of quality and the effects of events that preceded death. They described the efforts they used to confirm the quality of the tissue, using measurements of pH and gel electrophoresis. Purcell, PML 567, at 1618-19. Doctor Deth did not describe any methods used to confirm tissue quality, and I note that his CV does not reflect any publications with titles reflecting the use of PCR in research. He did not describe any research background in PCR.

I find Dr. Johnson's concerns about the reliability of this evidence very persuasive.[535] Without the type of data Dr. Johnson referenced and which would be contained in a peer reviewed paper, I cannot accord this evidence other than minimal weight. S*ee Snyder*, 2009 WL 332044, at *110 (noting problems in PCR testing that occur even in the laboratories that use it frequently and the need for redundancy in quality control measures).

E. General Criticisms Proffered of the Waly Study and the Deth Unpublished Work.

1. Apples and Oranges: Neurons vs. Neuroblastoma Cells.

Doctor Deth's use of neuroblastoma cells, and his efforts to equate them to human neurons,[536] were roundly criticized by the witnesses who responded to his

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[533] A. Purcell, et al., *Postmortem brain abnormalities of the glutamate neurotransmitter system in autism*, NEUROL. 57: 1618-28 (2001) ["Purcell"], filed as PML 567.

[534] Doctor Johnson described microarray analysis as "a fancy way of [doing] PCR." Tr. at 4322.

[535] Because this evidence was presented for the first time in Dr. Deth's testimony, I do not fault respondent for failing to respond to it at greater length.

[536] In his expert report and testimony, Dr. Deth stated that "thimerosal is toxic to human cortical neurons and neuronal cells grown in culture." PML 713 at 3; *see* Tr. at 613-14. In his report, Dr. Deth cited to three studies for this point: (1) M. Herdman, et al., *Thimerosal Induces Apoptosis in a Neuroblastoma Model via the cJun N-Terminal Kinase Pathway*, TOXICOLOG. SCI. 92(1): 246-53 (2006)

testimony. Some criticisms were discussed above; others follow.

Doctor Johnson explained that the neuroblastoma cell line is a self-renewing cell line, usually produced from a tumor, that demonstrates uncontrolled growth. Such cell lines often have aberrant numbers of chromosomes and frequently contain multiple genetic mutations. Tr. at 2205-06.

Neuroblastoma cells have a specific defect called dedifferentiation. Most neuroblastoma cell lines have characteristics of glial cells, and express glial proteins, ones not normally found in neurons. They are cheap and easy to use, and experiments in them can be performed quickly. Tr. at 2206. However, it is impossible to extrapolate from results in these cells to results in human neurons. Tr. at 2206-07.

The two primary authors of the Charleston and Vahter papers co-authored a paper which noted that neuroblastoma cells were more susceptible to methylmercury than other cell types. *See* Mottet, PML 197, at 385. The James 2005 study also reported that neuroblastoma cells were much more sensitive to mercury than glioblastoma cells. PML 7 at 3 (reporting a 48-hour toxicity threshold in the glioblastoma cells versus a three-hour toxicity threshold in the neuroblastoma cells).

In his rebuttal testimony, Dr. Deth acknowledged that the cells he studied were not brain cells, but because they were cell lines used frequently in biological studies, they would yield important information that can be further considered in neuronal cell cultures. Tr. at 3935-36.

While it is true that neuroblastoma cells are used frequently in preliminary work, Dr. Deth failed to rebut the evidence demonstrating that the neuroblastoma cells contain characteristics that significantly undercut his conclusions. They have abnormal methionine synthase, are more susceptible to mercury's effects, and behave more like glial cells than neurons.

2. Effects Too Small to Be Measured.

In his report, Dr. Deth stated that "[t]he threshold effect for thimerosal reduction of [glutathione] is approximately 0.1 nanomolar, indicating a remarkably potent influence

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["Herdman"], filed as PML 24; (2) D. Baskin, et al., *Thimerosal Induces DNA Breaks, Caspase-3 Activation, Membrane Damage, and Cell Death in Cultured Human Neurons and Fibroblasts*, TOXICOLOG. SCI. 74: 361-68 (2003) ["Baskin"], filed as PML 253; and (3) D. Parran, et al., *Effects of Thimerosal on NGF Signal Transduction and Cell Death in Neuroblastoma Cells*, TOXICOLOG. SCI. 86(1): 132-40 (2005) ["Parran"], filed as PML 21. Doctor Johnson correctly pointed out that the Herdman and Parran studies involved neuroblastoma cells, not human cortical neurons. Tr. at 2208-09. He was incorrect in so characterizing the Baskin study, which did involve the use of human cortical neurons in culture, albeit at much higher concentrations of thimerosal than were used in Dr. Deth's experiments.

on cellular redox status in human neuronal cells."[537] Pet. Ex. 713 at 4. Doctor Jones commented that this statement caught his attention because 0.1 nanomolar is "such a remarkably low level that there's no analytical technique that I know of that would be sensitive enough to pick up that type of an effect on a glutathione system." Tr. at 2720. Since he developed one of the major methods in use for detecting effects on glutathione, Dr. Jones was well aware of the sensitivity of the methods in use. Doctor Jones stated that there is no method available to detect the effect reported. Tr. at 2721.

Because he was unaware of any method to detect such a small change, Dr. Jones reviewed the literature, finding remarkably similar levels of thimerosal used in the studies he examined.[538] Tr. at 2721-22. The published work on thimerosal toxicity shows results at the micromolar level. Tr. at 2724.

Doctor Johnson was also highly critical of the results reported from nanomolar amounts of thimerosal. He noted that one advantage of using readily available cell lines is that other researchers across the country are using the same cells. If relatively consistent results are obtained from several different laboratories using the same cells, the results are likely to be reliable. Tr. at 2223. An effect at two or three orders of magnitude lower than those reported by other laboratories is not understandable or expected. Tr. at 2223. Doctor Deth's laboratory is the only one reporting effects at levels 100 to 1,000 times lower than those of other laboratories. Tr. at 2223-24.

Doctor Deth acknowledged that the doses of thimerosal at which the Waly paper showed effects were extremely low, at the nanomolar or even subnanomolar level. Tr. at 3937. He acknowledged that he was the only researcher to find effects at such low levels. Tr. at 3969-70. However, Dr. Deth noted that another paper, Carvalho, Pet. Tr. Ex. 7, showed inorganic mercury's effects at nanomolar levels on thioredoxin. Tr. at 3941. The Carvalho study involved mercury chloride and methylmercury, not thimerosal or ethylmercury, and measured effects on proteins, not cells.[539] Tr. at 2779-81.

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[537] Doctor Deth did not identify which of his studies produced this figure.

[538] A non-exhaustive list of the studies he examined appears on pages 11 and 12 of Res. Ex. K. Tr. at 2721-22. As examples, the Park, Herdman, and Humphrey studies all used low micromolar doses. *See* E. Park, et al., *Evaluation of Cytotoxicity Attributed to Thimerosal on Murine and Human Kidney Cells,* J. TOXICOL. & ENVTL. HEALTH, PART A 70: 2092-95 (2007) ["Park"], filed as RML 367; Herdman, PML 24 at 251; M. Humphrey, et al., *Mitochondrial Mediated Thimerosal-Induced Apoptosis in a Human Neuroblastoma Cell Line (SK-N-SH)*, NEUROTOXICOL. 26(3): 407-16 (2005) ["Humphrey"], filed as PML 8. The Parran study used nanomolar doses, but they were administered to cells already dying, and thimerosal enhanced the toxic effect of a missing growth factor. PML 21 at 135. Tr. at 2722-23. The James 2005 study also used micromolar levels of thimerosal. PML 7 at 3.

[539] Doctor Jones testified that it would not be good science to extrapolate from such studies to what would happen in a cell culture, much less in an entire organism. Tr. at 2781-83.

3. Too Much Glutathione to Be Affected.

Doctor Jones convincingly refuted Dr. Deth's contention of significant effects on sulfur metabolism from TCV-level doses of mercury by demonstrating that the amount of glutathione available so greatly exceeds the amount of thimerosal in vaccines that no real effect on glutathione levels could occur or persist.

Doctor Jones testified that the total thiol level[540] in the body is approximately 20,000 micromoles (µmol) per kilogram of body weight. Total glutathione is approximately 800-1000 µmol per kilogram of body weight. Tr. at 2707-08; Res. Tr. Ex. 9, slide 6. The recommended daily dietary intake is about two-thirds to half of the total glutathione content of the body. Tr. at 2709; Res. Tr. Ex. 9, slide 6 .

A cumulative dose of thimerosal from all vaccines would be approximately 200 µg, or about 1 µmol per kilogram of body weight.[541] Tr. at 2711-12; Res. Tr. Ex. 9, slide 6. For comparison purposes, food products also contain materials that, like thimerosal, react with and bind to glutathione. The reactive material in four ounces of milk contains 10 times the reactive material in 200 µg of thimerosal; four ounces of apple juice contains four times the amount of reactive material in vaccines. Tr. at 2713-14; Res. Tr. Ex. 9, slide 7. Natural fluctuations in glutathione levels vary from 25-30% over the course of a day. Tr. at 2715; *see also* Res. Tr. Ex. 9, slide 8. This natural variation is far greater than the effect of a response to all the thimerosal received via TCVs, even if administered all at once.

The rate at which glutathione cycles in and out of blood and cells is approximately 1 µmol per kilogram of body weight per minute. Tr. at 2717. Thus, the amount of glutathione being turned over as the result of normal metabolism per minute is more than would be needed to detoxify the total load of thimerosal received in six months of vaccinations. Tr. at 2718. The receipt of a TCV would not change the amount of glutathione in the body in any detectable way. No instrumentation is good enough to detect the effect, if any, of a TCV on glutathione levels. Tr. at 2718. Even if the entire amount of thimerosal received in six months were administered at one time, it would take less than one minute for the body to replace the glutathione necessary to bind to and deactivate that thimerosal. Tr. at 2719.

Doctor Deth challenged Dr. Jones' testimony that apple juice would deplete

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[540] Because heavy metals can bind to any thiol, the total thiol content of the body provides binding sites for any heavy metal, including mercury. Tr. at 2709.

[541] Doctor Jones was quite generous in his computations, as the 200 µg figure he used is higher than the cumulative amount of thimerosal contained in vaccines received by most children by one year of age. He used the assumption that this dose was received by a 1-kilogram child (2.2 pounds), which is a far lower body weight than that of most newborns. Based on these figures, he calculated the 1 µmol/kg of body weight figure, which clearly overestimates the amount, probably by a factor of 10. Tr. at 2712.

glutathione, pointing out that the effect of apple juice would be transient, while the mercury would remain. Tr. at 3898. It may be more accurate to state that some mercury will remain; a substantial part will be excreted. Doctor Deth was correct in asserting that glutathione does not bind to and detoxify all mercury ingested or injected. If it did so at 100% efficiency and remained bound and excreted, mercury toxicity would not be a problem. However, the point made by respondent's experts was not that glutathione would bind to all the mercury available; it was that all the mercury available would not impact glutathione levels in any measurable way.

In responding to Dr. Jones' criticism of the glutathione depletion aspect of his theory, Dr. Deth explained that the concept of stoichiometry applied. In testimony that appeared to shift dramatically from his glutathione depletion causing oxidative stress hypothesis, he explained that the effects he postulated did not depend on glutathione interacting with a given amount of thimerosal. Tr. at 3896. Because mercury enters and remains in the brain,[542] it is obvious that glutathione does not inactivate or bind with all the mercury available. Tr. at 3896-97. The target of the thimerosal is not glutathione; it is the small amount of regulatory proteins in the brain to which thimerosal binds. These proteins are taken up by astrocytes, neurons, and microglia. Tr. at 3897. Thus, it is not the quantity of glutathione that is relevant; it is the amount of the proteins that are mercury's primary targets. Tr. at 3897-98. He postulated that the interaction of cells to the mercury bound to thiols was responsible for the neuroinflammation found in the Vargas study: "So the point I just made, that the provocation of the inflammatory response is not because there's so much mercury that it depletes the glutathione one for one, that's not it. It's because those critical regulatory mechanisms are built upon sulphur (sic) and thiols binding the mercury, and it's their interaction that's causing the inflammation." Tr. at 3898.

Doctor Deth's late-in-the-game switch from mercury's impact on glutathione to its binding to otherwise unidentified "regulatory proteins" was unpersuasive. After considerable testimony about mercury's effects on transsulfuration and the methionine-methylation cycle and his many experiments that purported to measure these effects, Dr. Deth's new focus on "regulatory proteins" was disingenuous at best. Given the ubiquity of thiols and sulfur in the brain and elsewhere in the body, the tiny amounts of mercury administered through TCVs, and the even smaller amounts that will reach and remain in the brain, are unlikely to deplete the thiols available. Most mercury in the brain is already bound (*see* Tr. at 625-27), and only the small amount not already bound to thiols would be available to react with these "regulatory proteins."

4. Fluid Volume Measurements and Calculations of Effects.

Another significant problem with Dr. Deth's work involved how effects on cell

[542] There is some evidence to indicate that the inorganic mercury in the brain remains there because it forms strong bonds with selenium. *See* Clarkson and Magos 2006, PML 35, at 628.

cultures were calculated. In summary, respondent's experts indicated that, by varying the volume of fluid added to the cell culture, the researchers could manipulate the effects produced. This problem would be exacerbated when the substance added would affect only the cells, and not any component of the fluid.

As Dr. Deth explained, the cultured cells used in his experiments were grown until they were confluent, meaning that there was a single layer of cells at the bottom of the well in a petri dish. A solution was added to measure the biochemical changes being examined. The volume of the solution varied, but it had to cover the cells. In the wells used in Dr. Deth's experiments, the minimum amount required was 600 microliters (µL). Tr. at 3924. The actual amount used in the experiments was 2 milliliters (mL). Tr. at 3925.

Doctor Jones explained that this system exaggerated the effect of small doses of thimerosal on the cells. Because the study design involved thimerosal, which has a high affinity for thiols, the thimerosal would accumulate in the cells rather than remaining in the solution. Thus, the volume of the culture medium becomes relevant to the measurements of effects. *See* Tr. at 2725-29. To explain, Dr. Jones gave an example in which the culture medium and cells together constitute 1000 µM in volume. When 1 µM of toxic substance is added, a ratio of 1 to 1000 would be reported. However, if that toxic substance is entirely absorbed by the cells, it would be incorrect to call this a 1 to 1000 ratio because the entire amount of added substance would be taken up by the cellular fraction, without regard to the amount of fluid in the culture medium. If the cells constituted 1 µM of the 1000 µM total volume, the ratio of toxic substance to cells would actually be 1 to 1. Tr. at 2725-27; *see also* Res. Tr. Ex. 9, slides 9-10. In essence, the cells bear the full burden of the toxic substance, regardless of the amount of culture medium. Tr. at 2730-31.

High toxicity of thiol-reactive chemicals occurs when the total amount of the chemical is similar to the total thiol content of the cells. The toxicity threshold can be manipulated by changing the ratio of the volume of culture media to the number of cells in culture. Res. Tr. Ex. 9, slide 11. The fewer the cells in the culture medium, the lower the toxicity threshold will be because each cell is receiving more of the administered substance in the cultures with lower cell counts. Tr. at 2729. If, instead of using 1,000,000 cells, only 100,000 are used, only one-tenth the amount of toxic substance is needed to produce the same effect. This does not mean that the substance is more toxic, only that the toxic effects are concentrated on fewer cells. Tr. at 2729-30. Thus, studies of this nature show a dose response curve such that there is no toxicity at lower concentrations, but once toxicity begins, most of the cells die at the same time, reflecting that all of the cells have the same mechanisms of response to the toxic substance. Tr. at 2729.

I note that Clarkson and Magos 2006, PML 35, at 616, supported Dr. Jones' testimony in this regard. They reported:

> Numerous reports on *in vitro* actions of mercuric mercury may be found in the literature. *In vitro*, mercury can affect numerous cellular processes such as inhibition of enzyme function and blockade of cellular receptors and ion channels. These actions in turn can change both intra- and intercellular signaling processes of considerable significance to the nervous system. Such effects have been observed at an impressively low concentration of mercury in the incubating media. The problem with all these studies is that the cellular concentrations of mercury were not measured. Cells or subcellular components contain many binding sites for mercury, such as the ubiquitous -SH [thiol] ligands. The medium, on the other hand, usually contains few mercury binding sites. Consequently mercuric mercury rapidly leaves the incubation medium to attach to cellular components. How much binds to the cell depends on the ratio of the number of cells to the volume of the media. A relatively low cell number suspended in a large volume of media usually means the cellular concentrations will be much higher than the concentration that was added to the media. <u>It is therefore virtually impossible to translate such findings to equivalent levels in human target organs</u>.

PML 35 at 616 (emphasis added) (citation omitted).[543]

As Dr. Jones explained, studies of toxic substances that bind to thiols will show effects in the low micromolar range because the toxic effect is concentrated in the cells only, while the effects are being measured on the cells plus the culture medium by weight or volume. Tr. at 2728. These amounts are "grossly out of line with what you would see *in vivo*." Tr. at 2728.

In Dr. Deth's unpublished experiments, there is no way to know whether the conditions selected enhanced the reported toxicity. Tr. at 2730. Adding more culture medium or reducing the number of cells can manipulate the threshold for toxicity. Tr. at 2729-30. Doctor Johnson noted that Dr. Deth did not include dose curves in the Waly study, PML 257. [544] Tr. at 2218-19.

5. Use of *In Vitro* Data to Predict *In Vivo* Effects.

Doctor Roberts testified about his years of studying oxidative stress, including *in vitro*, animal, and human studies. Tr. at 2183. He commented that it was "very, very,

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[543] Although Clarkson and Magos were discussing mercuric mercury rather than ethylmercury or thimerosal, all three species have an affinity for thiols and would be expected to bind to them. *See* Clarkson and Magos 2006, PML 35, at 652.

[544] Doctor Johnson also noted that dose curves are essential in understanding the differential sensitivity of toxins. Dose curves allow comparison of the dosages at which different toxins first show an effect and at what dose the maximum effects are observed. Tr. at 2218-19.

very difficult" to extrapolate from *in vitro* data to what actually occurs *in vivo*. Tr. at 2184. A study on cultured cells can determine only if additional studies, such as animal studies, might be worthwhile. Tr. at 2184. Eventually, human studies will be necessary because "that's where the real answer is." Tr. at 2185.

Doctor Johnson concurred. He testified that *in vitro* studies have complications and drastic limitations. Tr. at 2204. Cell lines are grown in an environment that is not natural. Cell to cell communication is disrupted. Tr. at 2205. If an effect is found in a cell line such as a neuroblastoma cell line, then the next step is to see if the same effect obtains in a primary culture, such as mouse neuronal cells. Tr. at 2207-08.

In vivo, there would be extracellular material and different types of cells that would modulate the effects of the toxic substance.[545] In a monocellular *in vitro* culture, these protective mechanisms do not exist, and thus, the results from an *in vitro* experiment cannot be extrapolated to *in vivo* systems. Tr. at 2731. For example, omitting albumin from a culture would shift the toxic ratio for glutathione. Albumin, found in human plasma, has 200-400 times more thiols than in glutathione in human plasma. Tr. at 2731-32. Omitting nerve growth factor also shifts the toxic ratio. Without data regarding the culture medium, it is impossible to assess the validity of Dr. Deth's work, particularly given that his results are three or four orders of magnitude, or 1,000 to 10,000 times lower, than those reported in other papers. Tr. at 2732-33. The results in the published papers would be given "more credibility than an unpublished report where you didn't have the understanding of why the systems were different and why the bulk of the published literature was wrong." Tr. at 2734. Doctor Mailman concurred, noting that conclusions from even well-designed *in vitro* studies cannot be extrapolated to demonstrate clinical effects. Tr. at 2004.

In this case, the only evidence available is from Dr. Deth's laboratory. That evidence was obtained in the course of experiments that were not well-designed or controlled and that have not been replicated by other laboratories. Using such evidence to make the jump to causation in a complex human disorder would give the evidence weight it has not earned. Tr. at 2004-05. The fact that Dr. Deth had to explain that a housekeeping gene was used as a control in the PCR testing during his rebuttal testimony illustrates the difficulties inherent in relying on unpublished data, particularly data generated using PCR. Given the difficulties with PCR testing, details of how the testing was conducted were important, and those details were not supplied in the testimony. PCR evidence should not be relied upon without knowing key details. Tr. at 2000.

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[545] The effects of a lack of copper in the cell medium was illustrated in the Waly study. The thimerosal inhibition on methionine synthase primarily occurred in the copper-free medium. When copper was added, the effects of thimerosal on the neuroblastoma cells were considerably reduced. Unlike the neuroblastoma cells in culture, the human body contains copper in abundance. Tr. at 1827-28; Waly, PML 257, at 363. Copper was not added to the cell cultures in the unpublished experiments, although the fetal bovine serum used to feed the cultured cells contained some copper. Tr. at 3919.

6. Reliance on Unpublished Data.

Doctor Mailman quoted one of his mentors as saying: "[I]t ain't science until it's published." Tr. at 1999. Much of Dr. Deth's testimony was based on unpublished data. When a paper is submitted for publication, other scientists have a chance to review the experimental design, the nature of testing performed, the methods used, and the results obtained. The reviewers form their own conclusions based on the data submitted. Tr. at 1999-2000. When the data upon which a witness relies is unpublished, this control for validity is unavailable. The many problems noted by respondent's experts with the unpublished data amply illustrate the role of peer review, and the reasons for greater reliance to be placed on published data.

F. Genetic Predispositions and Oxidative Stress.

1. Overview.

This section covers the evidence concerning Dr. Deth's assertions that children with ASD have genetic differences that adversely affect their ability to handle oxidative stress and are unusually susceptible to environmental toxins such as mercury that may generate oxidative stress. Doctor Deth relied on several small studies showing biomarkers of oxidative stress in children with ASD to demonstrate their propensity to sustain oxidative injury and to show that oxidative stress might be causal of their ASD. He also relied on studies indicating that children with ASD have polymorphisms that suggest their ability to methylate DNA and respond to oxidative stress is impaired. From these findings, he concluded that children with ASD are more susceptible to the effects of mercury, and that the mercury in TCVs caused or contributed to the oxidative stress found. Doctor Deth also relied on a study demonstrating that mice with immune deficiencies are more vulnerable to TCVs, resulting in behavioral symptoms and pathological findings similar to those found in ASD.

Respondent's experts on oxidative stress, mercury, and sulfur metabolism were highly critical of Dr. Deth's assertions and many of the studies upon which he relied. The studies finding biomarkers of increased oxidative stress and/or impaired methylation in children with autism were small and characterized by their authors as preliminary. However, the most basic difficulty with these studies can be characterized as a "chicken or egg" question. Even if their findings are correct, the studies contribute little, if anything, to the issue of autism's causation because biomarkers of oxidative stress are found in most injuries and diseases, and oxidative stress in peripheral tissue says nothing about the oxidative state of the brain. Thus, they have little relevance to the causation issue.

The findings pertaining to polymorphisms are, according to their authors, preliminary. Even if they are found to be more applicable generally to children with ASD, at best, they demonstrate some susceptibility to metabolic problems; they say little to nothing about a susceptibility to mercury or other environmental toxins. The study

demonstrating the effects of TCVs on autoimmune sensitive mice could not be duplicated by a better performed study, and, for that reason, even Dr. Aposhian, who once cited the Hornig study as evidence for one of his "six pillars," no longer relied upon it.

2. Metabolic Evidence.

Relying on the James 2004 and 2006 studies[546] and work by the Geiers,[547] Ming,[548] and Chauhan,[549] Dr. Deth testified that plasma levels of methionine cycle and transsulfuration metabolites are abnormal in autistic individuals. Tr. at 536-37; *see also* Deth, PML 563, at 191. His testimony about plasma levels was supported by several small studies, but the conclusions he drew from the studies were not.

a. Ming Study.

The Ming study found that one F2 isoprostane,[550] as measured by an immunoassay,[551] was elevated in autistic children, as compared to controls, and markedly elevated in a subgroup of autistic children. Tr. at 2180; Ming, PML 124, at 380-81. The authors acknowledged that dietary supplements, vitamins, and medicines may affect oxidative stress measurements and that medical disorders such as epilepsy,[552] allergies, and inflammation may increase oxidative stress. Ming, PML 124,

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[546] PML 5 and 49, respectively.

[547] Doctor Deth testified that he had relied upon work by Dr. and Mr. Geier, but did not specify which articles. Tr. at 604-05. In the Deth article, PML 563 at 195, he cited to a 2006 Geier article that was not filed as an exhibit in the Theory 2 cases.

[548] X. Ming, et al., *Increased excretion of a lipid peroxidation biomarker in autism*, PROSTAGLANDINS, LEUKOTRIENES & ESSENTIAL FATTY ACIDS 73: 379-84 (2005) ["Ming"], filed as PML 124.

[549] A. Chauhan, et al., *Oxidative stress in autism: Increased lipid peroxidation and reduced serum levels of ceruloplasmin and transferrin - the antioxidant proteins*, LIFE SCI. 75: 2539-49 (2004) ["Chauhan"], filed as PML 481. Another article by A. Chauhan and V. Chauhan, *Oxidative stress in autism*, PATHOPHYSIOL. 13: 171-81 (2006), a literature review, was filed as PML 48.

[550] Isoprostanes are prostaglandins, which are small lipid molecules. DORLAND'S at 958; Tr. at 2181-82. Prostaglandins have been a major research focus for Dr. Roberts for a considerable part of his career. Tr. at 2161-63.

[551] An immunoassay is created by developing an antibody, usually against a protein, that binds to the substance to be measured. Tr. at 2181. By measuring how much of the antibody binds to the substance, it is possible to determine how much of the protein or other substance is present. Tr. at 2182. Antibodies against large proteins are generally more specific than antibodies against lipids. Tr. at 2181.

[552] I note that about 25-40% of those with autism have epilepsy, with epileptic discharges often found on EEGs performed early in childhood in autistic children without clinically overt seizure activity. *See* Tr. at 3267-68; Pardo, PML 72, at 486. Doctor Kinsbourne acknowledged that seizure activity was a

at 382. They did not find any associations of these factors with increased excretion of oxidative biomarkers in their study, but unlike the children with autism in the study, none of the control children had epilepsy, gastrointestinal disorders, or sleep disorders. Ming, PML 124, at 381-82 and Table 2. Regression was not associated with the oxidative stress biomarkers measured. Ming, PML 124, at 382.

Although Dr. Roberts testified that measurements of F2 isoprostanes were the most reliable way of assessing oxidative stress or oxidative injury in the body (Tr. at 2164-65), he also testified that measuring urinary levels of F2 isoprostanes by immunoassay is not reliable. Tr. at 2181-83. He explained that efforts to create a reliable and accurate immunoassay for measuring prostaglandins have uniformly failed, because biological fluids like urine and plasma contain too many substances that can interfere with antibody binding to these small lipid molecules. Tr. at 2182-83.

b. Chauhan Study.

The Chauhan study, PML 481, compared levels of malonyldialdehyde ["MDA"][553] in blood drawn from children with autism to that of their neurotypical siblings. The study involved 30 children with autism divided into two groups. These children were each paired with a typically developing sibling. The two groups were subjected to different testing protocols.

Of the 19 children in one group, 12, by parental report, had lost previously acquired skills.[554] Chauhan, PML 481, at 2540-41. Those without language regression were more similar in biomarker results to their typically developing siblings than the children with language regression were to their siblings. Chauhan, PML 481, at 2544-45. Although this suggests a possible biochemical distinction between autistic children with regression and autistic children without loss of skills, the very small numbers make drawing any conclusions from this study problematic, even if the measurement methods were reliable.

As Dr. Roberts testified, the measurement methods employed were "totally

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common phenomenon in ASD. Tr. at 875. Thus, it may be even more difficult to determine whether biomarkers of oxidative stress reflect epilepsy (subclinical or overt) or autism or both.

[553] Malonyldialdehyde is a product of the oxidation of fatty acids. Chauhan, PML 481, at 2541.

[554] Doctor Lord noted that parental reports of regression are not always accurate. *See* Tr. at 3572-73. As the authors of this study commented, although approximately one-third of children with autism undergo regression, 63% of children in this cohort had reportedly experienced regression. Chauhan, PML 481, at 2541.

unreliable." The type of assay[555] used to determine oxidative damage was not specific for MDA,[556] which is, in itself, a substance that is not specific for oxidative stress. Tr. at 2178-80.

c. James Studies.

The James 2004 study, PML 5, compared various plasma metabolites in children with autism to those in aged-matched control children. The study found biomarkers for impaired methylation capacity[557] and oxidative stress in the children with autism. James 2004, PML 5, at 1612-13. The ratio of SAM to SAH was approximately 50% lower in the autistic children (reflecting impaired methylation), and the GSH/GSSG[558] ratio was 70% lower in the autistic children (reflecting oxidative stress). *Id.* In a small subgroup of children with autism (eight children), various oral or injectable supplements were tested to improve the metabolic profile. The supplements succeeded in normalizing the methionine cycle metabolites and the GSH/GSSG ratio. *Id.* at 1613-14. Whether the normalized metabolic profile led to any clinical improvement was not examined in a scientific and quantifiable manner.[559] *Id.* at 1615.

Nineteen of the 20 children in this study had experienced regression. James 2004, PML 5, at 1612, 1615. Although the authors suggested that the oxidative stress and impaired methylation found in the children with regression may have contributed to their regression (*id*. at 1615), it may be more accurate to say that it may have

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[555] The assay was identified as a "TBARS" assay. Doctor Roberts testified that this assay cannot reliably measure MDA. Tr. at 2180. He explained that drawing blood causes platelets to activate. Activated platelets contain thromboxane synthase, an enzyme they use to make thromboxane. Tr. at 2179. For every molecule of thromboxane made, platelets also make a molecule of MDA. Thus, using detection of MDA in plasma to measure oxidative stress is not reliable, because the act of drawing blood generates MDA. Tr. at 2180.

[556] A lack of specificity means that, in addition to measuring MDA, it also measures other substances. Tr. at 2178.

[557] In Rett's disorder, the causative gene mutation is the MECP2 gene. *See* Rodenhiser and Mann, PML 459, at Table 1. This gene is involved in DNA methylation. *Id.* at 341. Brain autopsies of patients with ASD have also shown a deficiency in MECP2 expression. *Id.* at 346. Any impairments in methylation found in the children with ASD may thus stem from a genetic defect, rather than a susceptibility to environmental toxins.

[558] *See* D. Giustarini, et al., *Interference of Plasmatic Reduced Glutathione and Hemolysis on Glutathione Disulfide Levels in Human Blood*, FREE RADIC. RES. 38(10) 1101-06 (2004) ["Giustarini"], filed as RML 206 (discussing problems in using GSH/GSSG measurements based on spontaneous oxidation of GSH).

[559] In spite of this disclaimer by the authors, Dr. Deth nevertheless asserted that dietary supplements improved both metabolic profiles and neurologic status. Tr. at 611-12.

contributed to their autism.[560] As only one child with early onset autism was tested, there was no basis to imply that children with regression were metabolically different from those with early onset autism.[561]

The impetus for the James 2004 study, PML 5, was the similar metabolic profile of a dizygotic twin pair, one with autism and the other with Down syndrome.[562] The authors noted that children with Down syndrome have lower concentrations of methylation metabolites and lower glutathione concentrations than control children. *Id.* at 1611. This does not appear to be supportive of Dr. Deth's hypothesis; the fact that children with Down syndrome, a purely genetic condition, have a metabolic profile more like children with autism than that of typically developing children suggests that genetic anomalies in both, rather than environmental exposures, may account for their unusual metabolic profiles.

The James 2006 study, PML 49, also measured various metabolites in plasma, with similar, although not identical findings.[563] These included an impairment in methylation capacity (decreased SAM/SAH ratio) and in antioxidant capacity (decreased glutathione/GSSG ratio). James 2006, PML 49, at 954. The authors attributed increased plasma GSSG levels to oxidative stress. *Id*.

In both of the James studies, the authors noted the preliminary nature of their findings (PML 5 at 1615; PML 49 at 954). In his article on autism and oxidative stress, Dr. Deth also relied on these two James studies, but in this publication, he noted that the James study findings were preliminary. *See* Deth, PML 563, at 195; Tr. at 638-39.

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[560] In the James 2006 study, the authors commented on the 2004 study, stating: "The metabolic profile of children diagnosed with autistic disorder with regressive onset was found to be severely abnormal." PML 49 at 948. Without expressly so stating, the authors imply that children with regressive autism have a different metabolic profile than children with early onset autism. The authors did not explain that 19 of the 20 children tested in the 2004 study had experienced regression. With only one early onset sample, no valid statistical comparisons could be made between autism in general and regressive autism with regard to metabolic profiles.

[561] To illustrate the logical fallacy here, if the driving records of red Corvette owners are compared to those of drivers in general, any conclusion about an excess number of speeding tickets received by red Corvette drivers cannot be attributed to the color of the car, rather than to the model, without additional data about drivers of Corvettes of other colors.

[562] Down syndrome is a purely genetic disorder, associated with three copies of chromosome 21. DORLAND'S at 1815; James 2004, PML 5, at 1611.

[563] Doctor Jones noted that, with regard to the James 2006 study, PML 49, Table II, the levels of metabolites that are the highest are those most likely to be accurately measured. The levels of cysteinylglycine were very similar in both autistic children and the controls. Tr. at 2746-47. It was the second highest metabolite measured. This finding conflicts with Dr. Deth's assertions that mercury reduces the level of cysteine and that autistic children are more likely to be affected by this reduction. *See* Section VII.D.3.

d. Evaluation of the Studies and Opinions.

Doctor Deth relied on altered plasma levels of biomarkers for oxidative stress and impaired methylation as indirect evidence of oxidative stress or damage in the brain. He conceded that plasma levels may say little about glutathione levels or even oxidative stress in the brain. However, he commented, "the fact that the plasma is indicating very significant signs of oxidative stress at the level of the thiols is creating a very likely hope that the brain will also show that." Tr. at 3911 (emphasis added). He added that because plasma levels reflect the metabolic state of the liver, the source of sulfur resources for the brain, the brain is likely to be affected.[564] Tr. at 3911-12.

However, the expert on oxidative stress, Dr. Roberts, testified that a finding of oxidative stress in plasma or urine does not indicate that there is oxidative stress in the brain because the damage done by free radicals occurs where they are generated. Free radicals do not travel from the periphery to the brain; they react with what is nearby because they are so highly reactive. Tr. at 2173, 2176, 2183, 2185-86. Oxidative stress in the periphery can have many causes. Tr. at 2185.

Doctor Jones provided the most significant criticism of Dr. Deth's conclusion that evidence of oxidative stress in children with autism is evidence that oxidative stress is causal of autism. He testified that individuals with almost any disease will have lower glutathione levels than those found in healthy controls. This includes conditions as diverse as cardiovascular disease, diabetes, renal disease, liver disease, and lung disease. Reduced glutathione levels appear to be a general response to a disease process rather than a cause of it. Tr. at 2790. The ubiquity of increased oxidative stress makes it almost valueless as evidence of an oxidation-caused injury in ASD. In essence, the James 2004 study compared healthy children to those with a disorder, with predictable results.

Additionally, at least one study indicates that the GSH/GSSG ratio can be an unreliable marker for the existence of oxidative stress, and that reference values diverge significantly. The Giustarini study measured GSH and GSSG levels in healthy volunteers, finding that plasma GSH can spontaneously oxidize, generating GSSG, and is highly unstable after blood draws. RML 206 at 1102-03. This spontaneous oxidation can result in a 20-30% increase in GSSG. *Id*. at 1105. Red blood cell hemolysis, caused when drawing blood, and present in epilepsy, can also cause an increase in GSSG. *Id.* at 1105.

[564] I note that Dr. Aposhian expressed skepticism regarding the utility of measuring glutathione concentrations in the plasma because most glutathione is present in cells, not extracellularly. His criticism of Dr. James for not measuring liver glutathione levels suggests that plasma levels do not, in fact, reflect liver levels. Tr. at 285. Doctor Jones concurred that plasma values do not indicate what is happening in the brain with regard to oxidative stress or injury. Tr. at 2745-46.

3. Genetic Vulnerabilities to Mercury or Oxidative Stress.

Doctor Deth began his discussion of polymorphisms related to oxidative stress with a broad and unsubstantiated statement. He testified that:

> Now, the occurrence of autism is estimated to be one in 150 individuals, by the CDC. And so this tells us that exposure to thimerosal or other uniformly exposing agents in our society only affects a subpopulation of this society.

Tr. at 574. How the prevalence of autism (a correct statement) is related to thimerosal or other environmental agents being causal of ASD was left unspecified. Doctor Deth followed up this statement with a comment that "the subpopulation with autism has certain genetic features." Tr. at 574. In general terms, this second statement is correct; there was overwhelming evidence that autism is a highly genetic disorder, even if all of the genes that interact to cause autism have not yet been identified. *See* Section IV.C.2. Doctor Deth's assertion that these genetic features are connected to a susceptibility to either mercury or oxidative stress was not established by the evidence.

Doctor Deth reiterated that genetic susceptibility was an essential element of his theory of causation. He asserted that children with autism have polymorphisms that adversely affect their ability to: (1) detoxify or eliminate ethylmercury, (2) maintain normal oxidative and methylation status, and (3) maintain synchronization in neuronal signaling. Report of Dr. Deth, PML 713, at 2.

a. Hypersusceptibility to Mercury.

For evidence regarding a genetic susceptibility to thimerosal, Dr. Deth relied on the same evidence that Dr. Aposhian presented, asserting that some individuals cannot handle the same level of mercury as others. Tr. at 3917-18. Doctor Deth was quite vague about how many individuals are genetically predisposed to react to TCVs, or whether this predisposition applied to everyone with ASD *(see* Tr. at 618), although his comments about "uniformly exposing agents" (*see* Tr. at 574) suggest that it does.

Doctor Deth asserted that an impairment in glutathione-based detoxification could be classed as an efflux disorder, but this testimony was based on a shortage of glutathione. Tr. at 628-29. In view of the overwhelming evidence of the abundance of glutathione in the body, and the low levels of mercury to which children are exposed through vaccines and otherwise, this is unlikely as a biochemical cause for mercury efflux disorders or hypersusceptibility.

The only evidence of a genetic susceptibility to mercury, other than those proffered by Dr. Aposhian, was the Hornig study, PML 15. This study purportedly found that autoimmune disease-sensitive mice exposed to thimerosal showed growth delay and other changes, while mice strains with resistance to autoimmunity were not

affected. The affected mice also exhibited alterations at the neuronal cell level, with altered glutamate receptors and transporters. PML 15 at abstract.

However, the results from this study could not be duplicated.[565] The Berman study, RML 42,[566] replicated the Hornig study's protocol with very different results. Thimerosal, with and without accompanying vaccines, was injected into the same type of autoimmune disease-sensitive mice used in the Hornig study, modeling the childhood vaccination schedules. Additionally, one cohort of mice received a dose of thimerosal 10 times higher than that found in vaccines.[567] RML 42 at abstract. Performance on behavioral tests and on indices of early development were unaffected by thimerosal administration with the exception of locomotor tests in female mice.[568] RML 42 at 300.

In addition to mirroring the Hornig study, the Berman study included measurements of tissue mercury levels in blood, brain, and kidney, and measured the numbers of hippocampal pyramidal and granule cells.[569] It also added tests for social interaction and anxiety. Berman, RML 42, at 295. Co-administration of vaccine and thimerosal did not affect mercury levels in blood, brain, or kidney. Berman, RML 42, at 298. There was no evidence of disruption of the cellular structure of the hippocampus in the mice exposed to thimerosal and vaccines. There was no difference in the number of neurons nor any evidence of neuronal degeneration in the hippocampus. Berman, RML 42, at 299. The study could not verify <u>any</u> of the Hornig study's findings. *See* Berman, RML 42, at 304-07.

The authors concluded:

> No evidence was found that exposure to vaccine-associated levels of thimerosal, whether or not in combination with vaccine, resulted in abnormal somatic growth or altered the normal development or structure of the hippocampus. No deficits were observed in tests of complex behaviors that have been considered to be particularly relevant to the study of neurodevelopment and its disorders, including social interaction,

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[565] Doctor Aposhian agreed that the Hornig study's findings were not duplicated by the subsequent Berman study. Tr. at 449-50.

[566] R. Berman, et al., *Low-Level Neonatal Thimerosal Exposure: Further Evaluation of Altered Neurotoxic Potential in SJL Mice*, TOXICOL. SCI. 101(2): 294-309 (2008) ["Berman"], filed as RML 42.

[567] For both the same dose of thimerosal used by Dr. Hornig and for a dose 10 times higher, no pathological effects were observed. Tr. at 2214-15; Berman, RML 42, at 307.

[568] More complex behavioral testing did not show any effect. Berman, RML 42, at 305-06.

[569] The hippocampal pyramidal and granule cells have been identified by other studies as abnormal in individuals with Rett's disorder. Hornig, PML 15, at 11 (citing to Amir, RML 10, and a study by Bauman and Kemper that was not filed by either party).

> sensory gating, or anxiety. Only limited locomotor effects were observed, and these were primarily in female SJL mice in the open field at 4 weeks of age. Considered together, the overall pattern of results of the present study does not indicate marked or pervasive neurotoxicological deficits in neonatal SJL/J mice following injections of vaccine-associated levels of thimerosal. Particularly relevant to human health concerns, the current data do not provide support for the inference that neonatal thimerosal exposure is involved in the etiology of neurodevelopmental disorders that alter social behaviors such as autism.

Berman, RML 42, at 307 (citations omitted).

Doctor Johnson testified the mouse strain used by Hornig, the SJLJ mouse, did not, as Dr. Deth inferred in his expert report (PML 713 at 4), have any redox enzyme deficiencies. Tr. at 2210-11. He added that there was "absolutely no data supporting the fact that there is a REDOX enzyme differential. Now, I can understand the reason it's in there is because it supports his hypothesis in the sensitivity, but that's not an accurate representation of the mice." Tr. at 2211. Doctor Deth testified on rebuttal that his laboratory was, at the time of the hearing, examining glutathione levels in the same two strains of mice Dr. Hornig studied. In the "thimerosal vulnerable mice" (apparently referring to the SJLJ mice in the Hornig study), Dr. Deth testified that the levels of glutathione were about 40% lower. His laboratory also measured methionine synthase activity with both methylcobalamin and hydroxy methylcobalamin. The methionine synthase activity was also 40% lower in the "thimerosal vulnerable" mice. Tr. at 3947. These findings were made in the "last month or six weeks." Tr. at 3947. These unpublished findings were limited to the biochemistry, not to the behavioral differences observed in the Hornig study, PML 15. Tr. at 3948. Doctor Deth also noted that thimerosal treatment at 10 weeks did not affect the values observed. Tr. at 3948.

Doctor Johnson provided another reason for crediting the Berman findings over those of the Hornig study. The Hornig paper included slides from the mouse brains to illustrate their findings, as did the Berman study. Based on the relative quality of the slides submitted, Dr. Johnson had no confidence in Dr. Hornig's reported results. Tr. at 2211-12. He provided copies of slides from both papers to illustrate the difficulties he had with Dr. Hornig's work.[570] Tr. at 2212. Doctor Johnson described Dr. Hornig's images as "absolutely awful." Tr. at 2213. Based on his experience, Dr. Johnson opined that the tissue samples in the slides were improperly prepared. Tr. at 2213-14. In contrast, Berman's tissue slides[571] of brain sections comparable to Hornig's were, in Dr. Johnson's words, "absolutely beautiful," with the cellular architecture clearly

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[570] *See* Res. Tr. Ex. 7, slide 5. The picture in the upper right represents the brain section when treated by the "vehicle," referring to the control solution without the vaccine. The picture in the bottom right is the brain section that received the thimerosal. Tr. at 2212.

[571] They were reproduced on the left side of Res. Tr. Ex. 7, slide 5. Tr. at 2214.

reproduced. Tr. at 2214.

The defects Dr. Johnson noted on the Hornig slides were obvious, even to an untrained observer. Both studies used antibodies to stain specific proteins in brain tissue.[572] The tissue architecture in Berman's study is more easily discerned. Tr. at 2215-16. The comparable areas on the Hornig slides show tissue full of holes,[573] which may reflect intense nonspecific antibody staining. Tr. at 2217. Doctor Johnson testified that if slides demonstrating this pattern were presented to him, he would tell the researcher to go back and do the experiment again because the tissue degeneration makes the potential for artifactual data extremely high. Tr. at 2217. For these reasons, Dr. Johnson placed more weight on the Berman data than that of Hornig. Tr. at 2218.

Doctor Deth attempted to respond to the criticisms offered of the Hornig study, but indicated he was not an expert in histochemistry. Tr. at 3945-46. However, he had examined Dr. Hornig's immunohistochemical staining for EAAT3, the cysteine transporter, and saw evidence that the EAAT3 transporter was significantly up-regulated in the thimerosal treatment group. This suggested that the cell was making efforts to get more cysteine in response to the thimerosal exposure. Tr. at 3946. He caveated his testimony on this point by stating that he did not have the expertise to make a quality judgment of the histochemical staining techniques, and that the interpretation of such staining was subjective. He thought the differences Dr. Hornig described were clear. Tr. at 3946-47.

Doctor Deth also commented on the Laurente study, PML 668, involving hamsters administered "vaccine level" doses of thimerosal. Tr. at 3953. He noted that t the Laurente paper favored Hornig's findings. Tr. at 3987. However, he agreed that Berman was unable to find an effect in spite of using a considerably higher dose of thimerosal.[574] Tr. at 3987.

In the conflict between the Hornig and Berman studies, I credit the testimony of Dr. Johnson over that of Dr. Deth. Unlike Dr. Deth, Dr. Johnson did have expertise in histochemical staining. Furthermore, he provided evidence for his assertions, unlike Dr. Deth. I am unwilling to rely on Dr. Deth's descriptions of his own work on either the measurements of oxidative biomarkers in the "thimerosal vulnerable" mice or with

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[572] Slides from each study were reproduced on Res. Tr. Ex. 7, slide 4. The two slides on the left were from the Berman study with lines drawn from them to comparable areas in the Hornig slides. The boxes on the Berman slides were enlarged in the two slides appearing on the bottom right side of Res. Tr. Ex. 7, slide 4, showing the neurons in the clear area. Tr. at 2216-17.

[573] This is particularly evident on the Hornig slides labeled "c" and "d" appearing on Res. Tr. Ex. 7, slide 4. Tr. at 2217.

[574] The Laurente study was discussed in more detail in Section VI.D.2.e., with Dr. Brent explaining that the dosing schedule made the hamsters mercury-toxic. *See* Res. Ex. EE at 14.

regard to the EAAT3 cysteine transporter in these mice. His *ipse dixit* is simply not enough to counter Dr. Johnson's greater expertise and the contrary findings of no observed effects from the Berman researchers.

b. Polymorphisms Relating to Oxidation and Methylation.

As evidence that children with autism have polymorphisms that affect their ability to respond to oxidative stress, Dr. Deth relied on the James 2006 study, PML 49. Doctor James focused on polymorphisms, which are normal variants of genes, involved in methylation and transsulfuration.[575] Tr. at 574. Doctor James measured metabolites in plasma, and attempted to correlate those with various polymorphisms of six different genes involved with metabolic processes. In comparing autistic children to control children, the James 2006 study found that certain combinations of polymorphisms that affect methionine metabolism were more likely to be found in autistic children. James 2006, PML 49, at 953-54; Tr. at 576-77.

Based on this study, Dr. Deth asserted that children with autism are genetically more prone to develop oxidative stress and are more likely to be adversely affected by exposure to thimerosal. Tr. at 574, 576-77. James 2006, PML 49, at 953-54. However, the James 2006 study attributed the altered levels to a genetic predisposition, not to mercury interference. James 2006, PML 49, at 954. There was no indication that the study focused on autistic children with regression, or that the polymorphisms associated with a higher risk of metabolic anomalies had any connection to regression. Doctor Deth agreed that these polymorphisms also occur frequently in the general population,[576] while suggesting that heavy metal toxicity might be an environmental condition turning the alleles into risk factors for ASD. Tr. at 577.

The James 2006 study did not report whether the case children (those with autism diagnoses) had experienced regression nor whether the severity of autism symptoms was associated with severity of metabolic imbalance. *See* PML 49 at 947, 952. The authors also noted that abnormalities in the methylation cycle and

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[575] The genes investigated in the James 2006 study involved the two polymorphisms of the gene that controls methylene tetrahydrofolate reductase ["MTHFR"], which makes methylfolate for use by methionine synthase. Tr. at 574. The study also examined the reduced folate carrier ["RFC"] gene, which manufactures the proteins that transport folate into cells; the transcobalamin II gene, which produces the enzyme that transports cobalamin into cells, affecting the activity of methionine synthase; the catechol-o methyltransferase ["COMT'] gene, which determines the duration of dopamine action; and glutathione S transferase ["GST"] gene, and in particular, the M-1 form of that gene. *See* James 2006, PML 49, at 953-54. Certain polymorphisms in the MTHFR gene have been shown to control altered DNA methylation in response to diet, alcohol consumption, and hormone replacement therapy. *See* Rodenhiser and Mann, PML 459, at 343.

[576]The polymorphisms in the James 2006 study are normal variations, not mutations, and are shared by varying percentages of the population. Some may be present in as many as 50% of the population. Tr. at 619-20.

transsulfuration pathway have been found in heart disease, cancer, birth defects, and other neurologic disorders. *Id.* at 953. Based on the differences in frequency of several alleles between control children and those with autism, the authors strongly suggested that the metabolic abnormalities they observed in many of the autistic children were genetically influenced. *Id.* at 954.

The specific polymorphisms present in higher numbers of autistic children in the James 2006 study contradicted several aspects of Dr. Deth's hypothesis. Table III in the James 2006 study, PML 49 (reproduced on Dr. Deth's slide 39, Pet. Tr. Ex. 3), lists a number of different polymorphisms for six genes. Those in which the children with ASD differed significantly from the control children were listed in bold typeface. Doctor Jones noted that, in several of the genes in which a significant difference was found, the genetic variant in the autistic children would have a protective effect against oxidative stress. Tr. at 2754-55; Res. Tr. Ex. 9, slide 27.

Doctor Deth agreed that some of the gene variants would have a protective effect, but because of the confidence intervals, he did not think the protective effect was statistically significant.[577] Tr. at 3929-31. An examination of Table IV of the James 2006 study, PML 49, reproduced on Pet. Tr. Ex. 3, slide 40, demonstrates that at least two combinations of polymorphisms that Dr. Deth characterized as demonstrating a risk for oxidative injury suffered from the same problem with confidence intervals, making his assertions unlikely.

Another flaw Dr. Jones found in Dr. Deth's hypothesis came from the data on polymorphisms in the methionine synthase reductase gene. Tr. at 2754. The data in the James 2006 study, PML 49, reflect that, in the autistic subjects studied, all of the variations in the gene that codes for methionine synthase reductase are associated with a protective effect. Tr. at 2755.

The presence in some children with ASD of combinations of polymorphisms associated with higher levels of oxidative stress does little to advance Dr. Deth's hypothesis, because nothing associates these polymorphisms with a sensitivity to mercury or a propensity to oxidative stress. In view of the strong genetic contribution to ASD, the polymorphisms may simply reflect genetic differences between children with ASD and the control children. The polymorphisms may reflect part of the causal process in ASD. There is no evidence that suggests the polymorphisms are associated with any susceptibility to environmental toxins in general, or mercury in particular.

c. Genetics and Neuronal Signaling.

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[577] Doctor Deth also testified, based on his own research, that the polymorphisms with a borderline protective effect were not involved in neuronal cells. Tr. at 3930. He did not identify any published study supporting this assertion, and in view of his broad definition of "neuronal cells" and the focus of his work taking place in neuroblastoma cells with a methionine synthase deficiency, I give this assertion little weight.

There was no evidence adduced that those with autism have any polymorphisms associated with defects in neuronal signaling. Reasoning by analogy, Dr. Deth pointed to a polymorphism associated with neuronal signaling found in increased numbers of those with ADHD, and indicated that a similar signaling defect might be associated with autism. However, his own article indicated that this particular polymorphism had not been detected in increased numbers in children with autism. Deth, PML 563, at 194.

G. Conclusions Regarding Dr. Deth's Assertions.

Initially, to someone unacquainted with mercury's toxicology, ASD, or biochemistry, Dr. Deth's opinions on mercury, oxidative stress, and sulfur metabolism might appear to be solidly based and plausible. After all, mercury can be toxic to cells and is known to produce neurological injuries. Mercury does bind to glutathione, the body's primary antioxidant molecule, and thus might be expected to affect adversely the body's oxidative status. Mercury is known to bind to cysteine transporters, and thus might be expected to affect cysteine levels in cells, and thus adversely affect cells that cannot manufacture their own cysteine, such as neurons. There is evidence to indicate that mercury can cause proliferation of microglia and reductions in astrocyte numbers in at least some areas of the brain, which Dr. Deth equated to the neuroinflammation found in the brains of individuals with ASD. There is some evidence that children with ASD display biomarkers of oxidative stress in peripheral blood, and may even have some polymorphisms associated with higher levels of oxidative stress.

However, when critically examined, Dr. Deth's causal assertions fall apart. Mercury, at sufficient doses, is toxic to cells, but humans are born with mercury in their brains, blood, and hair as a result of maternal exposures. Humans continue to be exposed to mercury throughout their lives, and methods for detoxifying and eliminating mercury have evolved to account for this exposure. In populations with high mercury exposure, there is no increased incidence of ASD, and thus the low levels once found in vaccines are unlikely to be a cause or a substantial contributor to the condition.

Mercury, at sufficient doses, can produce neurological injuries, but not at the levels of mercury found in vaccines. The neurological injuries it produces are well established and do not resemble ASD. A comparison of autopsy findings in mercury's victims and autopsy findings from individuals with ASD do not show the same patterns of damage or injury.

Doctor Deth attempted to demonstrate that vaccine levels of mercury could adversely affect sulfur metabolism and produce oxidative injury in the human brain through a series of experiments on cells in culture. He represented the cells as "neuronal," although they were not neurons and had defects affecting the processes he attempted to measure. His laboratory experiments, funded largely by contributions from groups associated with the belief that vaccines cause ASD (ARI and SafeMinds), found adverse effects from doses of mercury between 100-10,000 times lower than those used by other researchers. Assuming, *arguendo*, that these experiments were properly

performed and produced correct results (both points about which I am unconvinced), the experiments contribute little to nothing to the causation hypothesis. *In vitro* experiments on cells in culture may suggest likely avenues for further research, but the complexity of sulfur metabolism presented in Dr. Deth's testimony and report demonstrates the robust systems in place in human beings to handle oxidative stress and produce the methylated products needed for cellular functioning, including DNA expression. I note that Dr. Deth heavily relied on mercury's effects on glutathione, but the evidence overwhelmingly illustrated that glutathione levels in the body would be unaffected by vaccine level doses.

Doctor Deth also relied heavily on evidence indicating that children with ASD display peripheral markers of oxidative stress, and that brains of those with ASD have evidence of neuroinflammation, which he equated to oxidative damage. He failed to mention that oxidative stress in the periphery is associated with many different diseases, but that peripheral levels do not represent brain redox status. He likewise failed to point out that neuroinflammation is found in many brain disorders and injuries, including those produced by trauma. Thus, a finding of oxidative stress or even oxidative injury says little about mercury as a probable cause of the stress or injury because there are so many other possible causes, including neuroinflammation as a response to the other pathophysiological findings in the brains of those with ASD.

Since ASD is a highly genetic disorder, it is unsurprising that preliminary studies have found some polymorphisms exist in children with ASD in higher numbers than in neurotypical individuals. It is equally unsurprising that some of these polymorphisms are associated with problems in oxidation or sulfur metabolism. Children with Down syndrome, an entirely genetic disorder involving mental retardation, also have oxidative stress levels higher than neurotypical children. Children with Rett's disorder, another entirely genetic condition, have impairments in DNA methylation, a sulfur metabolism problem. The preliminary findings in children with ASD say nothing about a genetic susceptibility to mercury or even that the oxidative stress levels found actually affect mercury detoxification.

Doctor Deth's own experiments were based on faulty premises regarding methylation of the D4 receptor and defects in methionine synthase activity in human neurons. His experiments detecting effects of nanomolar levels of mercury on glutathione, cysteine, methylcobalamin, and methionine synthase had so many flaws that they cannot be considered reliable as evidence. Respondent's experts in oxidative stress, sulfur metabolism, neurodegenerative disorders, and mercury pointed out the serious deficiencies in Dr. Deth's hypothesis, experiments, and conclusions. Their criticisms, coupled with the flaws in Dr. Deth's logic, his own acknowledgment that eliminating TCVs has not produced any decline in ASD rates (Tr. at 617-18), and the conflicts between his testimony and what is well established about mercury's toxicology, all convince me that Dr. Deth's hypothesis is not reliable, and cause me to accord his testimony and report little weight.

Section VIII. The Neuroinflammation Hypothesis.

A. Overview.

Doctors Deth and Kinsbourne presented hypotheses that involved persistent inorganic mercury in the brain causing neuroinflammation,[578] leading to autism. The majority of Dr. Deth's testimony focused on the effects of mercury on sulfur metabolism, leading to a state of oxidative stress in the brain, manifesting with the neuroinflammatory findings reported by the Vargas study, PML 69. His neuroinflammation hypothesis was similar, but not identical, to that of Dr. Kinsbourne, and he was less clear about how the neuroinflammation resulted in ASD. Doctor Kinsbourne's hypothesis attempted to fill that gap. Doctor Kinsbourne asserted that mercury-induced neuroinflammation caused excitotoxicity,[579] which manifested as overarousal of individuals with ASD, causing autistic behaviors.

Doctor Kinsbourne made it clear that his opinion did not depend on that of Dr. Deth, who "was studying at the molecular level a particular component of the broader process that I was invoking." Tr. at 904. However, Dr. Kinsbourne did not tie his neuroinflammation process specifically to Dr. Deth's oxidative stress model. Tr. at 905. For purposes of his hypothesis, it did not matter how the neuroinflammation was produced. *See* Tr. at 911-12.

However, Dr. Kinsbourne's hypothesis was based on Dr. Aposhian's opinions about the amount of mercury required to cause the excitotoxic process he proposed. Tr. at 864. As indicated in Section VI, I did not find Dr. Aposhian's calculations regarding the amount of mercury in the brain generated from vaccines to be correct. I did not credit Dr. Aposhian's testimony that TCVs could produce enough mercury to cause the widespread glial activation necessary to Dr. Kinsbourne's hypothesis. Nevertheless, because of the role of Dr. Kinsbourne's testimony in the general causation test case, I evaluate his general causation hypothesis[580] as if these

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[578] One paper defined neuroinflammation as "chronic, CNS-specific, inflammation-like glial responses." W. Streit, et al., *Microglia and neuroinflammation: a pathological perspective*, J. NEUROINFLAMMATION 1: 1-12, 2 (2006) ["Streit"], filed as PML 70. According to Dr. Kinsbourne, "[n]euroinflammation is the brain's innate immune system's response to invading organisms and foreign proteins and toxins." PML 717 at 13. It "is often associated with the activation, proliferation and ultimate disintegration of astrocytes, as well as increase in neural excitability." PML 717 at 13. According to Dr. Deth, the term "neuroinflammation" implies the presence of oxidative stress involving microglia, astrocytes, and neurons, produced by changes in sulfur metabolism. Tr. at 513-14; Pet. Tr. Ex. 3, slide 4. It appeared that each expert defined neuroinflammation according to his own hypothesis.

[579] Excitotoxicity is explained more fully, *infra*.

[580] Doctor Kinsbourne's testimony was limited to the issue of general causation; he did not offer opinions on the three individual Theory 2 cases. Tr. at 777-78. The specific causation opinions were provided by Dr. Mumper, whose opinion with regard to Colin is addressed in Section X.G.2., below.

evidentiary prerequisites had been met. I conclude that there are other fatal flaws in his hypothesis. The method of injury he proposed would lead to neuronal death, and eventually patient death, not ASD. The brain cell interactions he proposed are not consistent with the complex interactions that actually occur in human brains. Mercury's effects on the brain and the symptoms it produces do not resemble those of ASD. Doctor Kinsbourne's overarousal model of ASD is not new, but it has never been widely accepted because there is no evidence linking the behaviors Dr. Kinsbourne attributed to overarousal to physiological measurements of hyperexcitability.

B. Doctor Kinsbourne's Hypothesis.

1. The Hypothesis.

Doctor Kinsbourne asserted that neuroinflammation is the process by which ASDs are caused. Tr. at 814. In attributing ASD causation to neuroinflammation,[581] Dr. Kinsbourne conceded that neuroinflammation can have many causes and the specific cause cannot be determined merely by looking at the inflammation. Tr. at 810. Causative agents fall into three categories: viruses; toxins, such as heavy metals[582] or some drugs; and neurodegeneration.[583] All three of these causative agents are "on the differential" in trying to diagnose the cause of neuroinflammation. Tr. at 810-12. Because TCVs contain ethylmercury, a heavy metal, they belong on the list of potential causes of autism. They may be identified as causal through the process of differential diagnosis[584] when other causes have been ruled out. Tr. at 778-79; PML 717 at 3. Diagnosis of ASD as a mercury-induced injury would be "a conjoined effort by a neurologist and a toxicologist," and by a treating physician as well. Tr. at 843.

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[581] Doctor Kinsbourne was clear that he was not asserting that neuroinflammation is autism; rather, it is the process by which autism is caused. Tr. at 814.

[582] Mercury is considered a heavy metal. Doctor Kinsbourne would consider any source or form of mercury, including TCVs, in making a differential diagnosis of autism caused by mercury-induced neuroinflammation. Tr. at 812.

[583] Unless Dr. Kinsbourne intended the term "neurodegeneration" to include trauma and congenital injuries, Dr. Kinsbourne's list of causes for neuroinflammation was incomplete. There was substantial evidence that neuroinflammation may be a response to injury. *See* Section IV.G.4. From other testimony, it appeared that in using the term "neurodegeneration," Dr. Kinsbourne was referring to neurodegenerative diseases, such as Alzheimer's and Parkinson's, which cause inflammation secondary to neuronal death. Tr. at 811; *see also* Tr. at 947-48 (chronic neuroinflammation could lead to neurodegeneration).

[584] Doctor Kinsbourne described the process of differential diagnosis in the following manner. "When one is confronted by an individual with a particular problem, be it physical, or mental, or both, it is almost always the case that there's more than one possible cause of the appearances that you see. One then lists to the best of one's ability the various disease processes that could lead to that outcome and to the best of available investigative capability tries to find out which one of them it is ruling out the others." Tr. at 849.

In his expert report, Dr. Kinsbourne asserted that:

> [A] current view holds that ASD can be due to active inflammation involving specific territories of the brain over many years. One potential cause of such chronic inflammation would be a series of low-dose exposures to organic mercury, doses too small to cause substantial acute or focal neuronal damage and death, but doses sufficient to lead to the accumulation of [inorganic mercury] in astrocytes and microglia.

PML 717 at 13. The persistent mercury burden causes the inflammation to "become chronic and itself damaging to bystanding neighboring tissues." *Id*. "[M]ercury in the brain can cause autistic behavior problems," and any source of mercury should be considered as a potential cause of autism in a particular child. Tr. at 779, 842-43. He opined that, to a reasonable degree of medical certainty, mercury could induce neuroinflammation by affecting brain glutamate levels,[585] and thus result in autistic symptoms.[586] Tr. at 779-80, 814-15, 912.

The mercury-provoked microglial activation causes glutamate excess, which causes overarousal, which causes the autistic behaviors. Tr. at 875-76. With persistent mercury in the brain, the mechanism of injury would be ongoing or continuous. Tr. at 839. However, he was "not at all confident whether the amount of mercury in the vaccines is at the level to elicit this inflammation because that is something that, as I've explained, for which I need assistance from a toxicologist," referring to Dr. Aposhian's opinions on brain levels of mercury expected from TCV administration. Tr. at 912.

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[585] Glutamate is the brain's primary excitatory neurotransmitter. Too much glutamate is dangerous because it can damage neurons by causing them to fire too much and cause seizures, a process called excitotoxicity. Tr. at 797. Glutamate and GABA normally coexist in a ratio that decides the level of general excitation in the brain. Tr. at 803-04.

[586] One of the questions that prompted this response referred to the mechanism of injury "whereby neuroinflammation might express itself as the symptoms of regressive autism." Tr. at 814 (emphasis added). Doctor Kinsbourne's answers did not qualify the injury mechanism as causing only regressive autism. Indeed, in other testimony, he candidly stated that his mechanism of injury was not limited to regressive autism. Tr. at 901-03. Initially, he stated: "I'm putting it forward for regressive autism. Whether it extends to any other kind of autism, I haven't considered it in that context." Tr. at 903. He then contradicted himself:

> I don't believe for a moment that it only happens in regressive autism. I also believe that it has more than one cause. For example, if one gives a mother terbutaline during pregnancy and then finds neuroinflammation in the autistic child, that would be another cause of neuroinflammation. I wouldn't be surprised if there were other viruses than the measles virus and if there were other toxicants than mercury that could do the same thing. I began by saying that there are multiple potential causes.

Tr. at 903. When asked again if his hypothesis of neuroinflammation was restricted to regressive autism, he responded: "No. Not at all." Tr. at 904.

Doctor Kinsbourne acknowledged that the overarousal hypothesis was essentially the same hypothesis he presented in the Theory 1 cases.[587] He testified that the mechanism by which the autistic behaviors were provoked was not specific to mercury or measles virus; it can be caused by anything that triggers neuroinflammation.[588] Tr. at 911-12; 4152-53. Doctor Kinsbourne acknowledged that excess glutamate is not known to be a cause of regressive autism, or, indeed of any form of autism. Tr. at 908.

2. The Cellular Processes in Neuroinflammation.

Doctor Kinsbourne testified that, when confronted by an invader or toxin such as mercury, the brain's innate immune system responds by activating microglia. Tr. at 798-99. Activated microglia attack the invading substance by releasing ROS, cytokines, free radicals, and "other potential neurotoxins." PML 717 at 13. They may also respond by engulfing the invader. *See* Tr. at 795 (microglia act as phagocytes).

If the invader is successfully eliminated, then the reactive chemical attack stops. If the invader remains, then there may be "a chronic continuous outpouring of these cytokines and other agents that can now be damaging to astrocytes and damaging to neurons." Tr. at 800. In a persistent immune challenge, the number of microglia increase because there is more work for them to do. Tr. at 804. More microglia increase the potential for friendly fire to damage astrocytes, which, over time, die. Tr. at 804.

Astrocytes regulate the levels of glutamate in brain synapses[589] through transporters and receptors on the astrocytes that absorb excess glutamate. PML 717 at 18; Tr. at 797-98. Microglia also mediate the uptake and removal of excitotoxic neurotransporters, including glutamate, from the area of the synapses. Pardo, PML 72, at 489. The chemical agents, such as proinflammatory cytokines, released by "friendly

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[587] During the Theory 1 cases, Dr. Kinsbourne testified that the mechanism of injury–the glutamate-excitation hypothesis–was the weakest part of his hypothesis. *See* Tr. at 912-13. During the Theory 2 cases, he acknowledged this earlier testimony, but explained that this part of his hypothesis had "gotten stronger." He had not examined the issue of TCVs during the Theory 1 cases, and thus had not formed an opinion about TCV causation at that time. Tr. at 913-15. He began to consider the question of mercury only very recently, when he realized that mercury could cause the same neuroinflammation as viruses. Tr. at 915-17.

[588] Doctor Kinsbourne admitted that portions of his testimony in the *Cedillo* Theory 1 case (which involved his theory of virus-caused neuroinflammation) were virtually identical to his report in the Theory 2 cases. Tr. at 916. A comparison of page 16 of his report in *Snyder* with page 13 of his general causation report (PML 717) in the Theory 2 cases reflects that the only changes involved substituting "thimerosal-containing vaccines" for "measles virus." Tr. at 917-18.

[589] Neurons do not directly connect with each other. The gaps between neurons are called synapses, which are bridged chemically. Tr. at 796.

fire" can block transporters on the astrocytes, impairing their ability to mop up excess glutamate. Astrocyte interaction with activated microglia can also amplify glutamate release by the astrocytes. Tr. at 801; PML 717 at 18.

Because the astrocytes mediate the microglial attack by being "first in the firing line," the reactive chemicals released by the microglia might not cause direct neuronal damage. Tr. at 801. However, neurons may be damaged indirectly. If damaged astrocytes are not scavenging glutamate, it accumulates, "shifting the excitation-inhibition balance in the direction of overexcitation," and causing glutamatergic cells to fire more frequently. PML 717 at 18. This causes a general excitation of many parts of the brain and the level of excitation may be so great as to kill neurons. Tr. at 802; *see also* PML 717 at 21 (explaining harmful effects of excess glutamate on neurons). When the astrocytes malfunction or die, glutamate excesses occur, and, over time, there will be an increase in microglia, a decrease in astrocytes, an increase in gliosis, and, in severe cases, a loss of neurons. Tr. at 805.

Doctor Kinsbourne relied on the Aschner 2000 and Aschner 2007 articles[590] as evidence for this mechanism of injury. The Aschner 2007 study, PML 570, focused on the role of astrocytes in mediating methylmercury neurotoxicity. Citing to earlier studies, the authors noted that methylmercury preferentially accumulates in astrocytes and inhibits astrocytic glutamate uptake, increasing glutamate concentrations and "sensitizing neurons to excitotoxic injury." PML 570 at 286; *see also* PML 717 at 16. Doctor Kinsbourne noted this was the same excitotoxic process he had described. Tr. at 817. From these articles by Aschner and others, Dr. Kinsbourne concluded that mercury would create astrocytic death and microglial activation. Tr. at 872; *see also* PML 717 at 16 ("[Inorganic mercury] is also a medically reasonable cause of neuroinflammation and its sequelae in some children.").

Doctor Kinsbourne stressed that the neuroinflammatory process he described would cause abnormal functioning of neurons, not generalized neuronal death. Tr. at 823-24. Astrocytic death was likewise not a necessary condition; his hypothesis merely required that astrocytes be sufficiently impaired to permit glutamate to rise out of control and produce overexcitation in neurons. Tr. at 933. Even if the astrocytes themselves were not harmed by mercury, the presence of mercury in the astrocytes could attract an immune attack by the microglia, killing or damaging the astrocytes. Tr. at 934.

3. Mercury and Neuroinflammation.

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[590] Aschner 2000, PML 568; Aschner 2007, PML 570. The Aschner 2007 article, PML 570, was primarily a literature survey, followed by a depiction of a proposed role for oxidative stress in methylmercury toxicity. PML 570 at 288-90. I note that the article focused solely on methylmercury toxicity, and did not indicate whether the methylmercury had demethylated to inorganic mercury before generating its purported effects on various cellular processes. Neither Aschner study identified the quantity of mercury necessary to cause the effects described.

Although he deferred to a toxicologist concerning the quantity of mercury necessary to induce neuroinflammatory effects (Tr. at 860, 867), Dr. Kinsbourne discussed mercury's role in neuroinflammation at some length. He agreed that some of the inorganic mercury in every brain came from sources other than TCVs. Tr. at 813-14, 860. He opined "that mercury, in sufficient amounts, will set up the process of neuroinflammation with its consequences...regardless of the vehicle in which it comes, whether it's mercury vapor, or whether it's a vaccination, or whether it's fish, anything." Tr. at 860. He left it to others to ascertain that TCVs contained enough mercury to cause autism by the neuroinflammatory mechanism he described. Tr. at 856, 862-63.

He did, however, address timing. With respect to mercury from TCVs, he stated that ethylmercury was "likely to enter the brain while it is still detectable in the blood, so it will perhaps be a few weeks."[591] Tr. at 856. Vaccination with a TCV would result in a chronic low dose exposure because the ethylmercury degrades to inorganic mercury, which remains chronically present. Tr. at 858. The process of conversion to mercuric mercury would take from weeks to months. Tr. at 859. The deethylized or demethylized metallic mercury would remain in the brain to elicit the inflammatory actions Dr. Kinsbourne discussed, causing autistic symptoms. *See* Tr. at 858-59.

He would expect the immune system to react to toxins by producing inflammation within days or a few weeks. Tr. at 896. Some response might occur almost immediately after the toxin entered the brain, but the response might only become clinically apparent later. Tr. at 897. He could not definitively set the lower and upper bounds of the appropriate reaction time. Tr. at 897-98.

Under his theory, the neuroinflammation would continue as long as the inorganic mercury remained present. Logically, the inflammation would subside if the amount of mercury decreased, and increase if the amount of mercury increased, but Dr. Kinsbourne did not have any empirical evidence for either scenario. Tr. at 899-900; 4154-56. On rebuttal, he changed his position, indicating that the glutamate excess would not continue to increase as the inorganic mercury increased. He hypothesized that some of the regulatory mechanisms present in the body controlled the excess to a degree, preventing the glutamate excess from killing neurons. Tr. at 4153-56.

For evidence that the mercury in TCVs was sufficient, he relied upon Dr. Aposhian's report and some literature that suggested that toxicologists could determine that sufficient mercury would reach the brain. Tr. at 864-65. His report concluded:

[I]t is my opinion, to a reasonable degree of medical probability that a

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[591] I note that this statement conflicted with the evidence in the Burbacher infant monkey study, which found blood levels of mercury in the ethylmercury-dosed monkeys cleared very rapidly, on the order of about 8 days. Burbacher, PML 26, at 1019. In the Pichichero 2002 study, blood mercury levels in the two-month-old infants were measured 3-21 days after vaccination, and in about 1/3 of the samples, mercury levels were below the limit of detection. *See* PML 223 at 1738-39.

> series of TCVs can result in or contribute to an accumulation of [inorganic mercury] in the brain. The mercury in the brain may trigger an inflammatory response in some children...that results in a hyperglutamatergic state.

PML 717 at 24. When questioned about this statement, Dr. Kinsbourne emphasized that a toxicologist would have to determine whether the amount of mercury in TCVs was sufficient, responding: "In other words, in my differential diagnosis I would consult a toxicologist."[592] Tr. at 866-67.

Although everyone is exposed to some amount of mercury, and most children who were vaccinated in the 1990s received TCVs, only a small minority develop an ASD. To explain why only some children exposed to mercury develop an ASD, Dr. Kinsbourne postulated a genetic susceptibility in these individuals. He asserted that the genetic vulnerability in autism is such that a particular event, which is harmless to most people, is harmful to a subset. Tr. at 852-53. He testified that he could not provide the specific neurobiological basis for why some people become autistic, although most do not, after TCV exposure. He had not worked out what their vulnerability was, and could not state that it resulted from a lowered threshold for mercury's effects. All he could say is that the great majority of children who received TCVs emerged unscathed. Tr. at 853-55. He indicated that individuals with autism have glutamate receptor and transporter abnormalities, implying that these abnormalities may enhance mercury's neuroinflammatory effects. PML 717 at 18. However, he could not identify what would determine why one person would have excess glutamate as the result of inorganic mercury and another would not. Tr. at 4153-56. He knew of no quantitation of the amount of excess glutamate needed to produce the excitatory effects he postulated. Tr. at 4158-59.

Doctor Kinsbourne summarized the mechanism of injury as:

> [M]icromolar (trace) amounts of mercury derived from the breakdown of several different mercury compounds can damage astrocytes, releasing glutamate flow from control, damage the glutamate transporters on neurons, with similar consequences, compromise the function of mitochondria in the energy metabolism of cells, and lead not only to 'an unimpeded cytotoxic cycle' [citing to Aschner 2007, PML 570, at 286], but also an overactivated brain state.

PML 717 at 17.

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[592] At the time he wrote this opinion regarding TCVs and neuroinflammation, Dr. Kinsbourne had not directly consulted a toxicologist. However, he was aware of Dr. Aschner's work reporting that mercury in the brain could cause microglial activation and inhibition of glutamate reuptake. Tr. at 870. I note that the transcript referred to "glutamate reactate." Tr. at 870. From context, including the articles Dr. Kinsbourne was citing, the transcript should have read "glutamate reuptake."

4. Overarousal as a Result of Excitatory-Inhibitory Imbalance.

This subsection sets forth the testimony and sections of Dr. Kinsbourne's report in which he explains his overarousal hypothesis. There are internal, as well as external, contradictions in Dr. Kinsbourne's testimony and report, which are addressed below.

a. Doctor Kinsbourne's Model.

In what Dr. Kinsbourne characterized as the "overarousal model" of autism, excess glutamate increases the excitation-inhibition ratio, resulting in behavioral overarousal. Tr. at 824. He claimed that "[a]utistic behavior is precisely what one would expect if the brain's excitation/inhibition ratio were skewed in favor of excitation (as occurs in hyperglutamatergic states)." PML 717 at 20. He noted that "the higher functioning majority [of the ASD population][593] was overaroused" but that "a substantial minority of patients seems lethargic and underaroused," and that those with underarousal were those most intellectually handicapped.[594] PML 717 at 20. He cited to an article by Baron, PML 550,[595] and to his own questionnaire study, Liss, PML 373,[596] as support for these statements. He conceded that the overarousal model could not apply to all cases of autism, but might apply to most. PML 717 at 20.

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[593] In view of the otherwise unchallenged evidence of the high association between ASD and mental retardation (*see, e.g.*, DSM-IV-TR at 69), Dr. Kinsbourne's assertion that higher functioning autistic individuals constitute a majority of those with ASD is incorrect. He offered no support for this assertion.

[594] This statement, coupled with his testimony that those with regressive autism tended to be those more severely affected (Tr. at 780-81), sets up a conflict. If those with regressive autism are more severely affected and those who are more severely affected are those who are underaroused, the overarousal hypothesis cannot account for their behavior.

[595] This article was not filed. One page from a book edited by M. Grace Baron and others was filed as PML 550. The page cited a study by Goodwin examining cardiovascular responses in five individuals with autism. Another page from what was identified as the Goodwin study on the Petitioners' Master Reference List was filed as PML 496. This page is the mean heart rate level for "J.L," who was not otherwise identified. Based on the Baron article, Dr. Kinsbourne contended that autistic subjects have higher basal heart rates, a result of a higher rate of functioning of the sympathetic nervous system and reflecting a state of overarousal. Tr. at 825-26.

Whether someone looks aroused is not the same thing as arousal from a physiological standpoint. According to Dr. Rutter, the Goodwin paper first reviewed the problems other researchers had encountered in assessing whether someone appeared to be aroused and tying that appearance to physiologic evidence of arousal. The authors then compared responses in five individuals with autism and five controls, attempting to find physiologic evidence for arousal. The study was small, and, like the earlier research, its results were inconclusive. Tr. at 3316-17.

[596] Doctor Kinsbourne is listed as the senior researcher on this study. He described his role as developing the questionnaire used to query parents about "overfocusing." Tr. at 910-11. Doctor Rutter described the Liss paper, PML 373, as a questionnaire study of parents describing their children's responses to sensations. Tr. at 3317-18. The weakness of the study was its use of observations of the children's responses, rather than objective measurements of responses to sensory stimuli. Tr. at 3318.

According to Dr. Kinsbourne, this creates "a situation which is consistent with one of the existing models of what brain change it is that underlies autistic behavior and which I called in my report 'the overarousal model.'" Tr. at 824. This proposed model connected neuroinflammation to manifestations of autistic behavior. Tr. at 824-25. He contended, citing his own 1980 article, PML 460,[597] that autistic symptomatology could be accounted for as either an attempt to escape from the effects of overarousal or the effects of overarousal. PML 717 at 20.

b. Tying Overarousal to Autistic Behavior.

According to Dr. Kinsbourne, the consequences of this state of overarousal manifest as three types of autistic behavior. Tr. at 826. First, as arousal increases, focus of attention constricts. As an example, Dr. Kinsbourne pointed to the restricted focus of autistic individuals. Rather than looking at a person's face, an autistic individual might focus only on an ear. Tr. at 827. He suggested that this is what makes autistic individuals disproportionately better at simple tasks rather than complex ones. Tr. at 829; *see also* PML 717 at 20 (pointing to echolalia as a consequence of overarousal).

The second category of manifestation is seeking environments that are low in stimulation. Tr. at 829. Individuals with ASD do not tolerate change well. Tr. at 830. They acquire very detailed information in very narrow categories. Tr. at 830-31; *see also* PML 717 at 22 (attributing to overarousal failures in tests of "theory of mind,"[598] as well as the tendency of those with ASD to be solitary and engrossed in unusual topics).

The third category involves responses to overstimulation. When placed in new situations, children with autism go out of control as a result of overstimulation. Short of these "meltdowns," children confronted with too much stimulation engage in stereotypic behaviors such as hand flapping, whirling, and repetitive finger motions, all of which serve an internal purpose of dearousing. Tr. at 832. Doctor Kinsbourne interpreted certain behaviors, such as lining things up, as a self-soothing mechanism to hold down the level of stimulation. Tr. at 831. He called them adaptive preferences for dealing with threatening environments. Tr. at 832; *see also* PML 717 at 20-22 (attributing stereotypic behaviors as attempts to lower neural excitation levels and "stimming" as an

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[597] M. Kinsbourne, *Do Repetitive Movement Patterns in Children and Animals Serve a Dearousing Function?* J. DEVEL. & BEHAV. PEDIATRICS 1(1): 39-42 (1980), filed as PML 460. In his expert report, Dr. Kinsbourne either mistakenly indicated that this article was published in 1987 or was referring to another article. *See* PML 717 at 20. His citation to page 117 of PML 460 suggests that he may have had another article in mind, as PML 460 ends on page 42.

[598] The ability to understand others through assessing social situations has been called the "theory of mind." Tr. at 3270-71. Doctor Rutter explained that neurotypical individuals are good at recognizing what others are thinking from social context and behavioral clues. Autistic individuals are not. Tr. at 3271-72.

action performed for its calming effects, and gaze avoidance and the need for sameness as "defensive" efforts to minimize overarousing inputs).

He also attributed epilepsy and subclinical EEG disturbances, which are common in those with ASD, to overexcitation. PML 717 at 18, 21; Tr. at 875-76. Doctor Kinsbourne asserted that EEG studies and neuroimaging show that some brain systems, such as the amygdala, are overaroused in those with ASD, but did not identify any specific studies for this point. Tr. at 826.

5 Studies Cited in Support.

a. Overview.

Although Dr. Kinsbourne cited a number of studies as supporting his model of autism as a consequence of an excitatory-inhibitory imbalance, many either do not support the points for which he cited them or the points he made were taken out of context. Doctor Rust generally characterized Dr. Kinsbourne as overstating the support found in these studies. Tr. at 2487. What emerges when these studies are critically examined is validation for Dr. Rust's characterization. The data Dr. Kinsbourne cited are not representative of the studies' findings, and much of the data contained in the studies do not support Dr. Kinsbourne's hypothesis. As Dr. Rust further observed: "Prominent countervailing data and theories are not considered." Tr. at 2465.

An occasional misstatement of a study might be expected in any expert's analysis of such complex issues. However, the pattern that emerges in Dr. Kinsbourne's citations is not that of an occasional misstatement. A scientist might well pick data from many different sources to serve as circumstantial evidence for a particular hypothesis, but a reliable expert would not ignore contrary data, misstate the findings of others, make sweeping statements without support, and cite papers that do not provide the support asserted.

In the subsections below, I set forth Dr. Kinsbourne's assertions regarding the support for his hypothesis found in specific studies or groups of studies, immediately followed by any issues concerning his assertions. I defer most critical comments concerning his overall hypothesis to subsection C., below.

b. The Studies.

(1) Neuropathology Studies.[599]

[599] Because most of the neuropathology studies were in general agreement with one another, these studies are addressed as a group. Doctor Kinsbourne's assertions regarding the Vargas and Lopez-Hurtado papers are addressed separately below.

Doctor Kinsbourne addressed several of the findings from the neuropathology studies, and asserted that their pathophysiology findings can be associated with autistic symptoms. PML 717 at 15. Doctor Rodier disagreed, testifying that most findings from these studies could not be linked to a particular autistic symptom or behavior. Tr. at 3038-39.

Doctor Kinsbourne also commented that the timing of TCV administration coincided with a vulnerable period of brain development. Inorganic mercury present during this period would induce "disruptions of glial cell function [leading] to abnormalities in brain development and maturation." PML 717 at 15. He neglected to mention that the neuropathology studies strongly indicated that the brain development and maturation processes in ASD were largely of prenatal origin. *See* Section IV.G.6.

Doctor Kinsbourne identified gliosis, found in the brains of autistic individuals in the Bailey study filed as PML 90,[600] as supportive of his hypothesis, calling gliosis "a sequel [sic] of the death of astrocytes in inflammation." PML 717 at 13. Doctor Rust disagreed with his characterization, noting that gliosis is a nonspecific finding that occurs in many brain diseases where there is no evidence for toxins or infection. Tr. at 2487; Res. Tr. Ex. 8, slide 67. Doctor Johnson pointed out that gliosis is not astrocyte death. Tr. at 2243-44.

Doctor Kinsbourne noted that pyramidal cells are particularly vulnerable to excitotoxic damage due to glutamate.[601] PML 717 at 18. In the next sentence of his report, he appeared to conflate pyramidal cells with Purkinje cells, noting that the loss of Purkinje cells in those with autism had been demonstrated, and might "in some cases represent the cytotoxic effect." PML 717 at 18; *see also* Tr. at 881 (acknowledging that Bauman and Kemper found fewer Purkinje cells than expected in the cerebellum).

Doctor Kinsbourne testified that inorganic mercury was the likely source of the Purkinje cell loss, stating: "I would expect inorganic mercury to set up the excitotoxicity potential that I've described, and, if there is excitotoxicity, the Purkinje cells are a very likely target because they're more vulnerable to excitotoxicity than most other cell types in the brain." Tr. at 878; *see also* Tr. at 881. He did not identify any source for the statement that ethylmercury or inorganic mercury caused the loss of Purkinje cells, and

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[600] Doctor Kinsbourne cited this study as "Bailey et al. (1998b PMRL #0090)." It appears that Dr. Kinsbourne may have meant the Bailey study at PML 220, rather than the Bailey study at PML 90. The Baily 1995 study, PML 90, is a twin study; the Baily 1998 study, PML 220, is one of the autopsy studies.

[601] The cited article, M. Hamann and J. Rossi, et al., *The electrical response of cerebellar Purkinje neurons to simulated ischaemia*, BRAIN 128: 2408-20 (2005), filed as PML 494, deals with the electrical response of rat and mice Purkinje cells to ischemia, a lack of blood. Doctor Kinsbourne's report referred to pyramidal cells, which are only mentioned in the article in passing. Even if the reference to pyramidal cells is a typographic error, the study is not supportive. It did not examine the vulnerability of Purkinje cells to excitotoxic damage; it examined the electrical response of Purkinje cells to ischemia. Purkinje cells release glutamate when blood flow is cut off.

I was unable to find one. Given the strong evidence that the loss of Purkinje cells occurred long before birth, Dr. Kinsbourne's attribution of their loss to inorganic mercury, presumably from TCVs, has a timing problem as well. *See* Section IV.G.3.b.

When confronted with evidence that one of the studies upon which he relied stated that Purkinje cells were not damaged by methylmercury exposure[602] (*see* Aschner 2000, PML 568, at 201-02), Dr. Kinsbourne's response was more than a little illogical. He testified that he was not attributing the loss of Purkinje cells directly to mercury poisoning, but rather to the excitotoxic effects of mercury. Tr. at 881-83, 879. That is, he was saying that high doses of methylmercury (which converts to inorganic mercury) will spare Purkinje cells, but low-dose exposure will kill them through excitotoxicity caused by inorganic mercury. The evidence established that doses of mercury sufficient to cause harm spared Purkinje cells, while damaging other cell types.

Doctor Kinsbourne agreed that methylmercury, but not ethylmercury, produced the loss of granular cells, another type of neuron. He also agreed that, at large enough doses, mercury will kill neurons. Tr. at 878-81. He acknowledged that "in methyl mercury poisoning, which we don't have in autism, the granule cells are more vulnerable than the Purkinje cells to being killed." Tr. at 883.

Rather than providing the "dramatic support" for his hypothesis that Dr. Kinsbourne asserted they did (PML 717 at 13), the pathophysiology studies undermined it, both in terms of the likely prenatal origins of the brain anomalies observed in those studies, and in the findings regarding specific cell types. Doctor Casanova's studies[603]

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[602] The fact that methylmercury damages granule cells, but spares Purkinje cells, and that ethylmercury causes far less damage to granule cells and likewise spares Purkinje cells does not appear to be in controversy, except perhaps for Dr. Kinsbourne. *See* Clarkson 2002, PML 182, at 13 (attributing ataxia from methylmercury to the loss of the granule cells, and noting that neighboring Purkinje cells are largely spared); Magos 1985, PML 175, at abstract and 263 (granule cell damage observed in rat brains after high levels of methylmercury exposure, but much less damage observed after higher levels of ethylmercury exposure; no damage to Purkinje cells noted); Clarkson and Magos 2006, PML 35, at 631 (in human methylmercury poisoning, damage was restricted to focal areas of the brain, the granule cell layer of the cerebellum; adjacent Purkinje cells spared).

[603] During rebuttal, Dr. Kinsbourne testified that one of Dr. Casanova's articles (filed as both PML 274 and RML 62) supported his hypothesis. Tr. at 4121-22; 4161-63. He referred to the following statement:

> Among several conceptual classifications, autism has been considered a disorder of the arousal-modulating systems of the brain. According to this theory, autistic individuals experience a chronic state of overarousal and exhibit abnormal behaviors to diminish this arousal. The arousal theory is of some interest because it is consistent with a reduction of inhibitory interneuronal activity.

RML 62 at 431 (citation omitted). This citation serves as yet another example of Dr. Kinsbourne "cherry-picking" data. The article itself asserts that the minicolumnar abnormalities occurred during gestation, hardly supportive of Dr. Kinsbourne's postnatal mercury hypothesis. After the overarousal statement

did not find a loss of pyramidal cells, the result predicted by Dr. Kinsbourne's assertions that they were particularly vulnerable to mercury's effects. Granule cells are damaged by methylmercury, but much less damage to granule cells is caused by ethylmercury. This suggests that the damage to these neuronal cells occurs before demethylation and is thus attributable by species to methylmercury. However, Dr. Kinsbourne asserted that inorganic mercury was the cause of neuroinflammation. The loss of granule cells occurs in autism only when the associated Purkinje cells are also lost. *See* Vargas, PML 69, at 78-79 (noting granule cell loss in the area of missing Purkinje cells). Doctor Kinsbourne could not explain why high-dose exposure would spare cells, but low-dose mercury exposure would damage them or impair their function.

(2) Lopez-Hurtado Study, PML 446.

Doctor Kinsbourne relied on the Lopez-Hurtado study's findings of decreased density of neurons and increased density of glial cells as evidence of neuronal death with gliosis. PML 717 at 13. However, his model did not predict neuronal death. Tr. at 881. As Dr. Johnson noted, the findings of neuronal loss in this study were not consistent with Dr. Kinsbourne's hypothesis of a steady state of astrocyte death and dysfunction without a progressive disease process leading to neuronal death. Tr. at 2262.

(3) The Vargas Study, PML 69.

Like Dr. Deth, Dr. Kinsbourne also relied heavily on the Vargas study, PML 69, which found evidence of chronic inflammation and "an active ongoing neuroinflammatory process in the brain." PML 717 at 14. He testified that the Vargas study found some problems with neurons, but did not find much gliosis. Tr. at 835.

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quoted above, Dr. Casanova continued:

> It is known that the cortex contains inhibitory double bouquet cells that define minicolumnar organization for the brain, or what one researcher calls a "strong vertically directed stream of inhibition." The lateral inhibition caused by the GABAergic neurons helps to ensure individual minicolumn discreteness and during development, to impel adjacent minicolumns into establishing connections with functionally dissimilar sets of thalamic neurons.

RML 62 at 431 (citations omitted). Read in context, Dr. Casanova's statements have nothing to do with the brain-wide excitatory imbalance caused by mercury that Dr. Kinsbourne's hypothesis proposes. Doctor Casanova proposed that, if in minicolumn development, certain connective patterns are not formed, an individual's ability to "discriminate between competing types of sensory information" may be impaired. *Id.* This is not support for a postnatal state of overexcitation with neurons firing too frequently. Rather than a global brain excitation-inhibition imbalance, Dr. Casanova mentions the possibility of one occurring within the minicolumnar structure.

The microglial activation from the Vargas study and gliosis[604] from the Lopez-Hurtado study supported his view that the brains of individuals with ASD display chronic activity and reactivity. Tr. at 836-37, 876. According to Dr. Kinsbourne, the Vargas study reported "sweating"[605] of the microglia, some edema, and the presence of proinflammatory cytokines. Tr. at 876; *see also* PML 717 at 13 (neuroinflammation "is characterized by edema, activation of microglia...and local invasion of immune cells from the circulation"). Based on his hypothesis of astrocytic death and microglial activation, Dr. Kinsbourne would expect these neuropathological findings.

According to Dr. Kemper, Dr. Kinsbourne was incorrect when he said that edema was a characteristic of neuroinflammation. Tr. at 2849. Doctor Kemper testified that his own research had found no evidence of edema in neuroinflammation and that the Vargas researchers had not recorded its presence.[606] Tr. at 2849.

Doctor Rust testified that Dr. Kinsbourne misstated the findings and conclusions of Drs. Vargas and Pardo. Tr. at 2490-92. The Pardo paper indicated that neuroinflammation may represent a nonspecific repair process.[607] Tr. at 2493; Pardo, PML 72, at 492. Doctor Rust noted that Dr. Pardo's letter (Res. Ex. BB at 3) made it clear that the Vargas study did not find a toxic basis for the observed inflammation. Tr. at 2493.

Doctor Rust also explained that the Vargas study's findings with regard to

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[604] Doctor Kinsbourne equated gliosis with astrocyte death. *See* Tr. at 876. The Vargas study reported astrocytic activation, not astrocytic death. PML 69 at 71.

[605] Doctor Kinsbourne did not define this term and I could not find the term in the Vargas study.

[606] I did not find the term "edema" in the Vargas study, nor any references to swelling or increased fluid levels. During rebuttal, Dr. Kinsbourne was asked if the Petropoulos study (*see* H. Petropoulos, et al., *Grey matter abnormalities in autism spectrum disorder revealed by T2 relaxation*, NEUROLOGY 67: 632-36 (2006) ["Petropoulos"], filed as PML 320) supported his statement that neuroinflammatory processes "are typically accompanied by edema." He indicated that it could. Tr. at 4127-29. The authors did indicate that edema could account for some of the MRI findings in their study. They did not, however, indicate that edema was present, and noted that as the brain matures, fluid in brain matter is replaced by myelin and increased axon growth; the higher water content they found might indicate slower brain development consistent with developmental delay, rather than edema. PML 320 at 635.

[607] Unlike the Vargas study, the Pardo article actually mentioned oxidative stress. The authors commented:

> [T]he precise role of neuroinflammation in the pathogenesis and natural history of autism is still uncertain. Studies in animal models and other neurological disorders suggest that microglial activation and neuroinflammation may play a role in processes of injury as there is increased oxidative stress and tissue injury, however, there is also recent evidence that neuroinflammation may be associated with repair processes and regeneration.

Pardo, PML 72, at 492 (emphasis added) (citation omitted).

cytokines were very complicated because cytokines serve functions other than their role in inflammatory diseases, including roles in normal brain development. Because cytokines are present in many diseases, their presence does not necessarily indicate the presence of a condition causing inflammation. Tr. at 2492. Doctor Rust also noted that cytokines and chemokines are present in brain tissue and CSF in a number of conditions known to be genetically determined, such as Rett's disorder and tuberous sclerosis. Tr. at 2493; Res. Tr. Ex. 8, slide 73.

Doctor Kemper also took issue with the conclusions Dr. Kinsbourne drew from the Vargas and Pardo papers. Echoing Dr. Rust's remarks about neuroinflammation, Dr. Kemper testified that developmental abnormalities persisting since gestation could produce microglial activation, and that those developmental abnormalities would be consistent with the presence of neuroinflammation. Tr. at 2850-51. He noted that one of the major points of the Vargas paper was that microglial activation could act as a neuroprotective process.[608] Tr. at 2851.

The Vargas study found evidence of neuroinflammation in the brains of ASD patients, which provides support for Dr. Kinsbourne's hypothesis. However, neuroinflammation is such a nonspecific finding that its presence does little to advance the specific mechanism of injury Dr. Kinsbourne proposed. Further, the study found neuroinflammation in those with and without developmental regression, undercutting the link petitioners drew between neuroinflammation and regressive autism. The authors did not conclude that neuroinflammation causes autism. Tr. at 2854. They noted that it might represent a response to injury, rather than its cause. The Courchesne 2005 paper, relied upon by petitioners, similarly interpreted the Vargas study's findings. PML 104 at 589-90.

(4) The James 2006 Study, PML 49.

Also like Dr. Deth, Dr. Kinsbourne relied on the James 2006 study, PML 49, to demonstrate that autistic children may be "particularly vulnerable" to "oxidative stress." PML 717 at 14. The same criticisms of this study noted in Section VII.F.3.b. apply to Dr. Kinsbourne's assertions.

(5) The Block Study.[609]

Doctor Kinsbourne noted that "[m]icroglial activation and inflammation are implicated in a diverse range of neurological diseases, particularly neurodegenerative

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[608] I note that respondent's counsel asked many leading questions of Dr. Kemper during this portion of his testimony.

[609] M. Block and J. Hong, *Microglia and inflammation-mediated neurodegeneration: Multiple triggers with a common mechanism*, PROG. NEUROBIOL. (electronic publication with no further citation provided) (2005) ["Block"], filed as PML 559.

diseases." PML 717 at 14 (citing Block, PML 559). This 2005 literature survey does, indeed, stand for this proposition. However, the article also notes that "the gradual accumulation of neuronal death and the increase in disease severity across time is a unifying theme across the diverse classifications of neurodegenerative disease." Block, PML 559, at 2. As death of neurons is not part of Dr. Kinsbourne's model because neuronal death is not generally seen in ASD, the paper's findings with regard to neuronal death undercut Dr. Kinsbourne's hypothesis that ASD is the result of a steady state of neuroinflammation.

The authors note that activated microglia should not be classed "as exclusively beneficial or inherently deleterious, [and] it is likely that microglia can serve both functions." *Id.* at 3. The article discussed the role of activated microglia in a number of diseases, including Alzheimer's, HIV dementia, multiple sclerosis, and Parkinson's. *Id*. at 4-6. The article generally discussed neuronal death caused by microglial activation, and microglial activation in response to neuronal injury and death.

(6) The Aschner 2007 and Mutkus Studies.

For evidence of mercury-induced neurotoxicity, Dr. Kinsbourne cited to the Aschner 2007 study, PML 570. According to Dr. Kinsbourne, this study summarized evidence demonstrating that mercury compounds "preferentially accumulate in the astrocytes, and inhibit their uptake of glutamate." PML 717 at 16; Tr. at 823. He also cited to the Mutkus study, PML 571,[610] for this point. The Aschner 2002 article also indicated that chronic mercury exposure induces astrocyte swelling and that methylmercury mediates neurotoxicity via its effects on glutamate, causing excessive concentrations of excitatory amino acids. PML 568 at 200. Doctor Kinsbourne noted that these were the same points made in the Aschner 2007 article. Tr. at 821-23. He cited to several other studies indicating that neuronal dysfunction due to mercury exposure is primarily due to disturbances in astrocytes, as well as an inhibitory effect on neuronal glutamate transporters. *See* PML 717 at 16.

The Aschner articles do provide some evidence for Dr. Kinsbourne's assertions that mercury affects glutamate uptake by astrocytes and that mercury preferentially accumulates in astrocytes, but only with regard to methylmercury. A review of the Aschner 2007 study indicates that the effects are attributed to methylmercury; inorganic mercury is not mentioned with regard to the mechanisms discussed.[611] In his causal

[610] Doctor Aschner was listed as the senior researcher on this study. This study involved micromolar doses of mercury chloride on cultured hamster cells. Although it found effects on astrocytic glutamate transporter cells, the quantity and species of mercury, the fact that it was an *in vitro* study, and the type of cells studied all militate against substantial reliance on this study.

[611] Inorganic mercury is mentioned in this article only with regard to the creation of methylmercury by methylation of inorganic mercury in waterways, resulting in its accumulation in seafood. PML 570 at 285.

mechanism, Dr. Kinsbourne postulated an effect by inorganic mercury. For the articles to support Dr. Kinsbourne's hypothesis requires, as Dr. Brent noted, an inference that ethylmercury or inorganic mercury will produce the same effects as methylmercury. Tr. at 4334.

Doctor Johnson agreed with Dr. Brent. Tr. at 4324-25. He added that the Aschner studies demonstrated that, once micromolar doses of mercury triggered astrocytic dysfunction, a vicious cytotoxic cycle ensued.[612] Tr. at 4326. However, the micromolar doses required to produce astrocytic dysfunction in Dr. Aschner's work were much higher than would be seen in the brain after TCVs. Tr. at 4325.

(7) Rubenstein and Merzenich Article,[613] PML 530.

Doctor Kinsbourne cited a review article by Rubenstein and Merzenich, PML 530, for a number of points regarding overexcitation in autism. These authors hypothesized "that at least some forms of autism are caused by a disproportionate high level of excitation (or disproportionately weak inhibition) in neural circuits that mediate language and social behaviors." PML 530 at 256. They suggested that the "imbalance of excitation and inhibition could be due to increased glutamatergic (excitatory) signaling, or to a reduction in inhibition due to a reduction in GABAergic signaling." *Id*.

The authors advanced several possible causal mechanisms of overexcitation, including the presence of too many glutamate receptors, receptors that are too sensitive to glutamate's effects, too many neurons producing glutamate, or the inordinate amplification of neuronal signaling. The article also discussed the possibility that some forms of autism might be attributed to decreased inhibition, caused by deficient production of GABA, poor GABA signaling, too few neurons producing GABA, or deficiencies in GABA receptors. *See* Rubenstein and Merzenich, PML 530, at 260. Notably, the authors do not mention an imbalance caused by astrocytic damage from mercury exposure; they mention the TCV-ASD hypothesis, but do not discuss its merits.

This review article advances hypotheses that, in some respects, resemble those of Dr. Kinsbourne regarding overexcitation, indicating that others may consider a possible role for excitation-inhibition imbalances in ASD. However, the authors note that overexcitation may be caused by either increased glutamate or by too little GABA, but their hypotheses are not based on measurements of either. PML 530 at 256.

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[612] Doctor Kinsbourne was cross-examined on Dr. Aschner's statement, as it apparently conflicted with his model of astrocytic injury without astrocytic death. Tr. at 4168-69. He indicated that, *in vivo*, regulatory mechanisms could preclude the cycle from going out of control. Tr. at 4169-70.

[613] J. Rubenstein and M. Merzenich, *Model of autism: increased ratio of excitation/inhibition in key neural systems*, GENES, BRAIN & BEHAV. 2: 255-67 (2003) ["Rubenstein and Merzenich"], filed as PML 530.

Doctor Kinsbourne's hypothesis addresses only one of these alternatives. As Dr. Rust noted, Rett's disorder, which resembles ASD, appears to include a genetically determined defect in GABA production or signaling. Tr. at 2502.

(8) The Purcell Study, PML 567.

The Purcell study, PML 567, examined cerebellar tissue to measure gene expression. The researchers targeted the area where Purkinje cell loss had been observed and compared the findings in the brains of individuals with autism to those of controls, matching for gender, age, and postmortem interval. Purcell, PML 567, at 1618-19.

Doctor Kinsbourne cited the Purcell study to indicate that individuals with autism have glutamate receptor and transporter abnormalities, implying that these abnormalities may enhance mercury's neuroinflammatory effects. PML 717 at 18. He indicated the article was relevant because of the higher levels of GFAP, which is released by astrocytes under stress, found in the brains of autistic subjects. Tr. at 4116-17; Purcell, PML 567, at 1626. According to Dr. Kinsbourne, astrocytes may proliferate in response to stress, and that proliferation may contribute to the mechanism by which an individual develops autism.[614] Tr. at 4117. He also asserted that the Purcell study supported his hypothesis that disrupted glutamate transmission could account for some of the cognitive deficits seen in autism. Tr. at 4117-18.

Doctor Johnson described the significance of the Purcell study differently. He explained that the researchers identified some candidate genes that were different in autistic brains than in control brains. Tr. at 4322. Some of the genes investigated involved the EAAT1 and EAAT2 transporters that bring glutamate into astrocytes. Tr. at 4322. They found significantly more of both types of transporters in the autistic patients. Tr. at 4321, 4323-24. To Dr. Johnson, this suggested that autistic brains had a <u>greater</u> capability to handle glutamate than the brains of the controls. Tr. at 4324; Purcell, PML 567, at Figures 2 and 3.

In view of Dr. Kinsbourne's hypothesis that mercury interferes with astrocytic ability to mop up excess glutamate, evidence that autistic individuals have a greater number of glutamate transporters is not supportive.

(9) The Primate Studies.

In addition to his reliance on Dr. Aposhian's opinions that TCVs would produce sufficient mercury in the brain to cause or substantially contribute to neuroinflammation,

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[614] I note that astrocytic proliferation would involve an increased number of astrocytes, and, presumably, a thereby increased ability to take up any glutamate excess. Astrocyte proliferation would be inconsistent with Dr. Kinsbourne's hypothesis of impaired glutamate uptake due to astrocytic damage or death.

Dr. Kinsbourne also relied on Dr. Burbacher's infant monkey study, PML 26, and the Charleston adult monkey studies, PML 32, 33, and 116. Tr. at 864-65. Doctor Kinsbourne testified that if the monkey studies (which he referred to in general) did not in fact mirror the amount of mercury given to children, he "would lose confidence" in their conclusions. Tr. at 890. His testimony regarding these studies strongly suggested that he had not read them closely.

Doctor Kinsbourne incorrectly asserted that the infant monkey brains had signs of microglial activation and inflammation. Tr. at 888. The Burbacher study did not involve examination of the monkey brains for either microglial activation or inflammation. *See* PML 26 at 1016 (describing study methods).[615] On redirect examination, he testified that the Burbacher research team was currently looking at the brains of the monkeys for evidence of neuroinflammation, but did not explain where he derived this information.[616] Tr. at 939-40.

Doctor Kinsbourne also testified that the Charleston adult monkeys "were delivered mercury in amounts comparable to that which children used to get." Tr. at 868; *see also* Tr. at 868-69, 884-85. This was a gross misstatement of the amount of mercury administered to the adult monkeys, who received 50 µg of methylmercury per kilogram of body weight every day for periods ranging from six to eighteen months. Charleston 1995, PML 32, at 326. Assuming that an adult monkey weighed only two kilograms,[617] the adult monkeys received about as much methylmercury in two days as human infants receive from TCVs over their first two years of life.

Based on a series of leading questions on redirect examination, Dr. Kinsbourne corrected this reference, indicating that he was referring to the Burbacher infant monkey study, not the Charleston adult monkey studies. Tr. at 936-41. However, the infant monkeys in the Burbacher study did not receive vaccine level doses either; they received about 2.5 times more ethylmercury per kilogram of body weight than human infants received from TCVs.[618] The infant monkeys received it on a much more compressed timetable, over a period of 21 days, rather than the six month period of

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[615] The adult monkey studies had signs of microglial activation, but the adult monkeys received much higher doses of mercury.

[616] My review of the transcripts and the medical and scientific journal articles filed failed to disclose any evidence regarding a continuation of the Burbacher study. There were, however, several references to this continued research by petitioners' counsel. *See, e.g.*, Tr. at 38-39,1961-62; Dwyer Tr. at 299, 332. Attorneys' assertions are not evidence.

[617] Vahter 1994 indicated that the adult monkeys weighed between 2.4 and 6.1 kilograms, making this an underestimation. PML 60 at Table 1.

[618] Doctor Brent calculated this at more than three times the amount. Res. Ex. EE, at 5. For the reasons indicated in note 374, I found Dr. Brent's calculations to result in a slight overestimation of the difference.

human infants. Burbacher, PML 26, at 1016.

According to Dr. Kinsbourne, the Charleston adult monkey studies looked for astrocyte death in the cerebral cortex and the cerebellum. Tr. at 891. He indicated that if he were incorrect about the areas in which astrocyte death and microglial activation were observed his opinion would not change, because microglial activation was reported and the glutamate system is all over the cerebrum. Tr. at 891-94. On redirect examination, he reviewed the article and testified that the part of the brain examined in the Charleston 1996 paper, PML 116, was actually the thalamus. Tr. at 936. As Dr. Brent noted, there was little evidence of astrocyte loss found in the adult monkey studies; statistically significant losses were found only in the thalamus and only in the six-month and clearance groups. Tr. at 1941; Charleston 1996, PML 116, at Fig. 1.

Doctor Kinsbourne agreed that there were no behavioral disturbances observed in the adult monkeys. Tr. at 894. He did not recall whether the neuropathological findings in the Charleston adult monkey studies were similar to the neuropathological findings in the autistic patients. Tr. at 894. He commented that with "low doses of mercury" in the monkeys, and the brief time they stayed alive, the findings of mercury damage might be different from those on autopsy of autistic individuals many years after their condition manifested.[619] Tr. at 895.

(10) The Vezzani and Granata Study,[620] PML 569.

Doctor Kinsbourne cited the Vezzani and Granata study, PML 569, as support for his mechanism of injury: excess glutamate leading to overexcitation, causing neurons to become more excitable, and eventually to die or to experience seizure activity. PML 717 at 18, 21.

Doctor Rust discussed the study in more detail, noting that it did not support these points. The study had nothing to do with autism or mercury. It involved stimulating particularly sensitive cells in the hippocampus over a long period of time with a regular pulsed current, eventually producing an epileptic focus.[621] Tr. at 2484-85. He noted that the brain's internal regulatory mechanisms are so robust that the external stimulus had to be applied repeatedly before the cells broke down and seizures resulted. Doctor Rust noted that the experiment produced a regional tissue injury, not overexcited neurons. Tr. at 2485-86. Although the same brain region can be injured with excitatory amino acids (which include glutamate), it is an area that has particular

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[619] From context, this last statement likely applied to the Burbacher infant monkey study, PML 26 (apparently mistranscribed as "Burmeister"). Tr. at 894-95.

[620] A. Vezzani and T. Granata, *Brain Inflammation in Epilepsy: Experimental and Clinical Evidence*, EPILEPSIA 46(11): 1724-43 (2005) ["Vezzani and Granata"], filed as PML 569.

[621] One of Dr. Rust's areas of specialization is epilepsy. *See* Tr. at 2351.

biochemical and genetic features. Tr. at 2486. He also noted that Dr. Kinsbourne ignored the authors' conclusion that the changes they provoked were related to genetic transcriptional activation. Tr. at 2485.

(11) The Bezzi Study,[622] PML 367.

Doctor Kinsbourne cited the Bezzi study as support for his statement that astrocyte interaction with activated microglia can also amplify glutamate release by astrocytes. PML 717 at 18. The study does conclude that reactive microglia can amplify astrocyte glutamate release. Bezzi, PML 367, at 705-06. However, the study finding is much more limited than Dr. Kinsbourne suggested in his citation. The portion of the study examining the interaction among microglia and astrocytes initially involved three cell cultures: (1) an astrocyte culture almost devoid of microglial cells; (2) an astrocyte culture with microglial cells added in a ratio that resembled that found in mammalian brains; and (3) a pure microglial culture. Glutamate release was highest in the astrocyte plus microglia culture, but only when the microglia had been recently exposed to lipopolysaccharide.[623] Resting (nonactivated) microglia did not enhance glutamate release. PML 367 at 705. In general, this portion of the study supported Dr. Kinsbourne's assertion.

The second portion of the study involved measuring neurotoxicity. Low concentrations of a protein found on viral surfaces of the human immunodeficiency virus ["HIV"] produced rapid glutamate release from both human and rat astrocyte cultures containing activated microglia. However, prolonged exposure caused the death of neurons, unless the cell cultures contained substances that interfered with the action of the particular glutamate receptor being studied. Bezzi, PML 367, at 706-07. The receptor studied in this experiment involved a specific type of glutamate release, one that is normally tightly regulated. Bezzi, PML 367, at 707. The process used in this experiment caused extremely rapid release of glutamate, "whereas in most other known processes such as inflammation, its action is much slower." *Id*. at 708.

Doctor Rust noted that the most fundamental problem with Dr. Kinsbourne's interpretation of the Bezzi study is that the study conditions required the presence of healthy astrocytes to keep the neurons viable. Tr. at 2495; Res. Tr. Ex. 8, slide 75. Injury was not produced by chronic inflammation; it was produced by adding freshly activated microglial cells to the culture. Tr. at 2495-96. Finally, the result was not a glial injury with neuronal hyperexcitation; it was neuronal death. Tr. at 2496. The reason neurons died had to do with the interaction of glutamate and glutamine. Tr. at 2497. Doctor Kinsbourne focused on the presence of too much glutamate without discussing

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[622] P. Bezzi, et al., *CXCR4-activated astrocyte glutamate release via TNFα: amplification by microglia triggers neurotoxicity*, NATURE NEUROSCI. 4(7): 702-10 (2001) ["Bezzi"], filed as PML 367.

[623] Lipopolysaccharide (often abbreviated "LPS") is a substance found in bacterial cell walls. DORLAND'S at 1057.

the rest of the regulatory system in place between astrocytes and neurons. Tr. at 2497.

(12) The Courchesne 2005 Paper, PML 104.

In his report, Dr. Kinsbourne cited the Courchesne 2005 paper to support the existence of a vulnerable postnatal period of brain development in the first two years of life. PML 717 at 15. The Courchesne 2005 paper, PML 104, is an extremely detailed literature survey of the neurobiological studies of ASD and early brain development. Although it indicated that the first two years of life involve a wide variety of brain maturation processes when interference by environmental events might occur (PML 104 at 581-82), the authors did not posit postnatal events as the most likely cause of the developmental abnormalities occurring during this period, such as the dramatic growth in brain size and head circumference. They commented:

> In addition to scenarios in which an inflammation-inducing insult or proliferative error causes multiple further disruptions, neuronal overproliferation and glial activation could share a common genetic root. One example of a potential genetic base for many of the observed micro and macrostructural changes is the p27 gene. Its loss causes dysregulation of cell proliferation cycles, resulting in a 250% increase in glial cell numbers in the cerebellum and a 30% increase in hippocampal neurons.

PML 104 at 592 (citations omitted). The Courchesne 2005 article did not necessarily advocate a genetic cause for these events.

During rebuttal testimony, Dr. Kinsbourne was referred to a section of the Courchesne 2005 paper (PML 104 at 590) dealing with the role of glial cells in both neuroinflammatory reactions and in brain organization, that purportedly supported his hypothesis. In a series of leading questions, Dr. Kinsbourne was invited to comment on how glial cell disruption might cause the neuropathological changes Dr. Kemper and others discussed. Tr. at 4124-25. He was specifically referred to a paragraph stating:

> Excess glial production and/or activation have the potential to produce any or all of the previously discussed microstructural findings, including frontal minicolumn abnormalities and increased neuron counts.

PML 104 at 590; Tr. at 4125.

What was not included in the quotation was the preceding paragraph of the article. This paragraph indicated that the "glial and molecular abnormalities described by Vargas" could be "fundamentally neuroinflammatory reactions that begin prenatal or early postnatal or reflect aberrations in genetic mechanisms that regulate the normal role of glia during neural development and organization." PML 104 at 590.

Read in context, the two paragraphs indicate that impairments to the role of glial cells in neuronal migration and other brain architectural developments (a role acknowledged by respondent's experts) were not being attributed to postnatal causes. *See also* PML 104 at 588 (referring to migration abnormalities in minicolumn development as an explanation for the pathological findings in minicolumns in the brains of ASD patients); RML 67 at 426 (Dr. Casanova discussing prenatal timing of neuronal migration in minicolumns); Tr. at 4163-64.

c. Conclusions Concerning Citations in Support.

A careful examination of his cited references reflected Dr. Kinsbourne's penchant for extracting data and out-of-context references to support his position, while ignoring contrary data or remarks in the same study or article. Although some studies contained support for specific aspects of his hypothesis, the studies Dr. Kinsbourne cited were not supportive of glutamate excess as a cause of ASD.

6. Drug Trials.

a. Riluzole Trial.

As support, Dr. Kinsbourne asserted than an ongoing clinical trial was testing the disrupted glutamate transmission hypothesis by using drugs that block glutamate receptors to alleviate some symptoms of autism. Tr. at 4117-18. He referred specifically to a clinical trial of riluzole to treat children with autism. Pet. Tr. Ex. 13.[624] Tr. at 4118. The study announcement described riluzole as a drug that "reduces the activity of glutamate, a neurotransmitter involved in the brain circuitry affected in OCD,"[625] which has also been used to treat ALS, and was being investigated for use in acute depression. Pet. Tr. Ex. 13 at 1-3.

Doctor Kinsbourne testified that riluzole "has been shown to be effective in childhood obsessive-compulsive disorder." Tr. at 4119, 4148-49. Actually, the recruitment announcement indicated that it was being tested on adults with OCD, with this announcement extending the study to children. Pet. Tr. Ex. 13 at 3. He characterized the expanded study as testing the glutamate blocker "in children with autism-spectrum disorders." Tr. at 4119. Doctor Kinbourne's statements were misleading. Riluzole had not been shown to be effective in treating childhood OCD; that was the purpose of the study. *See* Pet. Tr. Ex. 13 at 1. The study was not testing the drug as a treatment for ASD. Rather, the recruitment efforts were focused on children and adolescents with OCD, including those with and without ASD. *Id*.

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[624] Petitioners' Tr. Ex. 13 is the study recruitment announcement. This trial exhibit was also filed as PML 757.

[625] "OCD" refers to obsessive compulsive disorder. DORLAND'S at 1299.

Conflating glutamate and neuroinflammation, Dr. Kinsbourne testified that if the neuroinflammation found by the Vargas researchers was helpful or protective, this study would never have been funded. Tr. at 4119-20. This statement presupposes that the neuroinflammation observed is caused by glutamate. That is Dr. Kinsbourne's hypothesis, but there is no evidence that glutamate is causal. What the study announcement indicates is that glutamate may be involved in the etiopathogenesis of OCD. It says nothing about glutamate's involvement in ASD. Pet. Tr. Ex. 13 at 2-3.

b. Minocycline.

Doctor Kinsbourne also asserted that the Vargas researchers[626] suspected that the neuroinflammatory process they observed was causal because "they are now administering an agent that counteracts microglial activation in an attempt to reduce or even cure the autistic manifestations." Tr. at 908-09. This testimony concerned another drug trial, one involving minocycline.[627] Pet. Tr. Ex. 9; *see also* PML 369 (an earlier version of the same study announcement).

c. Criticisms of Using Drug Trials as Causation Evidence.

Doctor Rutter referred to the minocyline grant proposal as a "long shot," but added that it was a proper thing for NIH to do. NIH has funded a large number of studies, including ones based on a claim from UCLA that fenfluoramine made a massive difference in autism. The drug was later withdrawn from the market because of toxic effects. The NIH also funded the secretin studies, which consistently showed it was not effective. Tr. at 3341-42. NIH has taken suggestions both plausible and implausible and funded studies regarding them. Tr. at 3343.

Doctor Johnson, a neurotoxicologist whose research focus is on

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[626] Doctor Kinsbourne's report and testimony asserted that the minocycline drug trial grant was made to Dr. Pardo's group. PML 717 at 15; Tr. at 908-09. There is no evidence in the publicly available documents pertaining to this study that Dr. Pardo's group is conducting the minocycline trial. At best, the evidence indicates that Johns Hopkins University (where Drs. Pardo and Vargas are located), is recruiting participants, along with the National Children's Medical Center in Washington, DC, and NIH. Pet. Tr. Ex. 9 at 1, 4. A reason for concluding to the contrary may be found in the Pardo paper, PML 72, at 492 (authors warning practitioners against treatments based on the assumption that neuroinflammation was causal of ASD). Another reason for questioning whether the Vargas researchers were involved in this drug trial concerns a misstatement of the Vargas study's findings in the drug trial recruitment announcement. It indicated that the Vargas study found that regressive autism was associated with chronic brain inflammation. This statement omitted the fact that, although the CSF portion of the Vargas study focused on children with regression, the brain tissue portion of the study included tissue samples from eight individuals without regression, three with regression, and four whose status was unknown. Vargas, PML 69, at Tables 1 and 2. It seems unlikely that the Vargas researchers would themselves misstate their findings.

[627] Minocycline is "a powerful inhibitor of microglial activation." Pet. Tr. Ex. 9 at 2. It has been used to treat Huntington's disease. *Id*.

neurodegenerative diseases, testified that the type of treatment for a neuroinflammatory disease does not necessarily implicate a cause. Tr. at 4316. Drug therapies treat symptoms. For example, in Alzheimer's disease, some symptoms are caused by the loss of a specific neurotransmitter, acetylcholine. Tr. at 4316-17. Most drugs approved for the treatment of Alzheimer's increase brain levels of acetylcholine, which results in an improvement of cognition. However, the treatment does not affect the underlying disease process. Whatever is killing brain cells continues to do so, unabated by the drug therapy. Tr. at 4317.

With regard to ASD, if neuroinflammation is part of the progression of the disease, treating it may alleviate some of the symptoms, but that does not imply that neuroinflammation is causing the disease. Tr. at 4317. I note that the minocycline trial is focused on counteracting neuroinflammation, which Dr. Kinsbourne conceded has many causes.

C. Responses to Dr. Kinsbourne's Hypothesis.

1. Overview.

The criticisms by respondent's experts of Dr. Kinsbourne's hypothesis were many and varied. Doctors Rust, Kemper, and Johnson described defects in Dr. Kinsbourne's descriptions of the cellular interactions and the effects of glutamate excess over time. Doctor Rust challenged Dr. Kinsbourne's attribution of autistic behaviors to overarousal. Doctor Kemper emphasized that postnatal mercury exposure could not account for the neurodevelopmental abnormalities he and others had documented and that the hypothesis ran counter to what was known about mercury's affinity for particular brain structures. He and Dr. Rodier also noted that mercury's observed effects on behavior did not resemble the behaviors seen in autism. Doctors Rust and Lord, who see, treat, and diagnose children with ASD, both opined that Dr. Kinsbourne's attribution of autistic behaviors to the effects of overarousal reveals his relative inexperience with children with ASD. Doctor Leventhal acknowledged that glutamate receptors may play a role in ASD, but rejected the excitotoxicity and overarousal hypothesis.

Respondent's experts did not contest that neuroinflammation is present in the brains of those with ASD. However, as Dr. Rust noted, inflammation is a nonspecific process,[628] in that its causes range from an infection to cancer. Tr. at 3425. Doctor Rutter did not find the specific proposition that inorganic mercury might cause neuroinflammation to be very startling because so many things cause neuroinflammation. Tr. at 3425.

[628] Although the transcript reads "Information is a very nonspecific sort of process," it is clear from the context that Dr. Rutter actually said that "Inflammation is a very nonspecific sort of process." Tr. at 3425.

Neuroinflammation is involved in almost every neurodegenerative disease, including Alzheimer's, Parkinson's, Huntington's, and ALS. Tr. at 4316. In these neurodegenerative diseases, the neuroinflammation, including gliosis and microglial activation, is a progressive part of the disease as a result of the pathologic process. As Dr. Johnson testified: "I don't think that anybody at least in the field would argue that they're a causative factor at this point, it is more an outcome." Tr. at 4316.

2. Cellular Processes.

Doctor Rust has published papers on the developmental aspects of astrocytes, their functions, biochemical operation, and relationship to other brain cells, particularly neurons. Tr. at 2482. He also has considerable expertise in the area of inflammatory diseases of children. Tr. at 2482-83. Based on his expertise, Dr. Rust concluded that Dr. Kinsbourne's characterizations of astrocytic and microglial changes in the brain are not consistent with these processes or with what is known about inflammation. Tr. at 2482. As Dr. Rust explained: "[W]e know a great deal about the regulation and the interaction of the systems that are involved and referred to, and [Dr. Kinsbourne displayed] absolutely no apparent understanding of the ways in which the system actually functions." Tr. at 2465-66. Doctor Kinsbourne did not consider the "absolutely necessary interaction between astrocytes and neurons and the very complicated business of counter-regulation for excitatory compounds in the synapse, and [displayed] no real understanding of the architecture that's in it as far as I can tell." Tr. at 2466.

As Dr. Rust explained, excess glutamate produces injury in the most active cells. Tr. at 2502. If Dr. Kinsbourne's hypothesis is correct, the deficits in autistic patients would worsen over time, causing epilepsy or cell death. In epilepsy caused by hyperexcitability, there is progressive tissue injury, producing changes in motor and intellectual function, and worsening epilepsy. Tr. at 2502-03. This is not what is seen in autism. Tr. at 2503. Although there are some progressive issues with regard to EEG changes and epilepsy in autism, those with autism do not show the progressive, nonspecific regional injury that is seen in epilepsy caused by hyperexcitability. Tr. at 2503.

Based on his experience in examining how astrocytes and neurons interact, Dr. Rust testified that Dr. Kinsbourne's views on neuronal excitation in the presence of astrocytic damage were simply incorrect. Astrocytes support neurons in a number of ways, including providing them with energy from their stores of glycogen. Tr. at 2506-07. If astrocytes are damaged or destroyed, neurons cannot function because they need support from astrocytes to do so. Tr. at 2507. Neurons need the additional energy support provided by astrocytes in order to become hyperexcitable; without these energy stores, neuronal function diminishes and then stops. Tr. at 2507. Neurons cannot go on being hyperexcitable for long periods of time if inflammation has caused damaged or dead astrocytes. Tr. at 2507.

There is a complex system of regulation in place between neurons and

astrocytes. Cells receiving glutamate can dial their receptors up or down. If there is too much glutamate, neurons or astrocytes can lose their receptors and not remake them. Tr. at 2499-500. This regulatory system can be injured, but when it is, the neurons die. Tr. at 2500-01.

Doctor Johnson, who has studied and published in the area of astrocytic function, also took issue with Dr. Kinsbourne's views of what happens when astrocytes are unable to mop up excess glutamate. Tr. at 4320-21. His work involves many of the brain mechanisms Dr. Kinsbourne discussed. Tr. at 2240. Doctor Johnson agreed that when astrocytes fail to take up excess glutamate, the short term effect is an increase in glutamate, which will accumulate in the synapses and bind to glutamate receptors in the neurons. The neurons that are on the postsynaptic side of the receptor will become hyperactive. However, in the long term, increased glutamate will cause the neurons to die. There are well-established models that demonstrate glutamate and glutamate agonists kill neurons. Tr. at 2246. A chronic glutamate excess is neurodegenerative. Tr. at 4324. Although glutamate is likely part of the pathogenic process in autism and brain diseases, a chronic glutamate excess causes astrocytic dysfunction, which leads to neuronal death. Tr. at 4327-29.

Doctor Leventhal, who has written about abnormal glutamate function and ASD, discussed the role that a glutamate receptor, Mglur-4, may play in neurodevelopment and neurotransmission in ASD. Like Dr. Rust, he testified about the complex interaction between glutamate and astrocytes that Dr. Kinsbourne's hypothesis did not address: astrocytes do play a role in regulating glutamate, but glutamate also regulates astrocytes. Dwyer Tr. at 280-83.

Neuroinflammation and oxidative stress play a role in a number of central nervous system diseases. These include Alzheimer's, Parkinson's, ALS, Huntington's, and HIV dementia. *See* Tr at 4315-16; *see also* Streit, PML 70, at 5-6. The witness with a research focus on such diseases, Dr. Johnson (*see* Tr. at 2199), testified that autism did not bear any resemblance to those diseases, which involve "neuro death." Tr. at 2202. He testified that if astrocytes are chronically dysfunctional, the neurons around them will die. Tr. at 2246-47. Once physical symptoms of a neurodegenerative disease manifest, the disease progresses, and neuronal cell death occurs in the region where the cells are stressed. The neuroinflammation in neurodegenerative diseases is a pathogenic process that progresses to cell death, and, eventually, to patient death. Tr. at 2250. Neurodegenerative diseases do not plateau. Therefore, Dr. Kinsbourne's hypothesis of chronic, steady cell destruction is, in Dr. Johnson's opinion, nonsensical. Tr. at 2247, 2255-56.

Doctor Kemper's criticism focused on the response of astrocytes to damaged brain structures, rather than the astrocyte-neuron interaction Drs. Rust and Johnson discussed. There is no evidence that microglia are destroying astrocytes in the brains of autistic individuals, because there is no good, credible evidence of astrocytic death or loss in ASD. Tr. at 2859-60.

The role of activated microglia in the innate immune response of the brain is very consistent with a response to the widespread defects in prenatal brain development that Dr. Kemper documented in his studies. Instead of astrocytes being impaired or inactive in autistic individuals, the literature suggests that astrocytes are quite active. Tr. at 2860. Neuroinflammation cannot explain the structural changes observed in the brains of those with autism, but those structural changes can explain the neuroinflammation observed. Tr. at 2860-61.

3. Mercury's Effects on the Brain.

Doctors Brent and Rutter both noted that the mercury-induced neuroinflammation hypothesis could not be specific for thimerosal because there are so many other sources for mercury. Tr. at 1956-57, 1960, 1964, 3426.

Mercury has an affinity for specific areas of the brain, a fact consistently noted in the mercury autopsy studies. Doctor Kemper discussed two additional studies, Shiraki,[629] RML 449, and Reuhl and Chang,[630] RML 395. Both showed mercury's affinity for the visual cortex, the motor cortex, and the sensory cortex in adults, with more diffuse patterns of involvement in neonatal exposure. Tr. at 2840-41, 2843; Res. Tr. Ex. 10, slides 23-25. Mercury's affinity for the vermis, an area in which autism-related structural changes are not found, was illustrated on Slide 24, Res. Tr. Ex. 10. Mercury's affinity is for the deeper parts of the cerebellum; in autistic individuals, the loss of Purkinje and granule cells involves areas close to the surface of the cerebellum. Tr. at 2841-42. In mercury toxicity, the Purkinje cells are spared, a striking difference between mercury exposure and autism. Tr. at 2842-43. The neuropathological findings in mercury toxicity and autism are not consistent. Tr. at 2844.

Doctor Kinsbourne's proposed mechanisms of injury from TCVs (or mercury in general) do not account for any of the development anomalies Dr. Kemper and others have found in autistic brains. Tr. at 2834. Doctor Kemper provided a list of clinical features and neuropathological findings in autism compared to those of mercury toxicity. *See* Res. Tr. Ex. 10, slide 26; Tr. at 2844-45. The clinical features and neuropathology of the two conditions do not overlap; in many cases, the findings in autistic brains are the opposite of those caused by mercury. Tr. at 2844-45.

Doctor Rust commented that if inorganic mercury causes overexcitation, and the amount of mercury increases over time, patients with autism would get progressively worse over time. Because human beings are continually exposed to various sources of

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[629] H. Shiraki, *Neuropathological aspects of organic mercury intoxication, including Minamata disease*, *in* HANDBOOK OF CLINICAL NEUROLOGY 83 (P. Vinkin et al. eds., 1979) ["Shiraki"], filed as RML 449.

[630] K. Reuhl and L. Chang, *Effects of Methylmercury on the Development of the Nervous System: A Review*, NEUROTOXICOLOGY 1: 21-55 (1979) ["Reuhl and Chang"], filed as RML 395.

mercury, brain inorganic mercury levels increase over time, even in the absence of TCV exposure. Doctor Kinsbourne's report indicated both that autistic symptoms plateau, but may also become more severe if epilepsy ensues. PML 717 at 6. Although he distinguished ASD from metabolic brain degeneration (*id*.), the implication of a steadily increasing toxic element causing a reaction is that there would be a steady deterioration in function. Tr. at 2511-12. That is not what is seen in autism; individuals with autism improve over time. Tr. at 2512. This is inconsistent with Dr. Kinbourne's hypothesis. Tr. at 2513.

4. Autistic Behavior and Overarousal.

Doctor Kinsbourne stated that "[a]utistic symptomatology can be classified into that which exemplifies the effects of hyperarousal and that which represents an attempt to escape from such effects or fend them off." PML 717 at 20. Doctor Rust called this statement "speculation," commenting that interpreting behavior of autistic individuals is best done by those who see a large number of them. Tr. at 2508. He indicated that there is "not one shred of evidence" that stereotypic behaviors lower neuroexcitation levels, in spite of Dr. Kinsbourne's claims in his report (PML 717 at 22). Tr. at 2509.

Doctor Rust also disagreed with Dr. Kinsbourne's opinion that autistic behaviors are manifestations of a hyperexcitable nervous system, indicating that it ran counter to the data and his own clinical experiences in working with autistic children. Tr. at 2433. A relatively inexperienced observer might mistake some autistic behaviors as hyperactivity or anxiety. Tr. at 2433. These actually reflect the systems dysfunctions present in ASD. Tr. at 2433; Res. Tr. Ex. 8, slide 41.

Doctor Lord testified that Dr. Kinsbourne's overarousal model has been around for 40 to 50 years and has been used to describe many disorders. Tr. at 3585. Many children respond to overstimulation; children with ASD may do so in more conspicuous ways and may have a lower threshold for stimulation. However, the behaviors demonstrated by an autistic child who is responding to overstimulation are the same behaviors that occur when the child is underaroused. Tr. at 3585-86. The behaviors that Doctor Kinsbourne characterized as evidence of overarousal occur in many different contexts. Tr. at 3586.

Doctor Rutter concurred with Drs. Rust and Lord. He commented that individuals with autism appear to experience both overexcitation and apathy on occasion. To be of evidentiary value for Dr. Kinsbourne's causation hypothesis, these apparent emotional states must be linked with what is happening physiologically, and that evidence is lacking. Doctor Rutter testified that no studies measure heartbeat and EEG changes, and no studies demonstrate that these changes occur in social situations. Tr. at 3319-20. If they are not linked to social situations, it is difficult to link the apparent over- or underarousal to the social reciprocity problems in autism. Tr. at 3320.

Doctors Rust and Rutter both noted that Dr. Kinsbourne failed to explain how overarousal leads only to regressive autism. Tr. at 2592, 3320-21.

D. Conclusions.

In his Theory 2 general causation hypothesis, Dr. Kinsbourne added a new coat of paint to an old building, but failed to shore up the building's basic structural failings. As Dr. Rust characterized it, Dr. Kinsbourne's hypothesis has "lethal problems in terms of scientific support." Tr. at 2495. Rather than producing ASD, the excitotoxic state Dr. Kinsbourne's hypothesis envisioned would produce neuronal death, followed by patient death. That is not descriptive of the natural history of ASD.

His whole hypothesis relied on "a toxicologist" (presumably Dr. Aposhian) to establish that exposure to TCVs could produce enough mercury in the brain, either alone or in conjunction with other environmental mercury exposure, to cause neuroinflammation. For reasons detailed at length in Section VI, Dr. Aposhian's opinion that TCVs would produce enough mercury to cause the effects postulated was not reliable.

Even if, *arguendo*, sufficient brain mercury is produced by TCVs, Dr. Kinsbourne's hypothesis cannot explain why most children with ASD improve over time, while the mercury levels in their brains are likely increasing over the same time frame from diet and other sources. His assertion that brain protective measures kick in at some point to ameliorate the effects of additional mercury was sheer speculation.

Doctor Kinsbourne opined that neuroinflammation produces ASD through a glutamate excess. None of the studies he cited measured glutamate levels in the brains of those with ASD. The evidence of neuroinflammation does not establish a cause for neuroinflammation, and there was ample evidence that it is a nonspecific finding with many possible causes, including a response to injury.

Witnesses with far better qualifications in research into neurodegenerative diseases and oxidative stress established that the cellular processes Dr. Kinsbourne described do not work the way he asserted. Doctor Kinsbourne's testimony about what happened to astrocytes in his model was inconsistent. He relied on the Lopez-Hurtado study's findings of gliosis, which he erroneously equated to astrocytic death. He relied on damage to astrocytes as an essential component of his theory of a glutamate imbalance, and indicated that astrocytic death was not required. Then, he postulated an increase in astrocyte numbers as responsible for causing ASD. He was not only inconsistent, he was wrong.

Although, on a theoretical level, other physicians and scientists have considered Dr. Kinsbourne's overarousal model as an explanation for autism's behavior, a mercury-produced glutamate excess is not a probable explanation for overarousal. As Dr. Kinsbourne conceded, glutamate has never been identified as a cause of ASD. What

mercury does in the brain is well-known. In sufficient doses, it is a potent neurotoxin, but not one that has ever been shown to cause autism or autistic symptoms. To properly place a factor on a list of differential causes for a disease or disorder requires some evidence that it is capable of causing that disease or disorder. To prevail, petitioners must establish by preponderant evidence that TCV exposure belongs "on the differential" as a cause for ASD. Even by this standard, which is much lower than that of "scientific certainty," petitioners' case falls well short.

Section IX. Conclusion.

A. Conclusions in General.

A diagnosis of ASD can be heartbreaking. Although most children improve, few ever lose the diagnosis. Most children with ASD will never live independently as adults. The true cost of ASD is borne by those who live daily with the condition and contend with its financial and emotional tolls. In the caring and compassionate words of Dr. Rust during the general causation hearing, those of us on the outside looking in "do not understand." Res. Tr. Ex. 8, slide 45; *see also* Tr. at 2434.

When petitions for compensation alleging that ASD was the result of childhood vaccinations were filed in mounting numbers, the OAP was created to help resolve the factual and legal questions the petitions presented. The Vaccine Program exists to compensate victims of vaccine injuries easily, quickly, and with generosity, but entitlement to compensation requires more than a sincere and honest belief that a vaccine is responsible for causing ASD. In these cases, as in all other off-Table cases, petitioners must establish by preponderant evidence that a vaccine can cause ASD, and that it did so in their children's cases. The evidence produced in the Theory 2 cases alone was voluminous and highly technical, and the hypotheses presented were very complex. This illustrates not only the difficulty of making factual conclusions regarding that evidence, but also the utility of an omnibus hearing to produce and evaluate it. However, nearly a decade after the OAP was created, all of the evidence produced to date is inadequate to demonstrate any causal connection between vaccines and ASD.

The TCV causation hypothesis emerged from a combination of mercury's long-established role as a neurotoxin, ASD's status as a neurological disorder, and the ubiquity of exposure to TCVs prior to the perceived emergence of ASD's symptoms. The Faroe Islands studies suggested that maternal methylmercury exposure during gestation was a statistically significant predictor of poorer performance on some neurological tests. Although the Seychelles Island studies did not make the same findings, the Faroe Islands studies were some evidence that smaller doses of methylmercury than previously thought could cause neurological harm. The Internet

likely played a role as well, according to at least one commentator.[631]

The focus on TCV causation of regressive ASD emerged in the Theory 2 cases as a consequence of what Dr. Kinsbourne called the "striking" and "shocking" presentation in some cases of regression, in which apparently normal toddlers lost skills and sociability. Without an understanding of how behavior at age two could be caused by some brain systems coming on line while others were disconnected, it made sense for parents and others to look for a more recent triggering event. Most children with ASD had received vaccines containing "a known neurotoxin" and, equating the reference dose for methylmercury to ethylmercury, parents voiced concerns about the amount of mercury children received in vaccines. Even the prestigious IOM called the mercury hypothesis "biologically plausible" in 2001, although what the IOM meant by that term was not what the parents perceived.

However, over the following three years, more scientific studies were published. The toxicokinetics of ethylmercury were studied in primates and human infants, and every reputable study confirmed that methylmercury studies were not a good predictor of ethylmercury's effects. Well-conducted epidemiological studies found no connection between TCVs and ASD. In 2004, the IOM reexamined the TCV-ASD hypothesis and concluded, in the strongest terms available to it, that the evidence favored rejection of any causal connection. Since 2004, every epidemiological study except one has continued to find no connection between TCVs and ASD. The one study that found a connection was funded by the Petitioners' Steering Committee representing the OAP petitioners in this omnibus proceeding.

The Theory 2 cases may have continued to press the TCV-ASD hypothesis because some of the factual predicates for the hypothesis are well established. The strong beliefs of many parents (and a small group of physicians and scientists) that vaccines are causal undoubtedly played a role as well. Vaccines received by most U.S. children in the 1990s through the 2001-2003 time frame contained more than trace amounts of thimerosal. When injected, thimerosal is metabolized into ethylmercury. A small portion of this ethylmercury reaches the brain, where an even smaller amount is converted to inorganic (mercuric) mercury. Once converted to inorganic mercury in the brain, it is virtually immobile. At certain brain levels in primates, organic mercury has been shown to cause fairly widespread activation of microglial cells and some reduction in astrocytic cells. Activated microglia have been found in autopsies of the brains of patients with ASD in greater numbers than in the brains of neurotypical individuals.

In spite of these widely-accepted factual predicates, the TCV-ASD causation hypothesis has been rejected by the general scientific community for many cogent

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[631] *See* Baker, PML 599, at 251 (commenting that the "insinuation prevalent on the Internet that thimerosal was a dubious product smuggled into vaccines by avaricious drug companies" was one of the streams that converged to spread the TCV-autism hypothesis).

reasons. However, it continues to be pressed by a small group of physicians and scientists associated with groups such as SafeMinds, DAN, and ARI. Most of petitioners' experts were drawn from this group. Doctor Deth's research has been funded by them; Dr. Mumper is the medical director of ARI, and Dr. Aposhian has participated in ARI's "think tanks." Many of the published studies relied upon by the testifying experts, including nearly all of those relied upon by Dr. Aposhian in his "six pillars," were written by individuals associated with ARI and other similar groups. As discussed in Sections VI-VIII above, the conclusions of this group are not grounded on reputable and reliable scientific foundations.

The view that ASD is caused by mercury may have persisted because it provides some hope that ASD can be treated, and even cured. The general scientific consensus is that ASD is the result of prenatal developmental problems shaped largely by genetic and epigenetic contributions. This consensus provides little hope for parents of children with ASD. Mainstream science does not, at present, offer many effective therapies, much less offer hope of a cure. Mainstream science tells us that some manifestations of autistic behavior can be treated with drugs, behavioral therapy, and speech and language therapy, but that few children will lose the diagnosis or live independently in adulthood. Understandably, many parents have looked to practitioners who offer hope of improvement, and even a cure.

After extensively reviewing the testimony, expert reports, and other evidence, I have concluded that petitioners have failed in the general causation case to demonstrate that TCVs cause or substantially contribute to ASD. Their experts proffered hypotheses that were illogical, contrary to the weight of the evidence, and, ultimately, unpersuasive.

B. Qualifications of the Experts.

The quality of the expert opinions proffered in this case was heavily influenced by the expertise of the scientists and physicians offering them. Respondent produced an impressive group of physicians and scientists who were truly experts in the fields about which they testified. They had garnered awards from both peers and autism advocacy groups. Many had published hundreds of peer reviewed articles and book chapters pertaining to the subjects about which they testified. Doctor Rutter has been researching ASD for more than four decades, and Drs. Lord, Kemper, Rodier, Leventhal, and Rust have been involved in such research for nearly as long. Doctors Johnson, Mailman, Jones, and Roberts each had extraordinarily impressive qualifications in the highly technical subject matter about which they testified. Doctor Brent brought both a treating physician's perspective and a toxicologist's background to the discussion of mercury's effects on human beings, and clearly and carefully explained the significance of the science about which he testified. Only in epidemiology did the qualifications of petitioners' expert even approach those of respondent's, and even there, Drs. Fombonne and Rutter brought the additional expertise from their own research and publications in the epidemiology of ASDs. Doctor Goodman offered

much-needed insight into the IOM reports on TCVs and expertise on the issues of "subgroups" and biological plausibility.

In contrast, petitioners produced a very well-qualified epidemiologist, Dr. Greenland, whose opinion was so limited as to be essentially useless as part of a causation hypothesis. Because the factual predicates for his opinion on "clearly regressive autism" were not established, Dr. Greenland's primary contribution was pointing out the generally acknowledged weaknesses in the epidemiological studies of ASD and TCVs. Doctor Aposhian was qualified to opine on mercury, but lacked the qualifications in medical toxicology that Dr. Brent possessed. Doctor Deth's experience in mercury, sulfur metabolism, oxidative stress, and ASD was minimal and recently acquired, and paled in comparison to that of respondent's experts in academic background, teaching experience, research focus, publications, and awards and recognitions. Doctor Kinsbourne has not had a clinical practice in nearly two decades, and, in comparison to respondent's experts, relatively little experience before that in diagnosing and treating children with ASD.

I emphasize that the qualifications of the experts were not, standing alone, determinative in my conclusion that petitioners have failed to make a prima facie case for mercury's causal role in ASD. Not only were respondent's experts far better qualified to opine, the evidentiary quality of their opinions exceeded that of petitioners' witnesses. With very few exceptions, when one of respondent's witnesses cited a medical or scientific study for a point, the study fully supported that point. Their opinions were well supported by other evidence, and, when contrary studies existed, they were careful to explain why they found them unpersuasive or unreliable. In contrast, on many occasions when I read a study that one of petitioners' experts cited, I found that it did not provide substantial support for the point for which it was cited, or did so only in part, with the study as a whole being unsupportive of the proposition advanced by the expert. The studies that were supportive often had problems of their own in that they could not be duplicated by other researchers. Many of Dr. Aposhian's conclusions were drawn from studies that could not be duplicated. Most of Dr. Deth's opinions were based on his own unpublished work, certain aspects of which were, according to experts in the field, poorly performed and unlikely to be correct. Although peer review and publication are not necessary conditions for consideration in Vaccine Act cases, the problems with Dr. Deth's own work cast substantial doubt on the conclusions he drew from it. As respondent's experts correctly noted, Dr. Kinsbourne sometimes cited studies for unsupported propositions, misstated the degree of support found, and "cherry-picked" data from studies, while ignoring contrary data in the same study.

C. A Failure of Proof.

As Dr. Rust stated, a hypothesis that is so broad that anything from measles virus to an environmental toxin could cause ASD is unlikely to be correct. Tr. at 2514. Where the evidence was in conflict, the great weight of the evidence favored

respondent. Thus, I have resolved most of the factual disputes against petitioners. With regard to ASD itself, I concluded that there is no reliable evidence that regressive autism is a disorder distinct from that of classic or early onset ASD. The evidence for any postnatal causal factors, including environmental toxins, is very weak. The weight of the evidence is that ASD originates prenatally, with genetics playing a very strong role in its origin and manifestations.

1. TCVs Do Not Substantially Contribute to Brain Mercury Levels.

Humans are born with some mercury present in their brain as the result of maternal exposure to various sources of mercury. Inorganic mercury continues to accumulate in the brain over a lifetime from sources ranging from food products and dental amalgams to air and water. Mercury is considered a neurotoxin, and its neurotoxic effects are more pronounced when the exposure occurs in utero. Harmful effects are a function of dose and other factors, including the method of administration, the species of mercury involved, and the time period over which exposure occurs.

However, there is no reliable evidence that TCVs produced anything more than minuscule levels of inorganic mercury in the brain of infant monkeys exposed to approximately 2.5 times as much mercury as human infants received in TCVs. In contrast, autopsy studies of U.S. infants who died within a few days of birth demonstrated mercury levels much higher than those of the infant monkeys, likely a result of prenatal exposure. A number of studies established that at birth, human infants have blood mercury levels strikingly similar to those of their mothers.

Doctor Aposhian's contrary testimony and calculations were based on faulty premises. Although the widespread use of TCVs contributed some amount to the level of inorganic mercury in the brain, the amount contributed was very small in comparison to amounts that accrue from environmental exposures over time. The levels of mercury that have produced toxic symptoms, including the subtle neurodevelopmental testing abnormalities observed in children from areas with high levels of dietary exposure, have all been much higher than those produced by TCVs.

2. Evidence that TCVs Produce Neuroinflammation is Lacking.

Although exposure to far higher doses of methylmercury has been observed to produce neuroinflammatory responses in the brains of adult primates, there is no direct evidence that the ethylmercury from TCVs produces the same effects. The circumstantial evidence that vaccine level doses can do so, even in conjunction with other mercury exposure, is likewise lacking. Microglial activation is not specific to mercury, other heavy metals, or ASD; it occurs in many brain disorders, and may represent a response to injury, rather than its cause. An author of the Vargas study, one of the papers on which petitioners primarily relied, wrote that the neuroinflammatory responses observed in the brains of autism patients were not consistent with a response to a toxic exposure.

3. Mercury's Known Biological Effects in the Brain Do Not Resemble Those of ASD.

What mercury exposure does to the brain is well established, and neither the structures nor the cell types principally injured by mercury exposure are those that are malpositioned, damaged, missing, or destroyed in ASD. Petitioners' hypothesis requires that high level doses of mercury spare Purkinje cells, while low level doses damage them. The pathophysiological changes in the brain in ASD largely occur prenatally; prenatal exposure to high enough doses of mercury to cause observable neurological symptoms produces cerebral palsy and developmental delays, but has not been observed to produce anything resembling ASD's core symptoms. Mercury causes damage to discrete anatomical regions of the brain associated with motor coordination; motor skills are largely unaffected in ASD.

4. The Symptoms of ASD Do Not Resemble Symptoms Produced by Mercury Exposure.

Doctor Rodier, the one witness with considerable expertise in both mercury exposure and ASD, testified that there are no similarities between ASD and either ethylmercury poisoning or mercury poisoning in general. Tr. at 3033. If ASD results from a hypersusceptibility to mercury in a small group of children, one would expect the symptoms of this group to resemble closely those of mercury poisoning victims, with a lower dose producing similar effects in those genetically hypersusceptible. It does not. Sensory and motor disturbances are the first effects observed in mercury poisoning; language, communication, and social skills losses are among the first symptoms observed in ASD.

5. There is No Evidence of Hypersusceptibility to Mercury in Individuals with ASD.

Although both Drs. Aposhian and Deth testified about a hypersusceptibility to mercury, or mercury efflux disorder, there is no reliable evidence that one exists. The studies on which Dr. Aposhian relied could not be duplicated by other researchers. At best, preliminary evidence that children with ASD have higher biomarkers of oxidative stress suggests that they may be more affected by administration of substances that produce oxidative stress, but there is no evidence that they respond differently to vaccine level doses of thimerosal. To point to the existence of ASD as validation of that aberrant response is simply circular reasoning.

6. Postnatal Causes for ASD Are Unlikely.

The pathophysiological findings from the autopsy studies strongly point to a prenatal origin for nearly all the abnormal findings observed. The co-occurrence of dysmorphology in substantial numbers of those with ASD, and the dating of the origin of the dysmorphology to points in early gestation, buttresses the autopsy studies. ASD is

strongly genetic, and although there is not a 100% concordance rate for ASD diagnoses in monozygotic twins, epigenetics may account for the discordance. Doctor Rutter explained that the development of human beings is designed to work in a particular way, but genes do not tell each cell what to do. Genetics specifies a pattern, but the pattern may be altered by many factors. Tr. at 3269.

Injuries early in the prenatal period produce, as Dr. Rodier remarked, a cascade of further injuries in the nervous system. Tr. at 3057. As the authors of the Connors study, relied upon by Dr. Aposhian (PML 711 at 15), noted: "The neurobiologic mechanisms underlying autism are in place before birth." PML 73 at 876.

7. There is Insufficient Evidence that Regression or "Clear Regression" in ASD has a Separate Biological Basis.

Doctor Kinsbourne was unpersuasive in his attempts to establish that regression in ASD has a separate biological basis or even that it should be considered a separate type of ASD. His opinions were contradicted by several witnesses, each of whom had far more experience in diagnosis of ASD and research into how ASD presents. They described some loss of skills occurring in many, if not most, children with ASD, and rarely constituting the first sign or symptom of the disorder. Loss of skills is something apparent to parents; failure to meet milestones may or may not be. ASD may present in any number of subtle ways not readily apparent to untrained observers. Regression occurs in several genetically-caused disorders, clearly indicating that it need not be the result of a triggering postnatal event.

8. Neither Excitotoxicity nor Oxidative Injury is Likely as a Cause of ASD.

Glutamate may well play a role in ASD's symptomology, but a general level of excitotoxicity caused by mercury damage is unlikely as a cause for ASD. Doctor Kinsbourne hypothesized that mercury causes neuroinflammation, which causes damage to astrocytes, leading to overexcited neurons firing too frequently. This scenario, in the opinion of several of respondent's experts who have researched brain disorders, would lead to neurodegeneration and neuronal death. There is little evidence of neuronal death in ASD; neurons are frequently smaller and more numerous in ASD patients. Neuronal death progresses to patient death in other neurological disorders, most of which occur later in life. There is no evidence of progressive neurological injury in ASD.

9. Epidemiology Has Failed to Detect Any Connection Between TCV Exposure and ASD.

The epidemiological evidence presented was strong, but not dispositive, on the issue of general causation. These studies indicated that a causal connection between TCVs and ASD is unlikely, but not impossible. Because I have concluded that there is no evidence to show that "clearly regressive" autism exists as a separate phenotype of

the disorder, and have likewise concluded that there is virtually no evidence suggesting that regression in general constitutes a separate phenotype with a distinct etiology, I consider the epidemiology relevant to my ultimate conclusion on general causation. Strong epidemiological evidence indicates that TCVs are unlikely to play a causal role. Although most U.S. vaccines manufactured after 2001 contained no more than trace amounts of thimerosal, its removal had no effect on the prevalence of ASD rates, even considering that stockpiles of TCVs may have been used for a year or two after manufacturing ceased.

D. Conclusion.

The Theory 2 hypotheses have fared no better than the Theory 1 hypotheses. The evidence in favor of TCV causation of ASD is weak and singularly unpersuasive. Two processes that are not pathognomonic of any disorder, neuroinflammation and oxidative stress, were assigned a causal role in the development of ASD, but the presence of either or both in ASD patients says little to nothing about ASD's potential causes. If ASD can be caused by neuroinflammation and/or oxidative stress, then anything that can cause either of those conditions belongs, according to Dr. Kinsbourne's reasoning, "on the differential" for ASD causation. Petitioners have failed to demonstrate why TCVs–among all the possible causes of neuroinflammation and oxidative stress–are a probable cause of, or a substantial contributor to, ASD.

In the following section, I consider the evidence presented that pertains specifically to Colin Dwyer, and apply the general causation evidence to evaluate the merits of the claim for compensation filed on his behalf.

Section X. Colin's Specific Causation Claim.

A. Introduction.

The relevant procedural history pertaining to Colin's claim was set forth in Section I above and will not be repeated here. Colin's claim was timely filed and he received all the relevant vaccinations in the United States. His ASD has persisted for more than six months. Thus, all of the statutory prerequisites to entitlement have been established by preponderant evidence, except that of causation.[632] To prevail, petitioners must prove by preponderant evidence that Colin's ASD was caused by his receipt of TCVs. The record as a whole fails to demonstrate any causal relationship.

B. Evaluating the Medical Evidence.

Conflicts between contemporaneous medical records and subsequent statements, testimony, and medical histories are common in Vaccine Act cases, and

[632] Although the parties did not stipulate that the statutory prerequisites for entitlement to compensation were met in this case, respondent did not contest any statutory requirement, except that of causation.

this case is no exception. Two general legal principles guide the resolution of conflicts between contemporaneous records and later-adduced evidence. The first is that the absence of a reference to specific symptoms in a medical record does not conclusively establish the absence of symptoms during that time frame. *See, e.g.*, *Murphy v. Sec'y, HHS*, 23 Cl. Ct. 726, 733 (1991), *aff'd*, 968 F.2d 1226 (Fed. Cir. 1992) ("[T]he absence of a reference to a condition or circumstance is much less significant than a reference which negates the existence of the condition or circumstance." (citation omitted)).

The second principle addresses the degree of reliance commonly accorded to contemporaneous records. Special masters frequently accord more weight to contemporaneously recorded medical symptoms than those recounted in later medical histories, affidavits, or trial testimony. "It has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight." *Murphy*, 23 Cl. Ct. at 733 (1991) (citation omitted); *see also Cucuras*, 993 F.2d at 1528 (medical records are generally trustworthy evidence). Memories are generally better the closer in time to the occurrence reported and when the motivation for accurate explication of symptoms is more immediate. *Reusser v. Sec'y, HHS*, 28 Fed. Cl. 516, 523 (1993). Inconsistencies between testimony and contemporaneous records may be overcome by "clear, cogent, and consistent testimony" explaining the discrepancies. *Stevens v. Sec'y, HHS*, No. 90-221V, 1990 WL 608693, at *3 (Fed. Cl. Spec. Mstr. Dec. 21, 1990). The following medical history and the conclusions drawn therefrom are presented with these legal principles in mind.

I emphasize that I do not question the veracity of Mr. and Mrs. Dwyer. They are caring and devoted parents and I am confident that their testimony was based on their best recollections of an extremely difficult and stressful period in their lives. Not surprisingly, given the passage of time, some of the testimony conflated events, such as which vaccinations were received at a particular time, and what symptoms or behaviors Colin displayed at particular times. Thus, I rely primarily on the most contemporaneous medical records, including the Dwyers' accounts of relevant symptoms contained in those records, for my factual determination of when and how Colin's ASD manifested.

C. Vaccinations.

Colin's medical records reflect an order for a hepatitis B vaccine to be administered 24 hours after his birth on November 10, 1998, but the records do not reflect that it was administered.[633] *See* Pet. Ex. 19, p. 17. His first hepatitis B

[633] When a vaccination is administered, health care providers record the vaccine's manufacturer and lot number, and the anatomical site of administration. It appears from other records (*see, e.g.*, Pet. Ex. 1, pp. 88-89) that New York required vaccinations to be recorded on a particular form. No form pertaining to this particular hepatitis B vaccination was filed. Other than the first two columns (the date the order was given and the nature of the order), the page of the medical record containing the order is blank, including the spaces for recording the date and time the vaccination was given and the injection site. Pet. Ex. 19, p. 17. Although Mrs. Dwyer testified that she believed this vaccination was actually administered (Dwyer Tr. at 66-67), she did not testify that she observed its administration. Based on the medical records, I find that it was not administered. It appears that Colin's pediatrician did not think Colin had

vaccination was actually administered on November 23, 1998, when Colin was 13 days old. Pet. Ex. 1, pp. 1, 17, 80. He received a second hepatitis B vaccination on December 30, 1998, at seven weeks of age. Pet. Ex. 1, pp. 17, 79, 89.

Colin received his next set of vaccinations at nearly three months of age, on February 2, 1999, when he received DPT,[634] poliomyelitis ["IPV"], and Hib. Pet. Ex. 1, pp. 1, 17, 77, 88. These were followed by DPT, IPV, and Hib vaccinations on March 26, 1999, when he was four and one-half months old. Pet. Ex. 1, pp. 1, 17, 75. On May 27, 1999, when Colin was six and one-half months of age, he received his third DPT, Hib, and hepatitis B vaccinations. Pet. Ex. 1, pp. 1, 17, 74.

Colin received his only measles, mumps, and rubella ["MMR"] vaccination on November 22, 1999, when he was 12 months old. Pet. Ex. 1, pp. 1, 17, 70. He received Hib and varicella (chickenpox) vaccinations on March 1, 2000, when he was almost 16 months old. Pet. Ex. 1, pp. 1, 17, 67, 87. In his last set of vaccinations on July 10, 2000, at 20 months of age, Colin received DTaP and IPV vaccinations. Pet. Ex. 1, pp. 1, 17, 63, 86; *see also* Pet. Ex. 1, p. 5 (a record with an illegible date but reflecting that Colin was eight years old, noting that "Dad declines further vaccinations"); Pet. Ex. 1, p. 44 (a medical record entry on January 13, 2004, indicating that the Dwyers were "refusing vaccines" for Colin).

Petitioners did not submit any direct evidence of the actual amounts of thimerosal contained in the individual vaccinations administered to Colin. Their expert, Dr. Mumper, testified about the total amount of thimerosal Colin received, but she did not explain how she derived that amount. Dwyer Tr. at 112-13; *See* Pet. Ex. 13, p. 3. The IOM 2001 Report, RML 254, estimates the ethylmercury levels in the vaccines[635] that Colin received as follows: the four doses of DPT/DTaP could have contained a total of 100 µg; the four doses of Hib could have contained a total of 100 µg; and the three doses of hepatitis B could have contained a total of 37.5 µg. This would be a possible cumulative total of 237.5 µg of ethylmercury[636] between his initial hepatitis B vaccination

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received this vaccination, because he administered a hepatitis B vaccination at 13 days of age (Pet. Ex. 1, pp. 1, 17, 80), too soon for a second hepatitis B vaccination under the recommended childhood vaccination schedule for hepatitis B vaccinations. *See* CDC Childhood Immunization Schedules (follow "1998" hyperlink).

[634] Colin's vaccination record lists the first three vaccinations as "DTP" (diphtheria, tetanus, and whole cell pertussis) and the fourth as "DTaP" (diphtheria, tetanus, and acellular pertussis) whereas the individual records from his check-ups indicate they were all DTaP vaccines. *Compare* Pet. Ex. 1, pp. 1, 88 *with* Pet. Ex. 1 pp. 74, 75, 77, 86. Either formulation, if it came from a multi-use vial, likely contained thimerosal. IOM 2001, RML 254, at 27-28.

[635] The IPV, MMR, and varicella vaccines do not contain thimerosal. IOM 2001, RML 254, at 27.

[636] This cumulative total is the same as that contained in Dr. Mumper's report; she counted three hepatitis B vaccinations instead of four in her report. Pet. Ex. 13, p. 3; Dwyer Tr. at 112-13.

at two weeks of age and the final TCV at 20 months of age.[637] IOM 2001, RML 254, at 28. If Colin had actually received four hepatitis B vaccinations, the total would have been 250 µg.

D. Colin's First Year.

1. Prenatal and Neonatal Records.

Both Drs. Mumper and Leventhal agreed that Colin's prenatal course was essentially normal. Pet. Ex. 13 at 2; Res. Ex. CC at 1. At birth on November 10, 1998, Colin weighed almost eight pounds, and had Apgar scores[638] of nine at both one and five minutes. Pet. Ex. 19, p. 6.

2. Early Medical Care and Treatment: Birth to One Year.

The records of Colin's medical care in his first 12 months document a relatively healthy baby. Colin had periodic check-ups at South Shore Pediatrics, with well child visits at 13 days (Pet. Ex. 1, p. 80), seven weeks (Pet. Ex. 1, p. 79), two and one-half months (Pet. Ex. 1, p. 77), four and one-half months (Pet. Ex. 1, p. 75), six and one-half months (Pet. Ex. 1, p. 74), and at 12 months (Pet. Ex. 1, p. 70). Colin experienced some mild illnesses: colds, fevers, bronchitis, rash, and bloodshot eyes, all common complaints in infants. Pet. Ex. 1, pp. 73, 75, 76, 78. There was no suggestion that these illnesses were either unusually severe or excessive in number.

Colin's physical development during this period was normal. His weight ranged from the 50th percentile at birth up to the 90th at two months of age. He was in the 50th percentile again at six months of age, but declined to the 25th percentile by about one year, when he was noted to eat "hit or miss." Pet. Ex. 1, pp. 67, 70, 74, 75, 77, 79, 80-81. Colin's mother testified that he sat up on his own at three months,[639] pulled himself up at six months, and started to walk at nine months. Dwyer Tr. at 30. His early social development appeared normal: at 13 days he smiled, responded to sound, and

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[637] Using Dr. Aposhian's estimates of thimerosal content in Pet. Ex. 21 at 4, the totals are the same.

[638] The Apgar score is a numerical assessment of a newborn's condition, usually taken at one minute and five minutes after birth. The score is derived from the infant's heart rate, respiration, muscle tone, reflex irritability, and color, with from zero to two points awarded in each of the five categories. *See* DORLAND'S at 1670.

[639] This testimony is substantiated by medical records. Pet. Ex. 12, p. 3. That page is undated, but from the records accompanying that page, it was likely filled out in January, 2004. Pet. Ex. 12, p. 1. However, Mrs. Dwyer told a speech therapist on May 31, 2001, that Colin sat up at "approximately 6 months of age." Pet. Ex. 10, p. 1. The pediatric neurologist who evaluated Colin for autism recorded that Colin sat unassisted at six months. Pet. Ex. 2, p. 7. Although his pediatrician's handwriting is not very clear, the record of his six month check-up appears to say that he was "Tripod Sitting" at that point. Pet. Ex. 1, p. 74. I note that sitting unassisted typically occurs at six months of age. NELSON TEXTBOOK OF PEDIATRICS ["NELSON'S PEDIATRICS"], Table 8-1 (18th ed. 2007).

regarded faces. Pet. Ex. 1, p. 80. He was smiling and cooing at two and one-half months (Pet. Ex. 1, p. 77), and babbling and laughing at four months (Pet. Ex. 1, p. 75).

E. Period Surrounding Initial ASD Symptoms and Diagnosis.

1. Colin's Development from 12 to 16 Months of Age.

In Colin's second year, he displayed some language skills, with the records reflecting that he had three to five words at his one-year well child check-up on November 22, 1999. His pediatrician observed him babbling with an occasional word (Pet. Ex. 1, p. 70) at this visit. At his 15-month check-up (when he was nearly 16 months old), he was "talking some."[640] Pet. Ex. 1, p. 67.

The experts differed regarding whether these visits reflected normal language development, with Dr. Mumper testifying that the notations at one year and 15 months indicated normal development. Dwyer Tr. at 105-07. However, Dr. Leventhal testified that the "talking some" comment at Colin's 15-month well child check-up was not a notation a pediatrician would use to describe normal development. Instead, it indicated a problem with Colin's speech. Dwyer Tr. at 262-63.

In addition to his well child check-ups during the first half of his second year of life, Colin had doctor's visits for a febrile illness in December, 1999 (Pet. Ex. 1, p. 69), and a cough, congestion, and runny nose in May, 2000 (Pet. Ex. 1, pp. 64-66). In between these two illnesses, he received Hib and varicella vaccinations on March 1, 2000, at approximately 16 months of age, when the "talking some" notation was made. Pet. Ex. 1, pp. 17, 67.

2. Colin's Development from 17 Months to ASD Diagnosis.

a. Overview of Issues.

Petitioners contend that Colin suffered a developmental regression beginning at around 20 months of age. Pet. Post-Hearing Br. at 68. Mr. and Mrs. Dwyer both testified that they began to notice problems in Colin's development and behavior at around this time frame. Dwyer Tr. at 38, 79. A thorough review of the testimony and the contemporaneous medical records substantiates that Colin's developmental problems were noted between July and December, 2000, but there are conflicts

[640] Mrs. Dwyer's affidavit stated that Colin had five to six words by 12 months. Pet. Ex. 17 at ¶ 3. She testified that, between 12 and 20 months of age, Colin had about eight words in his vocabulary. Dwyer Tr. at 35 (listing mama, dada, ba-ba (*i.e.*, bottle), bye-bye, baby, bear, up, cookie). These numbers are larger than those appearing in the more contemporaneous medical records and reports discussed below. Even at the higher range of eight words by 20 months of age, Colin's vocabulary was below average. Most children use 10-15 words spontaneously by 18 months of age, and use between 50-100 at two years of age. NELSON'S PEDIATRICS at 49; *see also* Tr. at 1483-84 (testimony of Dr. Mumper regarding language abilities of 15- and 21-month old children). I note that Mrs. Dwyer reported that Dr. Baker asked if Colin had 50 words at his well child visit when he was 28 months old. Pet. Ex. 10, p. 1.

concerning the nature, timing, and severity of Colin's behavioral symptoms between the March 1, 2000 visit and the March 22, 2001 visit when he was referred for further evaluation. Because there were only two medical visits in this time frame,[641] my determination of whether Colin experienced any loss of skills is based primarily on parental recall and reports to other health care providers months or years after the events in question. Unfortunately, these reports conflict with one another and with the Dwyers' testimony.

b. July, 2000-February, 2001.

(1) Petitioners' Testimony.

Mrs. Dwyer testified that she noticed changes in Colin's development when he was around 20 months of age (which would have been around July, 2000), but also testified that these changes occurred "around the fall" of 2000, which would place the changes at closer to two years of age. Dwyer Tr. at 38. Mr. Dwyer testified that in "the fall [of 2000] or early in 2001," Colin began to exhibit obsessive-compulsive behaviors, hand flapping, and loss of engagement with others. Dwyer Tr. at 83-84. Mrs. Dwyer further testified that she suspected a link between Colin's autism and vaccines "[a]fter Colin had his last round of vaccinations, which was in July of 2000" and that "he started his gradual regression shortly thereafter." Dwyer Tr. at 65.

Both Mr. and Mrs. Dwyer testified that during the fall of 2000 and the winter of 2001, they observed changes in Colin's behavior and communication skills. Dwyer Tr. at 38-41, 79. Mrs. Dwyer testified that, during this time frame, Colin became uncooperative, agitated, and no longer enjoyed some activities that he previously enjoyed. Dwyer Tr. at 38-40. As an example, she described Colin's "complete[ ] reject[ion]" of bath time during this period, which he had "always loved."[642] Dwyer Tr. at 38-39.

Mr. Dwyer echoed the observation that it was more difficult to engage Colin in activities they had done in the past, and he described uncooperative behavior during the fall of 2000. Dwyer Tr. at 79. Mrs. Dwyer described that, at Christmas, 2000, Colin, then two years of age, sat in a bin that his father had padded with pillows and blankets, never acknowledging the family members there for the occasion and taking no interest in unwrapping gifts. Dwyer Tr. at 39.

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[641] Colin had a well child visit at 20 months, on July 10, 2000. Pet. Ex. 1, p. 63. Colin had only one other pediatric visit between July, 2000, and March, 2001, when he was seen for a cough on October 16, 2000. Pet. Ex. 1, p. 62. This record does not reflect any concerns, other than those connected with his illness. Pet. Ex. 1, p. 62.

[642] At Colin's May 31, 2001 speech evaluation, Mrs. Dwyer reported that Colin "loves bath time and loves to play with water." Pet. Ex. 10, p. 2. Another evaluator reported on December 14, 2001, that "Colin loves the water and enjoys taking a bath." Pet. Ex. 3, p. 7. Either Mrs. Dwyer confused when Colin began resisting bath time or the resistance was short-lived.

Mrs. Dwyer testified that Colin "did not use his language the way he had been using it previously." Dwyer Tr. at 38. By spring 2001, Colin did not use words to communicate, did not like to be touched or held, and did not like to wear clothes. Dwyer Tr. at 39-40. She also testified that he stopped eating, lost weight,[643] and developed diarrhea. Dwyer Tr. at 40. When asked to identify the physical symptoms that occurred around the fall of 2000, she testified that the most profound physical symptom she observed was "his complete rejection of food." Dwyer Tr. at 68. She commented that he had been eating pureed foods, and then "he just absolutely rejected every food that we put in front of him." Dwyer Tr. at 68. She testified that he had normal bowels, but then developed chronic diarrhea that would leak out of his diaper. Dwyer Tr. at 68-69. By way of dating these symptoms, she indicated that they were reported to Colin's pediatrician at the March, 2001 visit. Dwyer Tr. at 69. The record of that visit does not reflect this report. Complaints of chronic diarrhea and eating problems are likewise not reflected in any of the medical records over the next 12 months.[644]

(2) The Contemporaneous Records.

Colin was 20 months old when he received DTaP and IPV vaccinations at a well child visit on July 10, 2000.[645] Pet. Ex. 1, p. 17. The medical records from this check-up are consistent with some concerns about his speech development, but the concerns appear to have been those of his pediatrician, not his parents. Pet. Ex. 1, p. 63. The

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[643] Mrs. Dwyer's testimony regarding Colin's weight loss did not specify when it occurred, but the medical records contradict any suggestion of weight loss around the time of onset or diagnosis. In July, 2000, Colin weighed 24 pounds, 6 ounces, which was slightly above the 25th percentile, the same percentile where he was at one year of age. Pet. Ex. 1, pp. 63, 81. In March, 2001, Colin weighed 27 pounds, which was also at or slightly above the 25th percentile. Pet. Ex. 1, pp. 61, 81. Indeed, the records indicate that Colin's weight declined from the 50th to the 25th percentile between six and 12 months of age, and remained at or around the 25th percentile through 28 months of age. Pet. Ex. 1, p. 81. However, prior to beginning the somewhat unorthodox treatments with Dr. Kenneth Bock, Colin's weight had rebounded to the 50th percentile. *See* Pet. Ex. 4, p.1 (noting Colin's weight as 34 pounds on Apr. 19, 2002); Pet. Ex.1, p. 83 (growth chart indicating that weight would place Colin in the 50th percentile).

[644] The medical records say little regarding Colin's gastrointestinal functioning during the winter of 2000 and spring of 2001. The record of his March 22, 2001 pediatrician visit contains a section for "Elim.," which in the absence of other relevant categories on the form is likely "elimination." Pet. Ex. 1, p. 61. The two words written in this category are largely illegible, but the first is likely "BM," referring to bowel movements. The second may be "nml," an abbreviation for "normal," but because I am in doubt, the only conclusion I draw from this record is that no major complaints were recorded. With regard to later reports of bowel problems, there is a record of a telephone consultation in December, 2001, for vomiting and diarrhea, containing an instruction to follow up if the symptoms persisted, but no other medical records reflect bowel problems at or around the time of Colin's ASD onset or diagnosis. Pet. Ex. 1, p. 45. In records from April, 2002 (dated by reference as part of Colin's intake records from Dr. Bock), Colin's parents assessed his diarrhea in the last 30 days as occasional and not severe. Pet. Ex. 4, p. 48.

[645] Mrs. Dwyer reported to a health care provider in June, 2004, that Colin received a Hib vaccination at this visit as well. *See* Pet. Ex. 1, p. 29. His last Hib vaccination was received four months earlier, at the March, 2000 well child visit. Pet. Ex. 1, pp. 1, 17, 67.

physician's[646] notes reflect that Colin "[s]ays few word[s] (3-5)." Pet. Ex. 1, p. 63. This is the same number of words he was speaking eight months earlier at his 12 month well child visit. Pet. Ex. 1, p. 70. Although the handwriting is not clear, it appears that the pediatrician also wrote "repeats word when talked to," followed by a space and then an illegible word. Pet. Ex. 1, p. 63. This entry suggests echolalia.[647] Other notes indicated that Colin was eating with a spoon and drinking whole milk. These entries were followed by two illegible words, then an entry indicating "no concerns." Pet. Ex. 1, p. 63.

The pediatrician indicated "watch speech," followed at the end of the record by a stated intent to follow up at two years to "check speech." Pet. Ex. 1, p. 63 (recording "√ speech" in the "plan" section of the record). This record does not indicate how severe Colin's speech delay was at the time, but does reflect that Colin's speech was something his pediatrician intended to monitor.

Colin's next visit to his pediatrician was for illness, on October 16, 2000, with a complaint of coughing for one week without fever and with a runny nose. Pet. Ex. 1, p. 62. The record of that visit is limited to this complaint.

c. March, 2001 Medical Visit and Referrals.

Colin returned to his pediatrician's office on March 22, 2001, when he was a little over 28 months of age.[648] Pet. Ex. 1, p. 61. He apparently saw Dr. Lisa Baker, as later referral reports are addressed to her. *See* Pet. Ex. 1, p. 58. Mrs. Dwyer testified that the visit was prompted by concerns about Colin's developmental problems. Dwyer Tr. at 41. However, there are no concerns recorded in the section for them at the top of the form. Pet. Ex. 1, p. 61. The first entry reflecting any issue is in the physical exam section of the form, where Dr. Baker recorded "speech/[l]ang delay!" followed by her impression of "speech/[l]ang delay" in assessing Colin's neurological status. Pet. Ex. 1. p. 61.

In the plan section, Dr. Baker referred Colin for a speech evaluation, and noted that "Father told v. important" (underlining original), and noted that Mr. Dwyer "didn't seem interested [in early intervention]." Pet. Ex. 1, p. 61. She reiterated that she "stressed [the] importance" of early intervention to him. Pet. Ex. 1, p. 61.

Two months later, on May 31, 2001, a special education evaluator recorded Mrs.

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[646] The physician's signature is illegible and nothing else in the record reflects which doctor saw Colin.

[647] This suggestion is buttressed by Mrs. Dwyer's report of echolalia in her account of Colin's developmental problems to a special education evaluator in May, 2001. *See* Pet. Ex. 10, p. 2.

[648] The medical record contains the notation "2 yrs." This probably reflects that the visit was intended as the two-year well child check-up. It does not appear from the medical records that Colin had a well child visit at two years of age, although at the 20-month visit on July 10, 2000, the record indicated that a follow up was planned at two years of age to check his speech. Pet. Ex. 1, p. 63.

Dwyer's account of the March 22, 2001 pediatrician visit:

> Dr. Baker asked her standard questions upon reaching his two years of age mark. Dr. Baker asked Maria if her son was producing 50 words, then asked if Colin had a vocabulary of 25 words, and mom answered no, which was then followed by the question of whether or not Colin was putting two words together. When mom reported "no" to Dr. Baker's questions, he [sic] then referred Colin to TIPSE for a speech evaluation. Prior to this point, Colin's parents had no major concerns, however did notice that "Colin was not progressing as fast as his older brother did at that age."

Pet. Ex. 10, p. 1 (emphasis added). During this evaluation, Mrs. Dwyer reported to two different evaluators that Colin said "mama" and "dada" for a few months and then stopped. Pet. Ex. 10, pp. 6, 9.

In a section titled "Family Concerns." Mrs. Dwyer was recorded as saying that she suspected that "something might be wrong with Colin" and after the referral for speech evaluation, she began to think that something more might be wrong. Mrs. Dwyer researched on the Internet because she suspected PDD, and identified that "Colin had no language, no pointing, no response to his name, gets overwhelmed by people, and has poor eye contact. In addition, Colin has rote skill knowledge, echolalia and some sensory issues."[649] The Dwyers indicated that they were aware of these "delays" but hoped he would grow out of them. Pet. Ex. 10, p. 2. The Dwyers reported that "they became concerned when Colin turned two and was not yet responding to his name or communicating with others." Pet. Ex. 10, p. 11.

d. Diagnosis of PDD.

After the March, 2001 visit, the Dwyers sought out several services for Colin to determine what was wrong and how to treat it.

(1) Initial Evaluation.

On May 31, 2001, the Toddler-Infant Program for Special Education, Inc. ["TIPSE"] assessed Colin's development through testing and direct observations. Pet. Ex. 10, p. 4. Colin's social/emotional functioning was at an 18-to-24 month level (Pet. Ex. 10, p. 4), self-help at the 18-month level (Pet. Ex. 10, p. 5), and both cognitive functioning and fine motor skills at the 15-month level (Pet. Ex. 10, pp. 5-6). Colin's chronological age at this evaluation was two and one-half years. Pet. Ex. 10, p. 4. His gross motor skills were "on or near age level," although his fine motor skills were somewhat behind his chronological age. Pet. Ex. 10, pp. 6, 12.

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[649] From context, it appears that this research occurred after the pediatrician voiced her concerns. This timing is buttressed by Dr. Baker's records from the March, 2001 visit, and the emphasis she placed on Colin receiving early intervention services. *See* Pet. Ex. 1, p. 61. Doctor Baker's record does not reflect that the Dwyers communicated any concerns about Colin's development.

Colin's receptive language abilities were "well below his age level." Pet. Ex. 10, p. 6. He was "unable to follow one-step commands" and "did not imitate gestures" when they were presented. Pet. Ex. 10, p. 6. In addition to his poor receptive and expressive language skills, Colin displayed an inability to relate to his environment and reciprocate with others. He was easily frustrated and screamed and grunted at times. Pet. Ex. 10, pp. 6, 9. The evaluators recommended more formal evaluations, speech and language therapy, occupational therapy, and placement in a small toddler group program. Pet. Ex. 10, pp. 6-7.

(2) Doctor Fish's Neurological Evaluation.

After Colin's TIPSE evaluation, Colin saw Dr. Irving Fish, a pediatric neurologist, on June 14, 2001. The history the Dwyers provided indicated that Colin answered to his name and babbled on time, but did not speak on time. At around two years of age, Colin's parents noted that he lacked speech, had poor eye contact, poor social skills, and lack of response to simple commands. In a somewhat contradictory entry, Dr. Fish noted that Colin "began to speak at 2 and now can count to 15, knows some letters, uses words such as cat, dog and repeats words others say," but Colin did not use speech to communicate. Pet. Ex. 2, p. 7. Colin generally ignored others in the office, making only fleeting eye contact. He occasionally babbled and said words, but inconsistently responded to his name. Pet. Ex. 2, p. 8. Doctor Fish's impression was that Colin had Pervasive Developmental Disorder with significant autistic features and recommended applied behavioral analysis ["ABA"] therapy.[650] Pet. Ex. 1, p. 56; Pet. Ex. 2, p. 8. It did not appear that Dr. Fish conducted any standard diagnostic tests in making this assessment, as none were filed or mentioned in his two-page report.

e. Reports to Others Regarding Colin's Language.

Doctor Goldstein, the audiologist who tested Colin's hearing[651] on May 23, 2001, recorded that Colin had "no words at two years." Pet. Ex. 1, p. 58. In December, 2001, Colin's parents reported to educational evaluators that he said "mama" and "dada" at 18 months of age. Pet. Ex. 3, p. 2

In April, 2002, at Colin's initial visit with Dr. Kenneth Bock at the Rhinebeck Center, the Dwyers provided a history of Colin's health and development. Doctor Bock recorded that at 18 months of age, Colin was using "mama" and "dada" and making vowel sounds. Pet. Ex. 4, p. 1. At around his second birthday, he stopped responding to his name. He "lost speech, including dada" and lost eye contact. Pet. Ex. 4, p. 2.

In June, 2004, the Dwyers told Doctor Bruce Russell that they noticed changes in

[650] Applied Behavior Analysis is the "application of learning theory based on operant conditioning." Casanova 2007, RML 67, at 422. It "is the only intervention recommended by the Surgeon General" for ASD. *Id.*

[651] Colin's hearing was normal. Pet. Ex. 1, p. 60; Dwyer Tr. at 41-42.

Colin after "his 18 month immunizations." Pet. Ex. 1, p. 29.[652] There were no vaccinations recorded in Colin's medical records as administered at 18 months.[653]

3. Factual Determinations Regarding Onset and Regression.

Colin's feeding difficulties apparently began before his first birthday, with "hit or miss" feeding noted at the one year check-up, and a decline from the 50th percentile for weight at his six-month well child visit to the 25th percentile at the one year mark. By seven months of age, it is likely that Colin had received 187.5 µg of ethylmercury from TCVs. By 16 months of age, he had likely received a cumulative total of 212.5 µg of ethylmercury from TCVs. At 20 months of age, his cumulative total was likely 237.5 µg of ethylmercury from TCVs. At this point, however, Colin's ASD had already manifested with speech and language delays, as indicated below.

By 15 months of age, his expressive language development is more difficult to assess. The experts differed in their interpretation of the pediatrician's "talking some" assessment of Colin's language skills on March 1, 2000. In the absence of testimony by this pediatrician, I cannot conclude that the pediatrician was "talking in code" to convey that Colin's language development was no longer normal. Colin was talking at 15 months of age, and in the absence of an entry clearly reflecting concern or other evidence that Colin should have been using more words,[654] I cannot conclude that his expressive language development was abnormal at this point.

By 20 months of age, however, a different picture emerges. I conclude from the Dwyers' testimony and the medical record of Colin's July, 2000 visit that Colin's speech delay was obvious at that point.[655] He was speaking three to five words, the same

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[652] A portion of this record also appears with the rest of Dr. Russell's records as Pet. Ex. 6, p. 102. The more complete copy of this page appears in Pet. Ex. 1, p. 29.

[653] Colin received vaccinations at his 15-month and his 20-month visits. It is likely that the Dwyers were referring to one of these instances when Colin received vaccinations, or, more probably, a conflation of the two events. They identified the vaccinations that Colin received at this "18 month" visit as "DTap, Hib and polio." Pet. Ex. 1, p. 29. Colin received his last Hib at the 15-month visit, and his last DTaP and polio vaccinations at the 20-month visit. Pet. Ex. 1, pp. 1, 17.

[654] I note that NELSON'S PEDIATRICS, a standard pediatric textbook, indicates that four to six words at 15 months of age is typical development. *See* Table 8-1.

[655] In December 2001, a McCarton Center evaluator recorded Mrs. Dwyer's account that around the time of his second birthday, and after his MMR vaccination, Colin "stopped relating to his mother when she returned home from work and became a difficult child who often had tantrums." Pet. Ex. 3, p. 2. As Colin's only MMR vaccination was November 22, 1999, 12 days after his first birthday, the timing discrepancy precludes placing any reliance on this account by Mrs. Dwyer. I note that she reported this association of Colin's ASD with his MMR vaccination in a subsequent history. *See* Pet. Ex. 4, p. 3. This may reflect a problem with dating events or an awareness of the reported association of autism and MMR vaccinations that formed the primary basis for the Theory 1 OAP cases. Petitioners have not, however, alleged a causal association between Colin's MMR vaccination and his ASD in this proceeding, and to place Colin's emerging ASD behaviors in close temporal connection with his MMR vaccination would

number of words he had at one year of age. Pet. Ex. 1, pp. 63, 70. Although there was some evidence that Colin had speech delays prior to July, 2000, in that Colin's parents described his speech at 18 months to several health care providers as one or two words, plus vowel sounds, I cannot determine if he lost words after his first birthday and regained them by the twenty month check-up, or whether his language development simply reached a plateau at one year of age.

Additional behavioral problems emerged over the next eight months. They either had not manifested or were not of sufficient severity to be mentioned at Colin's sick child visit in October, 2000, but I accept Mrs. Dwyer's striking account of Colin's social interaction difficulties at Christmas time, 2000. However, the variances in the Dwyers' accounts of Colin's behavior and when he lost skills make reliance on some of their accounts difficult. Having heard their testimony and observed their demeanor, I am confident that they were testifying as accurately as their memories permitted. I accept that behavioral difficulties emerged gradually over the period between July, 2000 and March, 2001.

Conflicts between the testimony and records make it difficult to accept that some of the specific problems about which the Dwyers testified emerged during this time frame or were of the severity they indicated. I do not accept that Colin's feeding difficulties emerged only after July, 2000. Colin's weight was at the 25th percentile around his first birthday and also at the 25th percentile at 28 months of age. He did not lose weight during this time frame, and thus, there could not have been a "complete rejection of food."

Likewise, the accounts of chronic diarrhea are not supported by the evidence. The March 1, 2000 visit noted that Colin's elimination was normal; the July 10, 2000 visit was silent on the matter; the March, 2001 visit contains a largely illegible notation, but not one consistent with a report of chronic diarrhea. Pet. Ex. 1, pp. 61, 63, 67. My conclusion that Colin did not have chronic diarrhea during this period is buttressed by several other pieces of circumstantial evidence. In spite of being a picky eater, he did not lose weight. He had only one medical visit, for a cold, between 20 and 28 months of age. Parents concerned enough about a cold to seek medical attention for it would certainly have been concerned enough about diarrhea leaking out of their child's diapers to contact a physician. They did not. Colin was supposed to have a follow up well child visit at two years of age; instead, he was not seen again by a physician until 28 months of age. There were no reports of Colin having bowel problems separate from illness (*see* Pet. Ex. 1, p. 45) until the initial visit to Dr. Bock, in April, 2002.[656] I find these accounts in sufficient to show that Colin had chronic diarrhea in the fall and winter of 2000.

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render this petition untimely.

[656] The Dwyers mentioned to Dr. Russell several years later that the bowel problems began after Colin's 18-month vaccinations. Pet. Ex. 1, p. 29.

Colin did experience a regression in language after the 20-month check-up. Although his mother testified that he had five or six words at one year of age, his pediatrician recorded that Colin had three to five words by that point, and confirmed hearing at least one word, plus babbling, at his one year well child visit. Two reports, to the McCarton Center and to Dr. Bock, indicate that Colin said "mama" and "dada" at 18 months.[657] These same reports indicate that he was no longer using those words by his second birthday in November, 2000. More precise dating of the language loss is impossible, as his 15-month check-up does not indicate how many words he was speaking, and his 20-month check-up indicated he had three to five words. The report to Dr. Fish indicated that Colin had ceased talking around his second birthday.

I conclude that Dr. Leventhal was correct in asserting that Colin's language at 18-20 months of age was abnormal. *See* Tr. at 263. At 18 months of age, he should have been using 10-15 words, but had fewer. Even were I to credit Mrs. Dwyer's testimony that he had eight words at 20 months of age, this was not a normal vocabulary, and her testimony conflicts with the report to his pediatrician of only three to five words at 20 months of age. Although I cannot precisely date the time Colin lost the use of words such as "mama" and "dada," the Dwyers' testimony reflects that Colin's "gradual regression" (Dwyer Tr. at 65) began after the 20 month well child visit in July, 2000. Accepting this testimony in general, I must conclude that Colin was not developmentally normal at the time his regression began. This factual conclusion excludes Colin from the category of "clearly regressive autism" about which Dr. Greenland testified, and from the "striking" and "shocking" categorization about which Dr. Kinsbourne wrote and testified.

F. Medical Care and Treatment of Colin After Diagnosis.

1. Overview.

Colin's medical records after his diagnosis exceed 400 pages. In their efforts to aid their son, the Dwyers sought both conventional and unconventional treatments. Colin received conventional behavioral and speech therapy from several providers from the summer of 2001 through the time of the hearing in July, 2008, and received occupational therapy at least through the beginning of 2006. *See* Pet. Ex. 11, pp. 23, 61. Colin was periodically evaluated, and he made progress in both expressive and receptive language and behavior, although he remains impaired in both as compared to his typically developing peers.

His more unconventional treatments began in April, 2002, when he was first evaluated by Dr. Kenneth Bock and was placed on a gluten-free diet. A battery of tests

[657] Although these reports are not precisely contemporaneous, they were the closest in time to the events described. The reports do not definitively state that these two words were all that Colin was using at 18 months, although the context and circumstances do suggest that.

was performed at this visit as well. From June, 2002 through February, 2004,[658] he received a number of alternative therapies associated with the DAN program of treatments for children with autism. These therapies included various dietary supplements, glutathione, secretin injections, and chelation.

In 2004, apparently unsatisfied with Dr. Bock's approach,[659] Colin's parents tried another unconventional therapy regimen with Dr. Bruce Russell. Doctor Russell subscribed to the view that autism is a neuroimmune system dysfunction ["NIDS"],[660] and followed a NIDS treatment protocol based on this view. The most recent record from Dr. Russell was dated June 17, 2008, shortly before the hearing in Colin's case. Pet. Ex. 6, p. 71.

Because Dr. Mumper asserted that certain test results constituted evidence in support of the causation hypotheses advanced, these tests and the therapies to treat the problems they revealed are recounted at somewhat greater length than those involving Colin's schooling and behavioral and speech therapy. Although Colin's progress in the conventional treatment programs does not bear directly on the causation issues, certain aspects of that treatment are recounted when those evaluations coincided with the alternative treatments and evaluations.

Evidence from controlled studies indicated that some of the treatments to which Colin was subjected had produced results comparable to placebos. Colin was repeatedly chelated, but only the first chelation resulted in the excretion of any mercury. Finally, some of the test results upon which Dr. Mumper relied were normal when compared to age-appropriate values. Other tests were performed by laboratories that had significant quality control and reliability problems, points which Dr. Mumper acknowledged, while nevertheless citing the test results as evidence for the causation hypothesis.

2. Educational, Speech, and Behavioral Therapy.

Colin was periodically evaluated between the initial TIPSE assessment described above and May 4, 2007, the date of the most recent evaluation in his records. From shortly after his diagnosis with ASD in the early summer of 2001 through at least the

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[658] The year on the last encounter note is impossible to read. The month and day are October 21. Pet. Ex. 4, p. 27. Based on the previous encounter note (Pet. Ex. 4, p. 26), I conclude that the following one was also in 2003. There were records of test specimens collected in December, 2003. *See, e.g.*, Pet. Ex. 4, p. 53. Thereafter, Dr. Bock called in a prescription for Diflucan for Colin in February, 2004, and recommended, perhaps in a telephone consultation, further use of the Diflucan on March 5, 2004. Pet. Ex. 4, p. 28.

[659] Doctor Russell recorded this dissatisfaction at Pet. Ex. 1, p. 29.

[660] NIDS is Neuroimmune Dysfunction Syndrome, reflecting the belief of some health care providers that ASD is a physical ailment caused by a linked dysfunction in the brain and immune system. *See, e.g.*, http://www.nids.net. These providers use antibiotics, diet, and antifungal medications. *See id.* at http://www.nids.net/nidsfaq.htm. Doctor Russell diagnosed Colin with NIDS. *See* Pet. Ex. 6, p. 103.

spring of 2007, Colin had intensive speech and behavioral therapy, initially from TIPSE and Fischer Children's Services. Pet. Exs. 1, p. 53; 10, pp. 13-14; Dwyer Tr. at 43-44. An evaluation during the fall of 2001 indicated that little had changed in Colin's abilities from late spring 2001,[661] and Mrs. Dwyer testified that Colin's behavior and speech difficulties continued during the fall of 2001. *See* Pet. Ex. 2, pp. 3-6; Dwyer Tr. at 44. By early December 2001, the Dwyers had decided to remove Colin from TIPSE and treat him with intensive ABA therapy. Pet. Ex. 2, p. 6.

Colin was evaluated and tested at the McCarton Center for Developmental Pediatrics on December 14 and 27, 2001. Pet. Ex. 3, p. 2. Colin scored a 38 on the Childhood Autism Rating Scale ["CARS"], indicating he had an Autism Spectrum Disorder "in the moderate to severe range." Pet. Ex. 3, p. 7. Colin's overall development was in the significantly delayed range for his age, due mainly to his communication difficulties and rigid behaviors, and he was diagnosed as having "Pervasive Developmental Disorder/Autism Spectrum." Pet. Ex. 3, pp. 7-8.

At the end of 2002, Colin's therapy consisted of at-home ABA therapy and speech, language, and occupational therapy, totaling more than 35 hours per week. He also attended school three days per week for two hours at a time. Pet. Ex. 3, p. 13. Although the Dwyers reported that Colin "has been making good progress," the evaluators noted concerns. Pet. Ex. 3, p. 13. The evaluation questioned whether "his current program is effectively addressing his behaviors and tantrums . . . His lack of progress over the past year is very alarming and warrants a more aggressive and intensive program of intervention." Pet. Ex. 3, p. 18.

Evaluations in late 2005 and early 2006 indicated that despite progress in language, "Colin continues to present with significant behavioral challenges." Pet. Ex. 7, p. 2; *see also* Pet. Ex. 11, pp. 16-27. The most recent report from the McCarton School, dated April 12, 2006, observed that "Colin continue[d] to exhibit the same problem behaviors noted in January," while also noting that the family had observed that these behaviors were less frequent and less intense. Pet. Ex. 11, p. 2.

The Dwyers moved Colin to the Elija School, which specializes in children with autism, for the 2006-2007 school year. Pet. Ex. 8, p. 1. A May 4, 2007 progress report from the school detailed his progress that year, listing discrete tasks, and reflecting whether Colin had mastered them. At eight and one half years of age, Colin had 100% mastery of body parts, but followed the hand command to "stand up" with only 76% accuracy. He could use three-four word sentences, such as "I am seven," but was still working on "I need the bathroom." He was working on saying "hi" to greet his teacher. Pet. Ex. 8, pp. 2-6. He had mastered a number of skills, such as establishing and maintaining eye contact when his name was called and naming a number of objects.

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[661] This record is undated, but given that it accompanies a letter that Mrs. Dwyer wrote on December 3, 2001, which describes this record as Colin's "latest evaluation," it is likely the report was made in the fall of 2001. *See* Pet. Ex. 2, p. 6 (Mrs. Dwyer's letter).

Pet. Ex. 8, p. 9. His tantrums ranged from none to 32 per day, with a mean of five. Pet. Ex. 8, p. 12.

3. Treatment by Dr. Kenneth Bock, April, 2002 through March, 2004.

a. Overview.

Colin began seeing Dr. Kenneth Bock at the Rhinebeck Health Center on April 19, 2002.[662] Doctor Mumper described Dr. Bock as an "integrative physician," with whom she had "co-lectured," attended "think tanks," and discussed "medical problems in children with autism." Dwyer Tr. at 124. He apparently subscribed to the DAN approach to ASD treatment.

The Dwyers sought out Dr. Bock for a "biomedical"[663] approach to treating Colin. Pet. Ex. 4, p. 1. Doctor Bock treated Colin for slightly less than two years, from spring 2002 through early 2004. During this period, Colin had repeated medical testing, primarily conducted by laboratories that offered specialized testing focused on children with ASDs.[664] The wide range of treatments included the gluten- and casein-free diet,[665]

[662] The Dwyers had contact with Colin's pediatrician twice after the March, 2001 visit, before beginning treatment under Dr. Bock. In November, 2001, his pediatrician ordered a complete blood count and lead level; the lead level was normal and the CBC was normal except for lymphocyte and monocyte levels. Pet. Ex. 1, pp. 46-47. The second contact involved a telephone conversation with one of Colin's parents concerning a bout of diarrhea and vomiting on December 24 and 25, 2001. Pet. Ex. 1, p. 45.

[663] The "biomedical" approach to treating ASD has been described as a view that ASD is "a heterogeneous collection of discrete entities with different etiologies sharing a common presentation" and a view that "some forms of autism are not simply treatable, but curable." Baker, PML 599, at 249. This article indicated that the biomedical approach to treating autism was promoted by the Autism Research Institute. *Id.*

[664] Respondent introduced evidence that many of these laboratories had quality control problems sufficiently serious so as to render their test results highly questionable, if not completely unreliable. Doctor Mumper also testified about her own concerns about one of the laboratories. The specific issues with the laboratories are discussed below.

[665] Doctor Rust testified that the gluten-free diet is not helpful, except possibly in some cases of ataxia or migraine headaches. *See* Tr. at 2605-07.

chelation, dietary and vitamin supplements,[666] secretin,[667] glutathione,[668] methylcobalamin injections, as well as "off-label" treatment with a number of prescription drugs.[669] None of these treatments is FDA approved for the treatment of autism.

Although the records[670] from Dr. Bock's office contain consistent notes that Colin was progressing, these notes do not reflect any testing to confirm the reports.[671] In some cases Colin reportedly reacted well to treatments, but each positive reaction was short-lived, and the basic circumstances of his illness–communication difficulty and behavioral problems–remained. Colin did experience relative improvement in both areas, but the record fails to demonstrate that the "biomedical" treatments were responsible.

b. Initial Evaluation.

At Colin's first visit on April 19, 2002, Dr. Bock recorded the Dwyers' account of Colin's regression as beginning around his second birthday, when they "noticed [he] stopped reacting to his name," lost speech, eye contact, and social ability. Pet. Ex. 4, p. 2. Doctor Bock later noted that Colin's "decline may have started after his MMR"

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[666] Doctor Rust testified that he had not observed any efficacy to treatment by dietary supplements, with the caveat that parents do not always share what supplements their children are taking and when treatment with them begins and ends. Tr. at 2452.

[667] Doctor Rust testified that secretin has been subjected to careful study, and found to have no effect as an ASD treatment. Tr. at 2452-53. His comments were echoed by Dr. Fombonne, who testified that secretin has been shown to lack efficacy in autism treatment. In three separate randomized clinical trials, secretin did not differ from a placebo in efficacy. Tr. at 3703. NIH funded the secretin studies, which Dr. Rutter noted had consistently shown it was not effective. Tr. at 3341-42.

[668] Doctor Brent testified that huge amounts of glutathione exist in the human body. The small amount of glutathione found in supplements would not make any difference in the body's ability to handle heavy metals. Tr. at 4347-48.

[669] As of 2007, the only FDA-approved drug treatment for ASD behavioral symptoms was risperdal, to treat aggression, tantrums, and self-injury. *See* Casanova 2007, RML 67, at 422.

[670] All of Dr. Bock's records are handwritten and often extremely difficult or impossible to decipher.

[671] What the records do establish is that Colin did not thrive physically on this treatment program. At Colin's initial visit to Dr. Bock on April 19, 2002, his father reported Colin's weight at 34 pounds. Pet. Ex. 4, p. 1. This placed Colin, then about three and one-half years old, at around the 50th percentile for weight. *See* Pet. Ex. 1, p. 83 (growth chart). In June, 2002, when the treatments began, and after two months on a gluten-free diet, he weighed 33 pounds. Pet. Ex. 4, p. 4 (this record also contains a notation that Colin was eating more foods and had an improved appetite). By September, 2002, Colin was down to 31 pounds. Pet. Ex. 4, p. 9. In December, 2002, he weighed 33 pounds. Pet. Ex. 4, p. 15. Based on the growth chart at Pet. Ex. 1, p. 83, Colin, then four years of age, was around the 25th percentile. His weight in April, 2003, when he was about four and one half years of age, was 35 pounds, still in the 25th percentile. He had gained only 1-2 pounds in a year. Pet. Exs. 1, p. 83; 4, p. 23.

vaccination.[672] Pet. Ex. 4, p. 3.

The Dwyers reported Colin had a recent "miraculous speech breakthrough" that they attributed to his ABA therapy.[673] Pet. Ex. 4, p. 2. Colin also had behavior problems, including tantrums, hyperactivity, and trouble sleeping. The Dwyers had no complaints regarding Colin's gastrointestinal health, although he had soft bowel movements four to six times per day. Pet. Ex. 4, p. 2. A food diary of the four days prior to Colin's appointment shows that he was "dairy free" and ate a very limited diet.[674] Pet. Ex. 4, p. 39.

During Dr. Bock's exam, Colin displayed minimal eye contact, stimming, humming, irritability, moderate hyperactivity, and screaming. Pet. Ex. 4, p. 3. Doctor Bock's plan indicated the need for laboratory testing to look for underlying etiologies for Colin's condition. Pet. Ex. 4, p. 4.

c. Initial Testing.[675]

The initial tests ordered by Dr. Bock reported that Colin had low levels of carbon dioxide ["CO2"][676] and creatinine.[677] Other test results were reported as high, but Dr.

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[672] As Colin received his MMR shortly after his first birthday, this timing does not match what the Dwyers initially reported during the visit. In addition to this reference to an MMR vaccination and onset of Colin's symptoms, Dr. Bock also referred to a second MMR vaccination. *See* Pet. Ex. 4, p. 4. These references likely reflect Dr. Bock's belief that the MMR vaccination causes ASD, an opinion also held by Dr. Kinsbourne. *See* Tr. at 903. The MMR-ASD hypothesis was presented and rejected in the Theory 1 test cases. The Dwyers did not rely on any connection between Colin's MMR vaccination and his ASD symptoms in this case.

[673] The educational records filed do not reflect this breakthrough, but they do not include accounts of individual sessions, simply periodic updates and assessments.

[674] His diet consisted of bread, oatmeal, eggs, bananas, apples, cookies, chips, french fries, baked chicken, and carrots This food diary does not include a year. Given that the days recorded are April 15 through April 18, it is likely this diary was prepared for his first visit with Dr. Bock on April 19, 2002. Pet. Ex. 4, p. 39.

[675] Some of these tests appear to have been performed by an "in house" laboratory that used adult norms. *See* Pet. Ex. 4, pp. 126-30. When results are compared to a standard reference manual for laboratory testing, most of the results reported as high or low values are normal for a child of Colin's age. *See* MOSBY'S MANUAL OF DIAGNOSTIC AND LABORATORY TESTS (3d ed. 2006) ["MOSBY'S LABS"].

[676] I note that the listed norms of 23-29 reflect adult norms, as indicated by MOSBY'S LABS at 157. Based on the appropriate norms for children (20-28), Colin's level was not low.

[677] Creatinine is produced by muscle mass. Ordinarily, serum creatinine levels do not fluctuate, but renal disease or meals high in meat may cause elevations. Young children, such as Colin, typically have lower creatinine levels than older children or adults as the result of their lower muscle mass. *See* MOSBY'S LABS at 207. I also note that Colin was still at the 25th percentile in weight. In any event, Colin's result of 0.4 mg/dL was not low, based on norms for children of 0.3-0.7 mg/dL. *See* MOSBY'S LABS at 207.

Mumper did not indicate that these results were of significance for her causation opinion.

d. Subsequent Testing.

Over the next 20 months, Doctor Bock ordered many tests conducted at a number of different laboratories. I have grouped those results by the type of testing performed, omitting some that appear to have no bearing on the causation issues, and primarily focusing on those test results that Dr. Mumper thought had some relevance to the causation hypotheses. Because some of the laboratories Dr. Bock used were demonstrated to have reliability problems, in most cases, I also identify the laboratory.

Testing performed at Dr. Bock's in-house laboratory demonstrated relatively consistent results for Colin throughout this period, but because the laboratory applied adult norms to all tests, its reports erroneously indicated that some of Colin's results were abnormal.

(1) Amino Acid Testing.[678]

Great Smokies Laboratory[679] tested Colin's amino acid levels from a urine sample collected on May 28, 2002. Pet. Ex. 4, pp.116-25. The results showed "[m]ultiple deficiencies of essential and protein amino acids." Pet. Ex. 4, p. 119. The report suggested an amino acid supplement schedule. Pet. Ex. 4, p. 122.

(2) Oxidative Stress Testing.

On July 11, 2002, Colin's blood was drawn for more tests performed by Great Smokies Diagnostic Laboratory. These included a serum "oxidative stress panel," plasma cysteine and sulfate levels, and an "Essential and Metabolic Fatty Acids Analysis." The results were reported as abnormal for glutathione, cysteine, and sulfate. Pet. Ex. 4, pp. 96-98, 104-09. Testing in December, 2002, by Great Smokies also reported low glutathione, cysteine, and sulfate levels. Pet. Ex. 4, pp. 78-80.

(3) Celiac Disease Testing.

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[678] More than 90 diseases are associated with abnormal amino acid function, and most amino acid defects are genetic in nature. MOSBY'S LABS at 59-60.

[679] Doctor Mumper testified in the general causation hearing that, in her "best medical judgment," urinary mercury testing by Great Smokies laboratory was "unreliable." *See* Tr. at 1529-32. This was in reference to a specific test result in another of the Theory 2 cases. She explained that Great Smokies laboratory was one of the laboratories involved in her ongoing research project, which involved sending split samples to different laboratories. Based on the results, she indicated that she was not comfortable in relying on any testing from Great Smokies "in a matter of this much importance." Tr. at 1532-33. The test report itself indicated that the testing had not been "cleared or approved by the U.S. Food and Drug Administration." Pet. Ex. 4, p. 113.

Other tests ordered on July 11, 2002, included antibody testing for IgG, IgM, and IgA endomysial mucosal antibodies,[680] and gliadin antibodies,[681] performed by Immunosciences Lab, Inc.[682] Pet. Tr. Ex. 4, p. 99. The results indicated abnormal levels of antibodies for endomysial IgG, although the IgM and IgA antibodies were within range. Pet. Ex. 4, p. 99, 103. The gliadin antibody test was normal. Pet. Ex. 4, p. 101.

(4) Testing for GFAP and Myelin Basic Protein.

Colin had blood drawn on July 11, 2002, for neurofilament (GFAP) and myelin basic protein ["MBP"] IgG, IgM, and IgA antibodies, with testing performed by Immunosciences Lab, Inc. Pet. Tr. Ex. 4, pp. 100, 102-03. High levels of IgM antibodies for neurofilament (GFAP) and MBP were detected, although the IgG and IgA for both neurofilament and MBP were within range. Pet. Ex. 4, pp. 100, 102-03.

(5) In-House Testing.

Tests at the in-house laboratory on November 7, 2002, again reported that Colin had a low creatinine level.[683] Pet. Ex. 4, p. 83. Reported high levels on other tests were normal, when compared to age-appropriate norms. Another round of testing ensued in December, 2002. The results from the in-house laboratory again reported a low CO2 level, which was normal by age-appropriate norms. Pet. Ex. 4, p. 81; MOSBY'S LABS at 157. In January, 2003, the in-house laboratory again reported high and low creatinine and CO2.[684] Pet. Ex. 4, p. 70. Testing on February 25, 2003 reported that Colin's

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[680] Screening for endomysial mucosal IgA antibodies is used to identify celiac disease. NELSON'S PEDIATRICS at 1591. Celiac disease is an autoimmune disease caused by exposure to gluten-containing foods, such as wheat and rye. *See* DORLAND'S at 530. The normal IgA levels indicate that Colin did not have celiac disease and thus did not require a gluten-free diet.

[681] Tests for gliadin antibodies are also performed to diagnose celiac disease. *See* DORLAND'S at 100. The absence of these antibodies indicates that Colin did not have celiac disease and thus did not require the gluten-free diet Dr. Bock had recommended.

[682] Problems with Immunosciences Lab, Inc.'s reliability were discussed at Dwyer Tr. at 157-77. The laboratory does not use child-specific norms. Dwyer Tr. at 165; *see also* Res. Tr. Ex. 13-19 (identifying specific problems at this laboratory and subsequent governmental and court actions, concluding with the laboratory ceasing to perform clinical testing). Specifically, "results... since June 2002 from Immunosciences Lab Inc. may not be accurate or reliable." Res. Tr. Ex. 16 at 1; *see also* Dwyer Tr. at 169. I also note that respondent cited a number of cases from courts that have found Immunosciences' testing to be unreliable. Respondent's Post-Hearing Brief ["Res. Post-Hearing Br."] at 88.

[683] Colin's result of 0.3 mg/dL was actually normal, based on norms for children of 0.3-0.7 mg/dL. *See* MOSBY'S LABS at 207.

[684] Colin's CO2 level was only slightly low; his creatinine level was normal. *See* MOSBY'S LABS at 157, 207.

creatinine was low.[685] Pet. Ex. 4, p. 66.

(6) Metal Testing.[686]

A red blood cell elements test performed in December, 2002, by [LAB NAME REDACTED] [687] indicated the presence of arsenic, cadmium, and lead.[688] No mercury was detected. Pet. Ex. 4, p. 75. The commentary accompanying this test notes that Colin's copper levels measured high, and his selenium levels measured low, but the copper was within the reference range provided. Pet. Ex. 4, pp. 75-77.[689] I note that an earlier blood test for mercury and selenium by this same laboratory (in April, 2002) also failed to detect any mercury and reported Colin's selenium levels as normal. *See* Pet. Ex. 4, p. 131. This suggests that whatever affected Colin's selenium levels had nothing to do with his ASD diagnosis, and, instead, may have reflected the effects of the biomedical therapies performed by Dr. Bock. The low selenium level was detected in testing after Colin had received chelation, secretin, and glutathione treatments.

(7) Nutritional Testing.

Nutritional testing in January, 2003, by Metametrix Clinical Laboratory did not flag any results as low (although it marked some as high). Pet. Ex. 4, pp. 67-69. The report was followed by a recommended list of nutritional supplements. Doctor Mumper

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[685] The use of age-appropriate norms would indicate that the creatinine level was normal. *See* MOSBY'S LABS at 207.

[686] Colin's mercury testing is addressed in a separate section, but some of the results are mentioned here as well.

[687] In the general causation hearing, Dr. Mumper testified that, based on her experience, [this] laboratory had "a very good set of toxicologists on board," and that she had "relatively more faith in this lab's expertise," (Tr. at 1550), apparently referring to her concerns about Great Smokies Laboratory. Respondent produced evidence that a 1999 request by [this lab] to analyze hair samples was denied by the state of New York, based on the lack of good reference values. Res. Tr. Ex. 2; Tr. at 1564-65. Additionally, a 2006 report from the State of New York Department of Health, Res. Tr. Ex. 3, questioned a number of [the] laboratory practices. With caveats based on the fact that she had not read the entire exhibit and was unaware of corrective measures, Dr. Mumper indicated that Res. Tr. Ex. 3 was "very concerning." Tr. at 1567-68. Doctor Brent was quite critical of test results from [the lab Dr. Mumper used], including those for red blood cell metal levels, commenting that it is not the type of test that would be performed in routine medical practice, and does not have validated results that render it meaningful. Tr. at 1853-54.

[688] I note that Colin had a negative test for lead, testing below 1 µg/dL in November, 2001 (Pet. Ex. 1, p. 46), which was at the low level of the reference range provided. A year later, [the laboratory she used] reported Colin's lead level at the upper end of the normal reference range. Pet. Ex. 4, p. 73.

[689] A page is missing from this lab report that should fall between pages 76 and 77 of Pet. Ex. 4. The laboratory's discussion of the relevance of high copper levels is truncated due to the absence of this page, and discussion of other results from the test may be missing from the record.

testified that some of these results reflected results consistent with the causation theory. Tr. at 139.

e. Treatment.

During the period June, 2002-February, 2004, Colin received a wide variety of alternative therapies, described below. The treatments frequently overlapped, making attribution of any improvement to a particular treatment more difficult. In spite of Dr. Bock's enthusiastic assessments of Colin's progress, assessments that were sometimes shared by his parents, Mr. and Mrs. Dwyer eventually determined that these treatments were not working. A few months after leaving Dr. Bock's practice, Mr. and Mrs. Dwyer reported to Dr. Russell that Dr. Bock's biomedical interventions had not been effective.[690] *See* Pet. Ex. 1, p. 29.

(1) Gluten- and Casein-Free Diet.

Colin returned to Dr. Bock for a follow-up appointment on June 18, 2002. At this point, Colin had been on a gluten-free, casein-free diet since the April 19, 2002 appointment. Pet. Ex. 4, p. 4. His parents reported that his stools had improved and his bowel movements had dropped to three times per day.[691] Pet. Ex. 4, p. 4. Doctor Bock noted that Colin's appetite was also improved, his nasal congestion was better, and he "continue[d] to make nice strides [with] his speech." His parents reported that he was a "different child since Dec." and that he was making advances "across all areas."[692] Pet. Ex. 4, pp. 4-5. Doctor Bock observed that Colin was moderately hyperactive, was "wheeing" and "humming" during the exam, and did not make eye contact with him. Pet. Ex. 4, p. 5.

(2) Intravenous ["IV"] Glutathione.

Mrs. Dwyer signed the consent to experimental therapy for Colin's treatment with IV glutathione on July 24, 2002, and Colin received his first of many treatments on that

[690] Although Colin's parents reported that they did not think Dr. Bock's DAN-recommended treatments were effective, they later told Dr. Mumper that some of them were associated with his progress. Dwyer Tr. at 189; *see also* Dwyer Tr. at 56-57.

[691] In an apparent non sequitur, Dr. Bock included a note that Colin had lost weight and had a bloated abdomen after his second MMR. As Colin's vaccination records show only one MMR vaccination, which occurred some two years earlier, I cannot discern any reason for the notation, other than a misplaced attempt to link Colin's problems to an MMR vaccination. Pet. Ex. 4, p. 5; Pet. Ex. 1, p. 17.

[692] Colin had an at-home visit evaluation less than a week prior to this appointment with Dr. Bock. The evaluator wrote that "Colin has made excellent progress since I last evaluated him in December 2001" and that Colin was talking during the visit. Pet. Ex. 3, p. 12. She advised no changes in his therapy program other than to add some activities with a typically developing peer. Pet. Ex. 3, p. 12.

date.[693] Pet. Ex. 4, pp. 37-38. At Colin's August 28, 2002, follow up visit, the Dwyers reported that Colin had a "[p]henomenal, unbelievable response to the IV [glutathione]" that lasted for about three days. Pet. Ex. 4, p. 8. Even after three days, Colin was still "markedly better," learning to play the harmonica and singing the ABC song. Pet. Ex. 4, p. 8. Unfortunately, by the time of the August 28, 2002 appointment, Colin was having tantrums again. Pet. Ex. 4, p. 8. Nevertheless, Dr. Bock noted at the appointment that Colin was "not hyperactive presently" and was "[i]nteracting more [with his] brother." Pet. Ex. 4, p. 9.

At the September 30, 2002 follow up visit,[694] Dr. Bock prescribed further glutathione treatment. Pet. Ex. 4, p. 10. I cannot determine when the next dose was administered, but the records reflect that he missed a glutathione treatment on October 15, 2002, due to a fever. Pet. Ex. 4, p. 11. The Dwyers reported "slow steady progress" at his October 30, 2002 check-up, and Dr. Bock indicated an intent to continue IV glutathione and to start oral glutathione supplements. Pet. Ex. 4, pp. 11-12. He indicated a similar intent at the November 25, 2002 follow up visit. Pet. Ex. 4, p. 14.

At the December 20, 2002 visit, Mr. Dwyer reported that Colin was making slow, but steady, progress. Pet. Ex. 4, p. 15. Colin was reportedly "[a] little 'spacey' [after his] last IV glut[athione]" dose. Pet. Ex. 4, p. 15. There was no recommendation regarding continuing the IV glutathione at this visit; the next mention of glutathione treatment is a notation: "consider [undecipherable] IV glut in future," made on April 29, 2003. Pet. Ex. 4, p. 24.

The records appear to indicate that Colin was prescribed "TD" (probably referring to "transdermal") glutathione in September, 2003 (Pet. Ex. 4, p. 26), and an entry on October 21, 2003 indicated that he was tolerating transdermal glutathione (Pet. Ex. 4, p. 27), but there are no other references in the records indicating that Colin received glutathione treatment or that it had any effect.

(3) Intravenous Secretin.[695]

Doctor Bock prescribed secretin at the August 28, 2002 visit, and Mrs. Dwyer signed the consent to experimental therapy on that date. Pet. Ex. 4, pp. 9, 33-34. At the September 30, 2002 follow up visit after chelation and secretin therapy began, the

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[693] Because Dr. Bock's records do not reflect the actual administration of treatments, it is difficult to determine the number of treatments received by Colin. Doctor Russell summarized the instances of some treatments, but they do not entirely match up with Dr. Bock's records. *See* Pet. Ex. 1, p. 29.

[694] This visit occurred after chelation and secretin therapy began. To the extent that an improvement was attributed to a particular treatment, I have included those comments in the section relating to that treatment.

[695] The state of Dr. Bock's records makes it difficult to determine how many secretin treatments Colin received. Doctor Russell reported that he received three. *See* Pet. Ex. 1, p. 29.

Dwyers reported that Colin's bowels were "great" in response to the IV secretin. Pet. Ex. 4, p. 10. At the October 30, 2002 visit, Colin's stools were "excellent," but he had rough skin on his abdomen attributed to the IV secretin. Pet. Ex. 4, p. 11.

At the November 25, 2002 visit, the Dwyers "noted definite improvement [after] IV secretin." Pet. Ex. 4, p. 14. On December 20, 2002, Mr. Dwyer reported that after secretin, he was "much more with it," more compliant, and playing better with his parents and brother. Pet. Ex. 4, p. 15. Doctor Bock also recorded that Colin's bowels were "excellent" since omitting certain foods from his diet. Pet. Ex. 4, p. 15.

At Colin's January 21, 2003 visit, the Dwyers reported to Dr. Bock that "Colin definitely had a break through" on Christmas Eve with respect to his ability to interact with others. Pet. Ex. 4, p. 17. He had received his third secretin treatment two weeks prior,[696] and the notation suggests that the Dwyers linked Colin's increased socialization to that IV secretion treatment. Pet. Ex. 4, p. 17. They also reported that he was more conscious of other kids, and he was mimicking other children's behavior. Pet. Ex. 4, p. 17. They observed that he was "much happier," was having fewer tantrums, had "incredible balance," and had excellent bowels. Pet. Ex. 4, p. 17.

Doctor Bock recommended continuing secretin at the January and February, 2003 visits (Pet. Ex. 4, pp. 18, 20), but there were no other references to secretin treatment.

(4) Chelation.[697]

Doctor Bock prescribed chelation with DMSA at the August 28, 2002 visit, and Mrs. Dwyer signed the informed consent form on that date. Pet. Ex. 4, pp. 9, 35-36. A baseline urine specimen was collected on September 20, 2002.[698] Pet. Ex. 4, p. 93. He began the DMSA after this specimen was collected, and a post-provocation sample was collected on September 22, 2002. This sample tested at 17 µg mercury/g creatinine. Pet. Ex. 4, p. 90. This was the only test of any type that reported any detectible level of mercury, in spite of many more rounds of chelation.

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[696] It appears from the records that this may have been his fifth secretin treatment, but because the dates of the infusions are not reflected in the records produced, it is impossible to determine for certain.

[697] It is also difficult to determine how many times Colin was chelated, but Dr. Russell reported that he had 12 rounds of DMSA, and also received alpha lipoic acid ["ALA"]. Pet. Ex. 1, p. 29.

[698] Although the test results indicated that this was a post-DMSA-provocation test, Dr. Mumper testified that this entry was a mistake. Dwyer Tr. at 132. She testified that both Dr. Bock and Mrs. Dwyer told her that this urine specimen was collected prior to Colin's receipt of DMSA, in order to establish a baseline by which to measure post-provocation tests. Dwyer Tr. at 132. I credit Dr. Mumper's testimony on this point, as no mercury was detected on this test, but mercury was detected on a second specimen collected, post-provocation, on September 22, 2002. Pet. Ex. 4, pp. 90, 93.

At the September 30, 2002 follow up visit after chelation and secretin therapy began, the Dwyers reported that Colin was continuing to improve in social interaction, cognition, and speech. Pet. Ex. 4, p. 9. However, his behavior was not improving; he continued to have tantrums and hyperactivity, and was starting to line up objects again. Pet. Ex. 4, pp. 9-10. Colin was irritable during the appointment and did not make eye contact. Pet. Ex. 4, p. 10. Doctor Bock prescribed additional rounds of DMSA-provoked chelation. *Id*.

In October, 2002, after Colin's third round of DMSA, Colin's parents reported a short-term increase in behavioral problems. Pet. Ex. 4, p. 11. The Dwyers noted that they were not happy with Colin's ABA program, but that his time spent in school seemed to help. Colin was demonstrating an increase in receptivity after the first two DMSA courses. They indicated that "it calms him down, [increases] focus, helps [with] his behaviors, [and increases] his verbal [activity]." Pet. Ex. 4, p. 11. As this was around the time he missed the IV glutathione due to a fever, Colin's parents were able to attribute the "significant difference" to the chelation therapy. Pet. Ex. 4, p. 11. Doctor Bock added an impression of "heavy metal overload" and reduced the DMSA dose. Pet. Ex. 4, p. 12.

On November 3, 2002, Colin's second post-provocation urine test produced elevated levels of lead[699] but no detectible mercury. Pet. Ex. 4, p. 85. At a November 25, 2002 visit, the Dwyers told Dr. Bock that after his last chelation Colin had "his best day ever," and he tolerated the lower dose of DMSA much better. Pet. Ex. 4, p. 13. Further DMSA treatments were postponed pending laboratory results. Pet. Ex. 4, p. 14.

Apparently, chelation resumed sometime between the November 25 visit[700] and the next visit on December 20, 2002, because Mr. Dwyer reported that Colin was "tolerating [chelation] beautifully," but was also stimming more after treatment. Pet. Ex. 4, p. 15. Additional chelation was recommended. Pet. Ex. 4, p. 16. A post-chelation sample, taken on December 29, 2002, showed that all of Colin's results for the "potentially toxic metals" listed were within the reference range. No mercury was detected. Pet. Ex. 4. p. 73.

On January 21, 2003, Dr. Bock recommended additional chelation, adding ALA. Although Dr. Bock did not further elaborate on what ALA was, he was likely referring to alpha lipoic acid.[701] Pet. Ex. 4, p. 18. A refill of Colin's previous DMSA prescription was ordered on January 30, 2003. Pet. Ex. 4, p. 19.

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[699] The . . . test report characterized the lead level as elevated, but the norms were based on a non-chelated population. Pet. Ex. 4, p. 85.

[700] There is a record of a telephone call from Mrs. Dwyer on November 26, 2002, asking "if ok to do DMSA," but it does not indicate when the DMSA was resumed. Pet. Ex. 4, p. 14.

[701] It appears that ALA is another chelating agent.

At Colin's February 25, 2003 visit, the Dwyers told Dr. Bock that Colin was better after adding ALA to his DMSA chelation, and they noted that his receptivity and understanding had improved and his bad behavior had decreased. Pet. Ex. 4, p. 19. Doctor Bock indicated that laboratory tests for this round of chelation were in order. Pet. Ex. 4, p. 20.

[The] laboratory reported that Colin's urine sample, collected on March 2, 2003, after DMSA provocation, showed normal levels of arsenic, lead, and tin, but no detectible levels of mercury. Pet. Ex. 4, p. 63. At the March 25, 2003 follow up visit to Dr. Bock, his mother reported that he was mildly agitated in response to chelation. Pet. Ex. 4, p. 21. Mrs. Dwyer told Dr. Bock that she felt the ALA therapy was helping Colin improve his verbal and social skills, "esp[ecially] when [he] comes off the DMSA/ALA." Pet. Ex. 4, p. 21. On March 25, 2003, Dr. Bock's plan indicated a discontinuation of the DMSA. Pet. Ex. 4, p. 22. There are no additional records pertaining to Colin's chelation therapy, although in October, 2003, shortly before Colin's treatment with him ended, Dr. Bock recommended that the Dwyers consider DMSA/ALA therapy again. Pet. Ex. 4, p. 27.

In November, 2002, Dr. Bock recommended that the Dwyers consider TTFD,[702] administered transdermally. Pet. Ex. 4, p. 14. He repeated the recommendation in January, February, and March, 2003. Pet. Ex. 4, pp. 18, 20, 22, 23-24. Colin apparently began TTFD in September, 2003. Pet. Ex. 4, p. 26. On October 21, 2003, Dr. Bock noted that Colin was tolerating the TTFD. Pet. Ex. 4, p. 27. There are no other records pertaining to this treatment.

(5) Methylcobalamin (Vitamin B12) Injections.

Colin began receiving a trial course of methylcobalamin injections, as recommended by Dr. Bock, at the November 25, 2002 visit (*see* Pet. Ex. 4, p. 14), sometime in December, 2002. Pet. Ex. 4, p. 16. Mr. Dwyer signed the informed consent forms on December 20, 2002. Pet. Ex. 4, pp. 30, 32. By report, Colin did not react well to the methylcobalamin treatment. Pet. Ex. 4, p. 17. In response, Dr. Bock reduced the dose. Pet. Ex. 4, p. 18. Varying doses in February and March produced no further adverse reactions, but no improvement. Pet. Ex. 4, pp. 20-21. At Colin's March 25, 2003 visit, Dr. Bock recorded that Colin was tolerating the methylcobalamin without problems, but had not seen an effect yet. Pet. Ex. 4, p. 21. In April, 2003, Mrs. Dwyer reported that at a 12.5 milligram dose, Colin "did well" and had an improvement in language skills, but afterward had "diarrhea all day." Pet. Ex. 4, p. 22. Dr. Bock lowered the dose in response. Pet. Ex. 4, pp. 23-24. In May, 2003, an increased dose was contemplated (*see* Pet. Ex. 4. p. 25), but the next record is from September, 2003,

[702] Although Dr. Bock's records do not indicate what TTFD is or why he prescribed it, PubMed, a website of biomedical literature maintained by the U.S. National Library of Medicine, part of NIH, identified one article concerning the treatment of children with ASD with TTFD, thiamine tetrahydrofurfuryl disulfide. The abstract indicated that TTFD appears to function as a chelator.

and there is no mention of methylcobalamin at this visit (Pet. Ex. 4, p. 26), nor at any subsequent visit.

4. Treatment by Dr. Bruce Russell, Spring, 2004 to Summer, 2008.

Doctor Mumper did not appear to rely on any of Colin's test results or therapies used by Dr. Russell for her causation opinion, and thus I have addressed Dr. Russell's treatment of Colin in much less detail than that of Dr. Bock's treatment.

a. Overview of Dr. Russell's Treatment.[703]

Colin was treated by Dr. Russell at the Northern New York Autism Clinic from June 4, 2004, through at least June 17, 2008, a month before the hearing in Colin's case. Pet. Ex. 6, pp. 71, 103; *see also* Pet. Ex. 1, p. 29 (a more complete copy of the June 4, 2004 record). Doctor Russell apparently subscribed to the NIDS view of autism as an immunological disorder (*see* Pet. Ex. 6, p. 103 (recording his impression as "NIDS")), and his treatment reflected that approach.

The initial evaluation by Dr. Russell indicated that:

> [Colin had] been in ABA and a very intensive school program and has had significant improvement over the last year. Prior to that, he tried numerous biomedical interventions and homeopathic interventions. None of these previous interventions have been effective, except for Diflucan, which probably helped some. He has had 12 rounds of DMSA. He also had ALA. He had three secretin infusions.

Pet. Ex. 1, p. 29.

Doctor Russell also noted that Colin had an elevated ASO titer,[704] minimally elevated gliadin IgG antibodies,[705] and positive candida antibody tests.[706] He did not

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[703] A medical record that does not pertain to Colin Dwyer was filed as Pet. Ex. 6, p. 42. I have not considered this record.

[704] This was apparently referring to an Antistreptolysin O titer, a test used to determine whether a previous streptococcus infection has caused a disease such as rheumatic fever or bacterial endocarditis. MOSBY'S LABS at 103. Colin's level was reported to be 365 (Pet. Ex. 6, p. 56), which exceeds the age-normed level for children his age of 170-330. MOSBY'S LABS at 103.

[705] These antibodies are to proteins contained in wheat and wheat products and are suggestive of celiac disease. MOSBY'S LABS at 263. These results were in contrast to earlier results. *Compare* Pet. Ex. 6, p. 61 *with* Pet. Ex. 4, p. 101.

[706] Candida is "a genus of yeastlike [f]ungi," several species of which may cause human infections. DORLAND'S at 281-82.

mention any other positive results of concern.[707] His impressions were NIDS and PDD. He prescribed Diflucan, indicating that this was an off-label use. Pet. Ex. 1, p. 29. Doctor Russell wrote to Colin's pediatrician on June 4, 2004, recounting that Colin "had a number of interventions through Dan (sic) which were not successful," and indicating that Colin would be taking Diflucan and having liver function testing. Pet. Ex. 1, p. 28.

Doctor Russell's most recent progress note (from June, 2008) included the following two paragraphs, quoted in their entirety.

> The patient is a 9 year old male with a chief complaint of autism. His development has changed. He has developed increased language and new social skills. New language skills new words list (sic). New social skills include improved social skills. He has had an improvement in alertness, zoniness (sic), and brightness. There has not been any ill effect of the new medicines.
>
> The following interventions have been tried, including ABA, early childhood intervention, the DAN protocol, chelation, and megavitamin therapy. The following medications have been used, including valtrex,[708] famvir,[709] diflucan, nizoral,[710] celexa,[711] and zoloft.[712] Current active problems include impulsiveness and hyperactivity. Sensory problems

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[707] Although the record of Colin's first office visit with Dr. Russell is in June, 2004, Dr. Russell apparently arranged for extensive laboratory tests in March, 2004. Pet. Ex. 6, pp. 55-70. Colin also received what were labeled as a "Herpes Sim." and "Immune Def. Panel." Pet. Ex. 6, p. 57. Based on the negative results, it did not appear that Colin had been exposed to herpes simplex 1 or 2. Pet. Ex. 6, p. 57. Tests were also performed for Epstein Barr virus, cytomegalovirus, coxsackie virus, herpes virus 6, among others. Pet. Ex. 6, p. 60. He had high levels of antibodies to herpes virus 6, but not to any of the others. Pet. Ex. 6, p. 60.

[708] Valtrex is the trade name for valacylovir hydrochloride, an antiviral medication ordinarily prescribed to treat herpes viral infections, including chickenpox. PHYSICIANS' DESK REFERENCE (64th ed. 2010) ["PDR"] at 1702.

[709] Famvir is the trade name for famciclovir, an antiviral used to treat herpes viral infections. DORLAND'S at 673.

[710] Nizoral is the trade name for ketoconazole, an antifungal medication, used to treat Colin's "yeast." *See* Pet. Ex. 6, p. 97; *see also* DORLAND'S at 976. Doctor Russell noted that this was not an FDA-approved use for the drug. Pet. Ex. 6, p. 97.

[711] Celexa is the trade name for citalopram hydrobromide, an antidepressant in the selective serotonin-reuptake inhibitor (SSRI) class. A public health advisory regarding the use of antidepressants in children was issued in October, 2004. PDR at 1153 (noting that "Celexa is not approved for use in pediatric patients" due to an increased risk of "suicidal thinking and behavior").

[712] Zoloft is the trade name for sertraline hydrochloride, another SSRI class antidepressant. It is used to treat depression, OCD, and social phobia, among other conditions. DORLAND'S at 1686.

include auditory sensory defensiveness. Current medications include Zoloft Oral Tablet 50 mg. School reports cognative (sic) improvement and increased language.

Pet. Ex. 6, p. 71. Doctor Russell's assessment was that Colin had an Immune Mechanism Disorder and Immunity Deficiency.[713] Pet. Ex. 6, pp. 71-72.

b. Testing and Treatment.

Over the course of his treatment of Colin, Dr. Russell periodically tested Colin for antibodies to various bacteria and viruses. Tests were frequently repeated in spite of previous negative results and no evidence of active infection in the meantime.[714] Colin was treated with two antiviral drugs[715] and antibiotics,[716] but Dr. Russell never identified for what condition they were prescribed.[717] He also treated Colin with a number of antifungal drugs,[718] antidepressants, and asthma medications, as indicated above.

Colin's parents and Dr. Russell sometimes attributed Colin's progress to various

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[713] I note that paragraphs nearly identical to the two paragraphs quoted above (with the exception of the current medications list) appear on Colin's medical records for most other visits (*see, e.g.*, Pet. Ex. 6, pp. 73, 79, 82, 85, 89, 91, 93 for visits ranging from February, 2005 through January, 2008). There were occasionally more specific notations about a new skill, such as "sliding down stairs," appearing in the January, 2006 visit. Pet. Ex. 6, p. 95. The August, 2006 record is very similar, but notable in that it indicated that Colin "has not had an improvement in alertness, zoniness, and brightness" and that he was having fewer meltdowns. Pet. Ex. 6, p. 87 (emphasis added).

[714] For example, Colin consistently tested negative for herpes viruses 1 and 2 (*see, e.g.*, Pet. Ex. 6, pp. 2, 28, 44, 48, 57) from 2004-07. These viruses are associated with cold sores and genital infections. *See* MOSBY'S LABS at 772. None of Dr. Russell's records ever indicated that Colin had evidence of a herpes 1 or 2 viral infection.

[715] These were Famvir and Valtrex.

[716] The antibiotic identified in the records was Zithromax, which is the trade name for azithromycin. It is commonly prescribed to children for treatment of pneumonia, otitis media, pharyngitis, or tonsilitis. *See* DORLAND'S at 2075, 187-88. There is nothing in Dr. Russell's records to indicate that Colin had any of these conditions.

[717] Colin did test positive for herpes 6 virus, which is the virus that causes roseola (exanthem subitum), a short-lived disease of children that produces a rash and fever. A positive antibody test would suggest exposure. *See* DORLAND'S at 651 (exanthem subitum), 1642 (roseolovirus). Perhaps Colin's repeated treatment with Valtrex and Famvir, both drugs that target herpes viruses, was based on these antibody findings, but, if so, Dr. Russell did not explain that. Laboratory reports regarding his herpes 6 virus titers were sometimes inconsistent. *Compare* Pet. Ex. 6, p. 41 *with* Pet. Ex. 6, p. 39. These two tests appear to have been performed at different laboratories, with the high titer reported by Specialty Labs and the normal titer reported by Focus Diagnostics. Pet. Ex. 6, pp. 39, 41.

[718] These include Diflucan and Lamisil. *See* DORLAND'S at 712 (fluconazole), 1866 (terbinafine hydrochloride).

treatments. In June, 2004, Mrs. Dwyer noted that Colin had "made a lot of good progress" and was "much more verbal," but had struggled with OCD after a week on Diflucan. This went away after two weeks. Pet. Ex. 6, p. 103. Doctor Russell attributed this to "die-off," presumably of yeast. He indicated that he was "very happy with [Colin's] progress, and he seems to already be making major gains," apparently referring to the Diflucan treatment. For reasons not stated in his records, Dr. Russell prescribed Valtrex, an antiviral drug, to begin in two weeks. Pet. Ex. 6, p. 103. The Dwyers later reported that, after an initial "die-off period"[719] after starting Valtrex, they saw improvement in his speech and behavior, observations that were shared by Colin's teachers. Pet. Ex. 6, p. 102.

By way of comparison, progress reports from the McCarton School in January, 2005 observed that while Colin was progressing, "his compliance [was] still variable," and he continued to have tantrums and exhibit self-stimulatory behaviors. Pet. Ex. 11, p. 65. Colin, who was six years old at the time of these reports and had been undergoing alternative medical treatment for over two years, "communicate[d] his wants and needs using primarily 1-word utterances during spontaneous speech and 2-word utterances when provided with a model." Pet. Ex. 11, pp. 70-71.

In a brief note dated October 11, 2005 that may have been a telephone consultation, Dr. Russell commented that Colin had "slipped cognatively (sic) over the last month," something Dr. Russell attributed to a yeast problem. There are no contemporaneous lab results from this time pertaining to Colin's yeast levels.

The record from the McCarton School closest in time to this visit is a progress report from November 28, 2005. It indicated that "Colin continue[d] to demonstrate ... tantrumming and exhibit[] self-stimulatory and self-injurious behaviors." Pet. Ex. 11, p. 43. In fact, much of the "progress" described in this McCarton School record is almost identical to that described 10 months earlier. Both the progress and the problems described are nearly identical. *Compare* Pet. Ex. 11, pp. 43-46 *with* Pet. Ex. 11, pp. 65-68.

In January, 2006, Dr. Russell's progress notes changed to a computerized checklist and narrative format. *See* Pet. Ex. 6, pp. 95-96. At this point, his records of Colin's treatments appear in a more standardized format. Although the "History of Present Illness" section changed slightly from visit to visit, most of the entries are similar, if not identical, from visit to visit. The "Medication List" section included Colin's current medications; the "History of Present Illness" section included a list of most of the

[719] What had "died off" was not addressed in the record. Valtrex is an antiviral drug prescribed to treat herpes 1 and 2 infections, neither of which Colin had. Colin's pediatrician expressed his concern about the Valtrex treatment in an October 19, 2004 telephone call to Dr. Russell. Pet. Ex. 1, p. 23. The pediatrician noted that Valtrex appeared to be affecting Colin's liver function, based on AST and ALT levels (*see* Pet. Ex. 6, p. 53) and that he did not condone prescribing Valtrex to a five year old. Doctor Russell agreed that Colin should see a gastroenterologist. Pet. Ex. 1, p. 23.

interventions, medical and otherwise, Colin had received to date.

Changes in Dr. Russell's treatment and evaluation of Colin from June, 2006, through June, 2008, were minimal, as were the number of visits for which records were provided.[720] *See* Pet. Ex. 6, pp. 71-88. A gap appears in the records between September, 2006, and the next visit, in March, 2007.[721] *See* Pet. Ex. 6, pp. 84-85. In March, 2007, Dr. Russell suggested a trial of antibiotics, although he did not indicate what warranted antibiotic treatment, and nothing in the record suggested an infection. Pet. Ex. 6, p. 83.

Laboratory testing during the period between August, 2006, and the last records filed were not materially different from the earlier testing, with few exceptions. A slightly low CO2 level was reported in February, 2007 (Pet. Ex. 6, p. 24), but it was not low when compared to age-appropriate norms (*see* MOSBY'S LABS at 157). In the first homocysteine test performed on Colin, his results were normal. Pet. Ex. 6, p. 19. His creatinine was reported as low (Pet. Ex. 6, p. 19), but compared to age-appropriate norms, it was normal (*see* MOSBY'S LABS at 207). Allergy testing revealed no IgE response to several foods that had been previously reported as provoking an allergic response. *Compare* Pet. Ex. 6, p. 7 *with* Pet. Ex. 4, pp. 129-30. These were the last laboratory tests filed in Colin's records.

5. Genetic Testing.

In response to comments by Dr. Leventhal that Colin had not had any genetic testing (Res. Ex. CC at 7; Dwyer Tr. at 232), both Colin and Mr. Dwyer were genetically tested,[722] and petitioners properly supplemented the record with the results on March 31, 2009. The results indicated that Colin did not have an "imbalance" for the genomic sequences in the test, which was indicated as performed on patients with global developmental delays and "should have the capacity to detect...79 specific disorders/syndromes." Pet. Ex. 20, pp. 2-3. The results did not indicate whether Colin was specifically tested for genes associated with ASD or what the 79 specific disorders/syndromes tested were.

G. Expert and Treating Physician Opinions.

1. Treating Physicians.

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[720] Although Dr. Russell's notes usually ended with a note about returning to the clinic in a set period of time (*see, e.g.*, Pet. Ex. 6, p. 78 ('RTC in/on 6 weeks +/- 2 days")), the time between visits did not coincide with these instructions. In spite of the instructions, the next recorded visit was some six months later. It is impossible to determine if there are missing records, or just an extended time between visits.

[721] The first two pages of the March, 2007, record are duplicated at Pet. Ex. 6, pp. 81-82.

[722] There is no indication in the record whether Mrs. Dwyer was tested as well. Pet. Ex. 20, p. 2.

None of Colin's treating physicians causally connected Colin's TCVs to his ASD. Doctor Bock appeared to focus on Colin's non-existent second MMR vaccination as possibly causal.[723] *See* Pet. Ex. 4, pp. 3, 5. His treatment focus could be interpreted as implicating heavy metals in Colin's case, but as chelation continued in spite of the lack of mercury found, he may have been focusing on lead or arsenic. In any event, he never implicated TCVs as causal. Doctor Russell tested repeatedly for bacteria and viruses, but did not make any record notations regarding Colin's TCVs as a possible or probable cause.

2. Doctor Mumper.[724]

Echoing Dr. Kinsbourne's opinion on causation in general, Dr. Mumper opined "that thimerosal-containing vaccines must be on the list of differential diagnoses" for Colin's ASD. Dwyer Tr. at 151. Doctor Mumper testified:

> I reasonably looked for and did not find other alternative sources of mercury; that I looked for and did not find other alternative diagnoses for his pattern of regressive autism. Because his laboratory data and clinical course showed evidence of so many of the medical problems I would expect to be in a child with autism who had difficulty excreting toxins, it is my best professional judgment ... that thimerosal-containing vaccines substantially contributed to [Colin's] medical problems and his regressive autism.

Dwyer Tr. at 151-52. She held this opinion to a reasonable degree of medical certainty. Dwyer Tr. at 155.

Doctor Mumper relied on Dr. Aposhian for the existence of mercury efflux disorders. Dwyer Tr. at 196-97; *see also* Tr. at 1228. She relied on the largely negative mercury tests Colin received as evidence that he had difficulty excreting mercury, and on his only positive mercury test as evidence of an extremely elevated body burden of mercury. She also contended that the negative blood mercury tests were proof that he didn't have ongoing exposure from other sources. Dwyer Tr. at 135-

[723] MMR vaccines do not contain thimerosal; thus, even if Colin received a second, unrecorded vaccination, it would not implicate the causation theory in this case.

[724] Respondent argued that Dr. Mumper was not qualified to opine on ASD causation. *See* Res. Post-Hearing Br. at 81-82. The most significant of their points is that Dr. Mumper does not diagnose ASD in children; she requires her ASD patients to have an independent diagnosis before she treats them. *Id.* at 82; *see also* Tr. at 1480-81. There is a degree of inconsistency with being willing to opine on the cause of a condition, while declining to diagnose it.

37. However, it was Colin's "chronic" early exposure,[725] not acute mercury toxicity, that concerned her most. It was "the chronic exposure that accumulates at a critical developmental window" and particularly the very early exposure via the three hepatitis B vaccinations by seven weeks of age.[726] Dwyer Tr. at 199. These vaccinations resulted in mercury deposits in his "brain, kidney, fat and potentially lymphatic glands." Dwyer Tr. at 199-200. She also implicated Colin's low selenium levels as evidence of mercury problems. Tr. at 137.

Doctor Mumper agreed that Colin did not have the history of antibiotic use and ear infections that she found significant in the *Mead* case, nor the prenatal antibiotic use she found significant in the *King* case, but nevertheless believed that TCVs contributed to Colin's ASD. Dwyer Tr. at 188-89.

There was only one reference to Dr. Deth in Dr. Mumper's testimony in Colin's case, which was in response to a question by respondent's counsel. Dwyer Tr. at 163. During the general causation hearing,[727] she explained more about her reliance on his hypotheses regarding methionine synthase, methylation, and epigenetics, and thimerosal's effects on these processes. Tr. at 1224-29. She appeared to adopt his opinions on the role of sulfur metabolism and oxidative stress in ASD. She testified that Colin's low sulfate, cysteine, and glutathione levels would affect his ability to detoxify heavy metals (Dwyer Tr. at 131), but she did not mention his homocysteine level, which was reported as normal. *See* Pet. Ex. 6, p. 19. She also relied on Colin's laboratory testing for amino acids, citric acid markers, lactate, neurofilament, neurotransmitters, myelin basic protein, lipid peroxide, CO2, and mercury as evidence that he had problems with sulfur metabolism, oxidative stress, and neuroinflammation. Dwyer Tr. at 125-28, 133, 139-43, 145.

Doctor Mumper's opinion appeared to be primarily based on laboratory testing performed by Dr. Bock. Her opinion was not based on any one test result, but rather on the accumulation of a constellation of laboratory tests in conjunction with Colin's history. Dwyer Tr. at 200-01. The difficulty with these tests is that they were all performed a considerable period of time after Colin was diagnosed with ASD, and even longer after Colin's regression manifested. Thus, they are fairly weak circumstantial evidence of his health or oxidative stress status around the time of onset of his disorder, and at the time of his immunizations.

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[725] Episodic exposure through periodic administration of TCVs is not normally characterized as chronic. It may be that Dr. Mumper was referring here to the accumulation of inorganic mercury in Colin's brain as a result of this exposure.

[726] However, I have found that Colin received only two hepatitis B vaccines by that point.

[727] Petitioners expressly asked that I consider certain transcript pages of Dr. Mumper's testimony from the *Mead* and *King* hearing (Dwyer Tr. at 94-95).

More specific difficulties concern the bona fides of the laboratories performing the testing, and whether the test results were based on norms for children. Colin had some tests that reflected some degree of oxidative stress, but Colin's poor nutrition status represented a significant confounder in many of these results. Doctor Mumper acknowledged these testing limitations. *See* Dwyer Tr. at 177-78, 191-92.

Doctor Mumper conceded that the effectiveness of the DAN treatments provided by Dr. Bock could not be determined (Dwyer Tr. at 189-90), and thus it appeared that she did not rely on Dr. Bock's attributions of positive results from his treatments. The testing she did rely upon is discussed below.

a. Immunosciences Laboratory Testing.[728]

Colin's neurofilament and myelin basic protein IgM antibody tests in July, 2002 were mildly elevated, but the IgA and IgG antibodies for both were within range. Pet. Ex. 4, p. 100, 102-03. Dwyer Tr. at 125-28. The neurofilament test measures GFAP antibodies, and, according to Dr. Mumper, his elevated results reflect a possible "loss of structural integrity of the astrocytes and ongoing neuroinflammatory processes." Dwyer Tr. at 126. This suggests neuroinflammation or reactive gliosis, tying into Dr. Kinsbourne's testimony about neuroinflammation in children with autism,[729] pathology with astrocytes, and problems with glial cells. Dwyer Tr. at 126. She did not address the significance of the IgA and IgG being within range.

According to Dr. Mumper, the elevated myelin basic protein antibody test suggested that the myelin sheath surrounding nerve cells was degenerating, a process that occurs in multiple sclerosis. Dwyer Tr. at 127-28. Doctor Mumper interpreted these antibodies as a marker for autoimmunity, and noted that Colin had either eczema or a fungal infection at four months of age, which could be an early sign of an immune dysregulation. Dwyer Tr. at 161-62. Doctor Mumper agreed that this test result was not within the ambit of Dr. Kinsbourne's causation hypothesis, as he did not implicate demyelination as a part of his causal mechanism. Dwyer Tr. at 162. She acknowledged that the Vargas paper's authors did not equate neuroinflammation with autoimmunity, and she agreed that Dr. Deth was not proposing autoimmunity as a part of his oxidative stress model of autism causation. Dwyer Tr. at 162-63.

Doctor Mumper acknowledged that both of these tests were very nonspecific,

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[728] In spite of the fact that ASD cannot be diagnosed through laboratory testing, Immunosciences Laboratory offered a panel of tests called the "Premier Autism Panel," at a cost of $600.00. Additional recommended tests could be as much as $1200.00. Dwyer Tr. at 158-59. Tests for neurofilament and myelin basic protein were part of the Premier Autism Panel, as well as other testing panels. *See* Res. Tr. Ex. 13.

[729] Doctor Kinsbourne never commented on neurofilament antibodies as a marker for a neuroinflammatory process, a point Dr. Mumper acknowledged. Dwyer Tr. at 160.

and have been reported as elevated in individuals who were otherwise normal. Neither test directly measures brain inflammation. Dwyer Tr. at 163-64; *see also* Tr. at 1477.

A more basic problem with this testing is the fact that Immunosciences Laboratory ceased clinical testing in partial settlement of a lawsuit regarding the loss of the laboratory's certification to perform testing. Dwyer Tr. at 166-67, 176; Res. Tr. Ex. 19. Specifically with regard to the neurofilament and myelin basic protein testing, there were no written policies and procedures for patient preparation, specimen collection, storage and preservation, conditions for specimen transportation, and specimen acceptability and rejection. Dwyer Tr. at 173; Res. Tr. Ex. 18 at 5-6.

When she reviewed respondent's information regarding Immunosciences Laboratory, Dr. Mumper indicated that she "would give relatively less credence or perhaps even be forced to discount the reliability of those two particular lab tests given the information in the settlement agreement...." Dwyer Tr. at 176.

b. Great Smokies Laboratory Testing.

The glutathione, lipid peroxide, cysteine,[730] and plasma sulfate tests discussed below were all performed at Great Smokies Laboratory in July and December, 2002, when Colin was three and one-half to four years of age. Dwyer Tr. at 177. Although Dr. Mumper had testified earlier that she was not comfortable in relying on any testing from Great Smokies "in a matter of this much importance,"[731] she appeared to rely on these Great Smokies results in Colin's case. Doctor Mumper did not know whether these tests were normed for children. Dwyer Tr. at 177-78. These tests are not listed in MOSBY'S LABS, a manual for diagnostic and laboratory tests.

Doctor Mumper noted that Colin had reduced levels of the good type of glutathione, the type that helps with detoxification, immune function, mitochondrial function, and healthy gut epithelium, characterizing his levels as "in the red zone." Dwyer Tr. at 129; *see also* Pet. Ex. 4, p. 96. He also had high lipid peroxides, which measure lipid damage by oxidants and free radicals. Free radicals are a marker for oxidative stress. Dwyer Tr. at 129; *see also* Pet. Ex. 4, p. 96. Later in the same year, in December 2002, Colin had the same test with similar results. Dwyer Tr. at 129-30; *see also* Pet. Ex. 4, p. 78.

Doctor Mumper noted that Colin had low levels of cysteine, which is the precursor for glutathione, and a low cysteine level would suggest that he had a reduced ability to handle heavy metal toxicity. Dwyer Tr. at 131; *see also* Pet. Ex. 4, p. 97. Although Dr. Mumper attributed to the low level of cysteine to abnormalities in the

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[730] The transcript incorrectly reflects this as "cystine," although the laboratory reports involve cysteine. Dwyer Tr. at 177; Pet. Ex. 4, pp. 79, 97.

[731] *See* Tr. at 1532-33 (referring to results involving another child in the Theory 2 test cases).

methylation pathway (Dwyer Tr. at 131), the methylation pathway is controlled by dietary methionine (*see* Section VII.C.2.). She did not mention that Colin's homocysteine levels were normal in tests performed by another laboratory (Pet. Ex. 6, p. 19), and that homocysteine is a precursor for both cysteine and glutathione.

Colin also had low levels of plasma sulfate, which Dr. Mumper called a part of the detoxification mechanism dealing with excretion of toxins. Dwyer Tr. at 131; *see also* Pet. Ex. 4, p. 80.

c. Mercury Testing.

Both of Colin's blood tests for mercury were negative. If Colin had mercury in his blood, it was below the detection threshold. Dwyer Tr. at 178-79, 182-83; Pet. Ex. 4, pp. 75, 131. This test, coupled with the initial post-chelation test discussed below, indicated that Colin was not acutely exposed to mercury. Dwyer Tr. at 134-36.

The first (and only) positive test came after chelation. Doctor Mumper characterized it as very elevated, indicating a "significant body burden of mercury." Dwyer Tr. at 133. However, she admitted that this characterization was not based on any study of post-chelation mercury levels in children, and her characterization was based on "what she had been taught." Dwyer Tr. at 184-85, 201-04. She agreed that the test report itself indicated that the reference ranges used were representative of a healthy population without chelation or provocation. Dwyer Tr. at 184.

She noted that Colin's test results for mercury did not follow a pattern observed in research conducted by the ARI, which showed initial lead elevations after chelation, followed by mercury elevations. Dwyer Tr. at 182. She admitted the possibility that the tests showing undetectable levels of mercury indicated that he was not having problems excreting mercury on his own, but that the tests showing no mercury might indicate that Colin had mercury stores that were not accessible to chelating agents. Dwyer Tr. at 185. Doctor Mumper agreed that there was no data correlating the amount of mercury chelated to body burden of mercury. Dwyer Tr. at 203.

The only test to show detectible levels of mercury was performed by [LAB NAME REDACTED]. *See* Pet. Ex. 4, p. 90. Doctor Mumper indicated that if the post-chelation test from September 2002 were unreliable, she would have only a number of laboratory tests that were consistent with, but not specifically suggestive of, TCVs contributing to Colin's autism. Dwyer Tr. at 186. She acknowledged that the mercury excreted could not be attributed to any particular source of mercury, either ethylmercury or methylmercury. Dwyer Tr. at 186-87.

Doctor Mumper also noted that Colin's selenium level was low on one test (Pet. Ex. 4, p. 75), and indicated that "[s]elenium is one of the mechanisms that the body uses for glutathione function and to help get rid of mercury and so it will be used up when the body is trying to do that process." Dwyer Tr. at 137. While it is true that

inorganic mercury in the brain binds to selenium,[732] there is no evidence that brain levels of selenium are measured by plasma testing. Furthermore, there is no evidence that selenium is connected at all to glutathione. There was no evidence that selenium plays any role in forming glutathione precursors. Finally, Dr. Bock's early testing showed Colin's selenium level was normal (Pet. Ex. 4, p. 131); Colin's low selenium test followed a number of Dr. Bock's therapeutic interventions, including chelation, secretin, and glutathione treatments.

d. Other Testing.

Colin had one high lactate test. Pet. Ex. 4, p. 67. Lactate is an anaerobic breakdown product of glucose, and it tends to be higher when there is a lack of mitochondrial ATP. There is a very long differential diagnosis for what may cause lactic acidosis, including exercise or vomiting and diarrhea. Dwyer Tr. at 139. There was no other evidence that Colin had an ATP problem, other than possibly the elevated citric acid results from this same testing. Doctor Mumper testified that elevated citric acid markers are seen in people who have heavy metal toxicity, and that would be one of the differential diagnoses, based on these results. Dwyer Tr. at 140. She associated these results with a pattern that suggested interference with the citric acid cycle, by which cellular energy is produced. Dwyer Tr. at 141.

Although Dr. Mumper also considered Colin's CO2 testing in her opinion on causation (Dwyer Tr. at 141), the age-appropriate norms indicated that Colin's results were low on only one occasion. In any event, she acknowledged that a low CO2 level has a huge differential diagnosis, and can be present in any condition that would cause metabolic acidosis.[733] It can be low if the child is screaming before a blood draw. Apparently considering Colin's test results to be abnormal, she opined that the results were consistent with a mild, ongoing metabolic acidosis, although she admitted that Colin screamed frequently. Dwyer Tr. at 141, 190-91.

Colin had "extremely low levels of a number of different amino acids." Dwyer Tr. at 142-43; Pet. Ex. 4, pp. 116-17. Doctor Mumper thought that the low levels of

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[732] Selenium is generally believed to play a role in mercury detoxification by binding to inorganic mercury in the brain. *See* Mottet, PML 197, at 376-77. *See also* Clarkson and Magos 2006, PML 35, at 628. It is also considered an antioxidant. Selenium is a trace mineral required in small amounts and is obtained through diet. It is found in beef, fish, chicken, and turkey, as well as in some nuts and grains. NIH Office of Dietary Supplements, http://dietary-supplements.info.nih.gov/factsheets/selenium.asp (last visited Mar. 3, 2010). Colin's selenium deficiency may well have been related to his restricted diet.

[733] In commenting on Dr. Mumper's testimony in the *Mead* and *King* cases about CO2 levels, Dr. Brent noted that tests for serum CO2 should not be interpreted the way Dr. Mumper interpreted them. She testified that a low bicarbonate (CO2) level was indicative of acidosis and metabolic stress. However, these levels are very dependent on breathing speed. The more rapidly one breathes, the faster the reduction in CO2 levels. A crying child, not an uncommon scenario as the result of a blood draw, often results in a lowered CO2 level. Tr. at 1856-57.

methionine, taurine, cystathionine, and cystine were particularly important, noting the role of methionine in methylation. She also commented on the extraordinarily low amount of taurine, noting that it would place Colin "at a relative disadvantage in terms of his methylation biochemistry and in terms of his detoxification biochemistry." Dwyer Tr. at 143. Although poor nutrition can contribute to low amino acids, the end result is an impact on methylation biochemistry and detoxification biochemistry, suggesting both a marker and the cause of the problem. Dwyer Tr. at 191. The records reflect that Colin was a problem eater, which may be an explanation for why the amino acid levels were so low across the board. Dwyer Tr. at 192.

Doctor Mumper found Colin's laboratory results for neurotransmitters particularly important. Dwyer Tr. at 144-45. She testified that the metabolism markers for neurotransmitters were high, suggesting increased synthesis of epinephrine, norepinephrine, and dopamine. This reflects a sympathetic nervous system in overdrive. The sympathetic nervous system keeps someone agitated and would be consistent with reports of hyperactivity. Dwyer Tr. at 145. He also had an elevation in an analyte that reflects serotonin biochemistry. She thought the low level of kynurenate and elevated level of quinolinate were particularly significant, because quinolinate interacts with glutaminergic neurons. Overstimulated neurons can degenerate, and cause glutamate neurotoxicity. Dwyer Tr. at 146. A high level of quinolinate and a low level of kynurenate would lead to a suspicion of neurotoxicity. Dwyer Tr. at 146-47. However, these markers do not suggest a cause for whatever neurotoxicity might be present.

Two other markers Dr. Mumper found of significance were glucarate, which is "compatible with induction of enzymes to try to handle either toxic episodes or pesticide exposure or fungicides." Dwyer Tr. at 148. To the best of her knowledge, this function is not involved with detoxifying mercury. Dwyer Tr. at 148. The pyroglutamate is a marker for either glycine or glutathione deficiency. Dwyer Tr. at 148.

3. Dr. Haynes.

Doctor Haynes' report was "limited to an analysis of whether Colin Dwyer would be classified as at risk for mercury toxicity base[d] on his exposure to Thimerosal-containing vaccines (TCVs). His response to challenge testing and other metabolic abnormalities, demonstrated through testing of Colin, strongly support his genetic/ metabolic susceptibility to mercury toxicity." Pet. Ex. 15 at 2. Doctor Haynes did not specify what metabolic testing he considered pertinent to his opinion, which he held "to a reasonable degree of medical probability." Pet. Ex. 15 at 2.

He indicated that mercury-induced neurotoxicity was characterized by loss of voluntary movement, developmental delays, mental retardation, dysarthria,[734] seizure

[734] Dysarthria is speech that is slurred, slow, and difficult to understand. *See* DORLAND'S at 572.

disorders, and behavioral disturbances. Pet. Ex. 15 at 2. He did not indicate which, if any, of these conditions were present in Colin.

Doctor Haynes briefly mentioned that human detoxification mechanisms had considerable genetic variability. His opinion regarding the presence of such mechanisms in ASD was not highly illuminating. It consisted of one sentence: "Autistic syndromes often demonstrate metabolic markers that imply a genetic predisposition." Pet. Ex. 15 at 3. He did not specify a predisposition to what, nor did he indicate what markers, if any, Colin displayed. He also opined that "[c]helation testing" in Colin, as well as unspecified "other metabolic results conform to the susceptibility pattern found in mercury susceptible individuals." Pet. Ex. 15, p. 3. He did not explain the "pattern" to which he referred. He briefly mentioned glutathione, and that Colin demonstrated decreased levels of glutathione, apparently referring to the Great Smokies Laboratory testing. He asserted these test results showed a reduced ability to respond to oxidative stress. He indicated that Colin's pre-challenge and post-DMSA challenge urinary mercury levels "fit[ ] the model of mercury efflux disorder found in autistic children." Pet. Ex. 15 at 3. Once again, he did not indicate to what model he referred. I note that Dr. Mumper indicated that Colin's results were not typical of those found in other children with ASD who were chelated. Dwyer Tr. at 182.

Doctor Haynes' entirely conclusory three-page report never mentioned the dose of mercury Colin received. I did not find Dr. Haynes' report to be helpful in establishing a cause for Colin's ASD. Although some of the standard symptoms of mercury toxicity he listed were consistent with those reported by other witnesses and evidence, some were not. He implied that Colin was "mercury toxic," but never pointed to any evidence that Colin had symptoms consistent with such toxicity. As I cannot determine the basis for any of his opinions, I cannot assess their reliability, and thus am unwilling to give them much weight in a causation determination.

4. Doctor Leventhal.

Doctor Leventhal, respondent's specific causation expert, opined that Colin's TCVs did not cause or contribute to his autism.[735] Dwyer Tr. at 222. Although Colin experienced a loss of skills at certain points in his development, it was not a sudden regression.[736] Dwyer Tr. at 225. Based on the data he had examined, he did not think that regression was a separate phenotype.[737] Dwyer Tr. at 254-55.

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[735] As Colin had not been evaluated by the standard diagnostic instruments, the ADI and ADOS, Dr. Leventhal opined that the autism diagnosis was highly likely, but not definitive. Dwyer Tr. at 223.

[736] Doctor Leventhal indicated that he did not use the term "regressive autism" in his practice. Dwyer Tr. at 225.

[737] Consistent with the evidence in the general causation case, Dr. Leventhal testified that most children with autism experience some loss of skills. Dwyer Tr. at 256-57. He called the cases in which there is no prior abnormality "exceedingly rare" and the general view is that they are more a defect in

Doctor Leventhal testified that the record in Colin's case was not adequate to determine whether his development was completely normal prior to his regression, but his language development was not normal at 20 months of age. Dwyer Tr. at 263, 268. He noted Colin's relative decline in weight from the 50th percentile at his six-month check-up on May 27, 1999, dropping to the 25th percentile by his one year visit, and indicated that children with ASD tend to be picky eaters as early as four to nine months of age. Dwyer Tr. at 226; Res. Ex. CC at 2; Pet. Ex. 1, pp. 70, 74, 81. He considered this to be some evidence of emerging ASD, but declined to call it a definitive symptom. Dwyer Tr. at 264.

As for the testing that Dr. Mumper relied upon, Dr. Leventhal would not have ordered most of the tests. Even in the case of abnormal laboratory findings, the findings have to be correlated with a clinical finding in the patient in order to have relevance. Dwyer Tr. at 235. Laboratory values have to be considered in context. Dwyer Tr. at 238-39. He disagreed with Dr. Mumper that Colin's testing indicated that Colin had oxidative stress, neuroinflammation, methylation abnormalities, increased body burden of mercury, or heavy metal toxicity. Report of Dr. Leventhal, Res. Ex. CC, at 7. He called her conclusions "not supported by the record." *Id*. Direct evidence of neuroinflammation could be obtained by lumbar puncture if the clinical picture warranted testing. If he thought a child had brain inflammation, he would not rely upon peripheral blood markers. Dwyer Tr. at 236-37.[738]

Doctor Leventhal testified that autism is not entirely genetic, and that environmental factors contribute to the appearance of autistic symptoms. Dwyer Tr. at 246. Currently, only 1-2% of the children he has diagnosed with autism have a known, identifiable genetic cause. Dwyer Tr. at 249. Although there may be environmental contributions to ASD, TCVs have been carefully examined as possible contributors, and there is no evidence that they contribute to ASD. Dwyer Tr. at 285.

H. Evaluation of Specific Causation Experts and Their Opinions.

Both Drs. Mumper and Leventhal have significant experience in evaluating and treating children with ASDs. On the whole, Dr. Leventhal was better qualified to opine on ASD's causes than Dr. Mumper, given his more pertinent academic qualifications (he is a psychiatrist; Dr. Mumper is a pediatrician) and the nature of their practices (Dr.

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taking an appropriate history or an inability to measure problems in preverbal children. Dwyer Tr. at 258-59. In this, he disagreed with Dr. Rust, who testified that he was unable to find prior abnormal development in about 20% of the children he evaluated. *See* Tr. at 2388. In Dr. Leventhal's current experience, he could not find evidence of prior abnormal development in about 10% of cases, and, even in those, he assumed a failure to find the prior abnormality rather than one not existing. *See* Dwyer Tr. at 260-61.

[738] Doctor Rust also commented on the quality of the laboratories performing testing on children with ASD: "[T]he tendency has been for these laboratories to be sought out by a particular cadre of physicians whose views of autism fall outside that of the general medical community." Res. Ex. W at 7.

Leventhal practices at an autism center of excellence; Dr. Mumper at a pediatrics practice with a half-time focus on children with ASD and other developmental problems). I considered Dr. Mumper's experience with the Autism Research Institute in assessing her qualifications, but the amount of research it actually conducts is difficult to determine. The one publication filed (the 2005 ARI Monograph, PML 9) did not appear to be of high quality and there was no indication of peer review. *See* Section VI.D.2.d. In contrast, Dr. Leventhal was a co-author of one of the standard diagnostic instruments used in assessing children with ASD, and is involved in numerous other research projects in such fields as genetics and epidemiology.

Doctor Mumper's willingness to rely on testing she considered of dubious reliability gave me pause, in addition to her willingness to make causal determinations based on laboratory testing not specific for ASD. Many of the test results she relied upon could be attributed to nutritional problems in a child with an extremely restricted diet. Others focused on peripheral markers that could not reflect what was happening in the brain. *See* Dwyer Tr. at 159-60. She proffered opinions on Colin's mercury levels based on tests showing an absence of mercury in the presence of chelation, and opined that the one positive test result was extremely elevated without any reliable basis to do so.

On the other hand, some aspects of Dr. Leventhal's testimony suggested that he required scientific certainty, rather than a preponderance of the evidence, in order to opine in favor of causation. For example, he was unwilling to associate causally some prenatal exposures with ASD, although other of respondent's experts were of the opinion that a causal association was probable.[739] His summary dismissal of Dr. Rust, a highly qualified neurologist with significant experience in diagnosing and treating ASD, as "probably...a pediatrician" was also troubling. *See* Dwyer Tr. at 261.

On the whole, however, I found Dr. Leventhal's testimony more reliable and grounded in science than that of Dr. Mumper. Having conducted little to no research herself, Dr. Mumper relied on the opinion of Dr. Aposhian regarding mercury efflux disorders in ASD. I rejected that opinion in Section VI. She relied on Dr. Deth's opinions regarding sulfur metabolism and oxidative stress. However, even if the test results upon which she based her opinion regarding Colin's sulfur metabolism and level of oxidative stress are accurate and reliable, they say little about mercury as a causal

[739] He did not believe a causal relationship between prenatal thalidomide exposure and autism had been demonstrated (Dwyer Tr. at 247), although Dr. Rodier and others of respondent's experts opined that one was likely. He did not think a causal link between maternal rubella and autism had been demonstrated, although he noted that there was an "association" between the two. Dwyer Tr. at 248-49. With regard to terbutaline, he appeared to share the opinion of Dr. Rodier that no causal association had been demonstrated. Dwyer Tr. at 247-48.

factor.[740] Children with many diseases and disorders display markers of oxidative stress. Diet alone is a significant confounder of plasma levels of the oxidative biomarkers upon which Dr. Mumper relied, and she acknowledged that diet could skew these results. She relied on Dr. Kinsbourne's opinion about neuroinflammation in ASD (*see* Tr. at 1228-29), and tried to tie Colin's neurofilament test results to that opinion, but those results were performed by an unreliable laboratory. Furthermore, Dr. Kinsbourne did not suggest that neurofilament testing would be helpful or useful in detecting neuroinflammation. Most significantly, even if Colin had some degree of neuroinflammation, which the Vargas study, PML 69, would suggest is likely in those with ASD, neuroinflammation is so nonspecific that it would be of little evidentiary value to establish that mercury was its cause.

Doctor Mumper's willingness to rely on Colin's mercury test results as evidence of high levels of mercury in his body was particularly troubling. She admitted that his results were not typical of those she saw in other autistic children. She admitted that she knew of no research into normal mercury excretion levels after chelation against which Colin's one positive mercury test could be measured.[741] It appeared that regardless of the results for mercury levels, Dr. Mumper was willing to opine that they reflected mercury's role in ASD. If levels were low, it was because the child had excretion difficulties even in response to chelation or was hypersusceptible to the low level of mercury present. If the levels were high, then the child was retaining mercury, demonstrating excretion difficulties, and thus had more mercury available to cause neuroinflammation. Thus, either the presence or the absence of mercury in test results in a child with ASD could be interpreted as "proof" of a mercury excretion problem. Finally, because Colin did not appear to be exposed to mercury on any continuing basis from diet and was not breast fed, he likely had a lower level of mercury in his system than other children. Thus, his TCV exposure would not be likely to "tip him over the edge."

I. Applying *Althen.*

The burden on the petitioners in Colin's specific case is to demonstrate by preponderant evidence that Colin's ASD was caused by his vaccines. They asserted that the thimerosal component of those vaccines either caused or substantially contributed to his ASD. To meet their burden under *Althen*, petitioners must demonstrate by preponderant evidence "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the

[740] In this regard, I note that Dr. Mumper never mentioned Dr. Bock's use of methylcobalamin to treat Colin. According to Dr. Deth's hypothesis and experiments (*see supra* note 64 regarding Dr. Deth's research grant from ARI related to methylcobalamin; *see generally* Section VII.D.4), mercury adversely impacts methylcobalamin levels, but Colin was not responsive to methylcobalamin replacement.

[741] Doctor Mumper testified that there were no data that reflected mercury excretion patterns in children post-chelation. Tr. at 202.

vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Althen v. Sec'y, HHS*, 418 F.3d 1274, 1278 (Fed. Cir. 2005).

In their post-hearing brief, petitioners acknowledged their burden to establish each of *Althen*'s three factors by a preponderance of the evidence. Pet. Post-Hearing Br. at 78. Petitioners correctly noted that scientific certainty regarding causation is not required by the Vaccine Act, and that circumstantial evidence showing that a vaccine was a preponderant cause is sufficient. Pet. Post-Hearing Br. at 78. Petitioners framed *Althen*'s first prong as requiring them to demonstrate that the immunizations in question *can* cause the type of injury at issue, and the second prong as "addressing the question of whether the particular vaccines *did* cause the particular condition at issue." Pet. Post-Hearing Br. at 78.

1. Medical Theory.

Evaluating petitioners' medical theory is complicated by the many links in the chain of causation hypothesized. Some of the links are not reasonably subject to dispute, others are partially correct, and still others are just plain wrong. Concisely stated, their hypothesis is that Colin's "neurodevelopmental injuries are the result of a neuroinflammatory process triggered by inorganic mercury...deposited in [his] brain[] as a byproduct of exposure to TCVs in the first two years months [sic] of life." Pet. Post-Hearing Br. at 12. The inorganic mercury triggered neuroinflammation, characterized by the activation of the brain's innate immune system. This neuroinflammation produced two interrelated effects. First, it created an environment of oxidative stress in the brain, "with a complex cycle of impaired and disrupted biochemical processes that interfered with brain function." Pet. Post-Hearing Br. at 12 (Dr. Deth's hypothesis). Second, it produced an excess of glutamate, the primary excitatory neurotransmitter in the brain, leading to a persistent state of overexcitation or overarousal. Pet. Post-Hearing Br. at 12 (Dr. Kinsbourne's hypothesis).

Petitioners asserted that exposure to vaccines leads to an accumulation of "toxic" mercury in the brain. Pet. Post-Hearing Br. at 17. They asserted that inorganic mercury can cause neuroinflammation, which can disrupt neuronal functioning, leading to an excitatory-inhibitory imbalance, which is amplified by mercury-induced oxidative stress. *See* Pet. Post-Hearing Br. at 24, 33, 40-44. This imbalance manifested in the development of other symptoms of ASD in a genetically susceptible child. Pet. Post-Hearing Br. at 42, 54-58.

As the recitation and discussion of the evidence in Sections VI-VIII above demonstrate, petitioners failed to establish that their medical theory was probable, plausible, or reliable. They failed to produce sufficient reliable evidence to show that TCVs, either alone or in combination with other environmental mercury exposure, were a cause of ASD in children susceptible or vulnerable to such exposure. They failed to produce sufficient reliable evidence to demonstrate that TCVs, either alone or in

combination with other environmental mercury exposure, can produce mercury levels capable of causing neuroinflammation. Thus, they failed to show that TCVs belong on the list of potential causes of ASD.

They framed the general causation question in terms of regression. "Can TCVs in general be a substantial factor in causing autistic regression in some susceptible or vulnerable number of children?" Pet. Post-Hearing Br. at 78. Petitioners relied on the general causation evidence "to establish by a preponderance of the evidence that TCVs could have been substantial contributing causes of [the] autistic regression[]" in Colin's case. Pet. Post-Hearing Br. at 14. In making this argument, they appeared to distinguish Colin from other autistic children without loss of skills. *See* Pet. Post-Hearing Br. at 12 ("As a result of the impairment and disruption of brain function caused by TCV-induced neuroinflammation, each boy [referring to the three Theory 2 vaccinees] suffered a regression in his development, characterized by the loss of previously acquired skills"). Although they claimed that they were not seeking to show that regression is a separate diagnostic category or syndrome (*see* Pet. Post-Hearing Br. at 51), they relied on Colin's regression as a evidence of an environmental trigger or "second hit" demonstrating the effect of TCVs on a genetically susceptible child. Although petitioners argued that "none of the epidemiology addresses autistic regression of the sort these three boys experienced," they did not explicitly state that Colin experienced the "clearly regressive autism" about which Dr. Greenland testified. Pet. Post-Hearing Br. at 13.

Petitioners correctly asserted that they have no burden to present epidemiologic evidence demonstrating an association between ASD and TCVs, calling such evidence "scant, at best." Pet. Post-Hearing Br. at 13. The testimony of their own epidemiologist was even stronger. Doctor Greenland testified that he did not find the only studies purporting to show an increased risk of autism associated with TCVs–studies by Dr. and Mr. Geier–to be of evidentiary value. Tr. at 122-23.

While certain subpoints of their causation hypothesis–their medical theory–were clearly established or uncontested, most were not. Although they called their evidence "robust and reliable" and claimed that a *prima facie* case for causation in general had been established (*see* Pet. Post-Hearing Br. at 81), I have concluded otherwise.

Althen requires more than merely asserting a medical theory. Petitioners must offer a reputable medical theory, and inherent in that standard is a requirement that the theory be biologically plausible. *See Walther*, 485 F.3d at 1148 and *Pafford*, 451 F.3d at 1355-56 (petitioner's theory must be reputable). The theory of TCV causation is simply not reliable, and can no longer be considered "biologically plausible,"[742] in view of

[742] The IOM did use the term "biologically plausible" in referring to the TCV-ASD hypothesis in 2001, but what it meant by the term was something other than a reputable and reliable theory. *See* IOM 2001 Report, RML 254, at 83. By 2004, in view of the additional evidence accumulated in the intervening three years, the IOM rejected the hypothesis in the strongest terms available to it. IOM 2004 Report, RML

all that is known about mercury in the brain.

2. Logical Sequence of Cause and Effect.

Petitioners equated *Althen*'s second prong to establishing whether causation had been shown in Colin's specific case. Pet. Post-Hearing Br. at 78-79. They argued that "ample indirect and circumstantial evidence" established that Colin's TCVs caused neuroinflammation that caused his ASD. *Id.* at 81. Even if Dr. Leventhal applied a heightened evidentiary standard to determining causation in Colin's specific case, I have not. At best, the evidence established that Colin received vaccines that probably contained thimerosal and that he had a diagnosis of ASD. No sequence of cause and effect between the two can be logical, in view of the conclusion that petitioners have failed to establish a causal connection in general between ASD and TCVs.

Furthermore, Dr. Mumper's causal opinion is based, in large part if not in its entirety, on the opinions of Drs. Kinsbourne, Deth, and Aposhian, whose opinions I have rejected as scientifically implausible and unsound. Notwithstanding this defect, the specific factors she cited as important in Colin's case largely concerned testing performed by laboratories with questionable reliability. Many of the laboratory tests upon which she relied are not tests appearing in standard laboratory manuals or tests that would even be ordered by most practitioners, and the data they provide are not diagnostic of ASD. Treatments designed to target the "problems" noted in Colin's test results were not efficacious, either in the view of Colin's parents or in the view of Colin's subsequent treating physician.[743]

In their post-hearing brief, petitioners appear to acknowledge the problematic nature of Colin's test results. Although Dr. Mumper testified about a number of test results that contributed to her opinion that Colin's ASD was caused by his TCVs, in their post-hearing brief they only mentioned a "latent, genetic inabilit[y] to properly metabolize and excrete mercury." Pet. Post-Hearing Br. at 82. Colin's only positive mercury test occurred after chelation, and its results were not measured against any standardized normal values. In spite of numerous other rounds of chelation with a variety of chemical and "natural" chelators, no detectible levels of mercury were ever again excreted. This result is not compatible with a child with problems metabolizing and excreting mercury.

Petitioners' causation claim is unaffected by Dr. Greenland's opinion that the existing epidemiological studies of ASD cannot detect a causal connection with TCVs on a small subgroup. The hypothetical subgroup he described involved regression after previously normal development. Contrary to petitioners' assertions (*see* Pet. Post-

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255, at 3,7; *see also* Tr. at 3080.

[743] This comment should not be interpreted as concluding that Dr. Russell's testing and treatment regimen was any better at addressing Colin's ASD, although some of the drug therapies may have been effective in addressing specific components of his behavior.

Hearing Br. at 81), Colin was not developmentally normal at the time he received his last TCV. Colin's ASD had already begun to manifest by the time he was 20 months of age. Thus, Dr. Greenland's opinion that the epidemiological studies of ASD cannot rule out an effect on a small subgroup of children is irrelevant to Colin's case.

Ruling out known causes of ASD, as Dr. Mumper did in her report and testimony, is not sufficient to put TCVs on the list of possible causes. "Although probative . . . a simplistic elimination of other potential causes" is insufficient to show actual causation. *Moberly* 592 F.3d at 1323 (citing *Althen*, 418 F.3d at 1278); *see also Ruggiero v. Warner-Lambert Co.*, 424 F.3d 249, 254 (2d Cir. 2005) (using differential diagnosis to eliminate other causes is insufficient to demonstrate causation). Thus, the process of differential diagnosis cannot be applied to conclude that Colin's ASD must have been caused by TCVs, once other causes are ruled out. A differential diagnosis is only as good as the list of possible causes.

3. A Proximate Temporal Relationship.

Onset after vaccination is not enough, standing alone, to satisfy *Althen*'s third prong. Petitioners have the burden to demonstrate the existence of a "scientific temporal relationship." *Pafford v. Sec'y, HHS*, 64 Fed. Cl. 19, 29-30 (2005), *aff'd*, 451 F.3d 1352 (Fed. Cir. 2006). The time frame must be medically acceptable. *De Bazan* 539 at 1352.

Petitioners did not address this prong of the *Althen* standard in their briefs and this omission is a significant flaw. The failure to show that a disease arose in the time expected by the medical community means a petitioner is not entitled to compensation. *Pafford*, 451 F.3d at 1358-60. It is clear that Colin's ASD manifested with speech delay at or before 20 months of age, before he received his last round of vaccinations. At that point in his life, he had already received vaccines containing as much as 212.5 µg of ethylmercury. However, none of petitioners' experts opined on the time frame in which mercury must be received in order to cause autism in a developing brain. The weight of the evidence was that ASD's origins are largely prenatal, and thus any environmental insult contributing to its largely genetic cause must have occurred prenatally. Respondent's experts indicated that if post-natal causes played any role in the many neuropathological differences found in individuals with ASD, they must occur very early in the post-natal period, but the experts did not think postnatal causes were likely or probable.

At best, petitioners have demonstrated that Colin's ASD manifested after most of his vaccinations. That would be true of any child with this condition who had received vaccines, because ASD cannot be reliably diagnosed until at least one year of age, even if subtle indicators may have existed earlier. Most ASD symptoms become apparent to parents at 18-24 months of age, and thus onset will follow vaccinations in almost every child with ASD.

4. No Burden on Respondent to Establish an Alternate Cause.

Petitioners have failed to establish any of *Althen*'s three factors. Thus, they have failed to establish that Colin's vaccines were a substantial cause of his injury. Because they have failed to establish causation by a preponderance of the evidence, the burden never shifted to respondent to establish an alternative cause for Colin's condition. *De Bazan*, 539 F.3d at 1353-54.

5. Summary.

In concluding that petitioners have failed to establish that Colin's TCVs caused his ASD, I emphasize that I have not applied a heightened evidentiary burden. I did not require scientific certainty, nor direct evidence of causation. *Daubert* requires that an opinion be supported by something more than subjective belief; it must be grounded in "the methods and procedures of science." 509 U.S. at 590. There is no evidence that mercury has ever caused an ASD, only speculation that it might. At best, there is some evidence of an ongoing inflammatory process in ASD, but no indication that it is caused by mercury, and many indications that it is not. The excitation-inhibition theory is likewise unsupported in the peer reviewed medical literature; at best, there is some speculation that some ASD symptoms may be a reflection of an excitatory-inhibitory imbalance, but no proof of any biological overarousal when the symptoms are observed.

Scientists use the terms "hypothesis" and "theory" with very specific meanings. A hypothesis is an idea proffered to explain an event. A theory is what is developed after a hypothesis has been subjected to many attempts to disprove it, and thus, it is likely correct.[744] This is an important distinction, because in biology, almost anything is possible. The pertinent question is whether something is probable or likely. Petitioners had several hypotheses but nothing that approached a theory. As Dr. Rust commented: "Hypotheses are a dime a dozen." Tr. at 2373.

A number of governmental and non-governmental scientific agencies have looked at the issue of a relationship between TCVs and ASD. These agencies include the National Academy of Sciences, Institute of Medicine, American College of Medical Toxicology, American Academy of Pediatrics, World Health Organization, U.S. Center for Disease Control and Prevention, the European Medicine Agency, and the American Academy of Family Practice. Tr. at 1857-58; *see also* Res. Tr. Ex. 4, slide 47. They have all concluded that there is no causal connection between the two.

Unfortunately, the Dwyers (and uncounted other parents of children with ASD) have relied upon practitioners and researchers who peddled hope, not opinions grounded in science and medicine. My heart goes out to parents like the Dwyers who

[744] *See* Tr. at 1978-80, 4314-15.

struggle daily, emotionally and financially, to care for their children, but I must decide cases based on the law and not sentiment. The law in this case requires preponderant evidence that TCVs caused or substantially contributed to Colin's ASD, and, by that standard, petitioners are not entitled to compensation.

Section XI. Conclusion.

Petitioners have not demonstrated by a preponderance of the evidence that Colin's condition was either caused or significantly aggravated by his vaccinations. Thus, they have failed to establish entitlement to compensation and the petition for compensation is therefore DENIED. In the absence of a motion for review filed pursuant to RCFC, Appendix B, the clerk is directed to enter judgment accordingly. [745]

IT IS SO ORDERED.

s/Denise K. Vowell
Denise K. Vowell
Special Master

[745] Pursuant to Vaccine Rule 11(a), entry of judgment can be expedited by each party's filing a notice renouncing the right to seek review.