

Respondent's Exhibit EE

STATEMENT OF PATRICIA M. RODIER, PH.D.

A. QUALIFICATIONS

1. I am a medical research scientist. I focus on injuries to developing nervous systems. I currently hold the position of Professor of Obstetrics and Gynecology in the School of Medicine and Dentistry at the University of Rochester, in Rochester, New York.
2. I obtained my Doctorate in Experimental Psychology at the University of Virginia in 1970, and conducted post-doctoral research in embryology at the University of Virginia from 1971-1973. My research concerned the role of the timing of injuries to developing brain in determining the resulting abnormalities of brain morphology and function.
3. I am a member of several professional societies, and have served as President of the Behavioral Teratology Society and on the Governing Council of the Teratology Society. Teratology is the branch of embryology and toxicology that deals with abnormal development and congenital malformations of humans and animals. This discipline includes the identification and isolation of teratogens (substances that can cause abnormal development and/or malformations in the offspring if a pregnant female is exposed to them at certain vulnerable periods in pregnancy).
4. I have served on the US Food and Drug Administration's Food Science Advisory Board, the National Toxicology Program Board of Scientific Advisors, and the National Research Committee on Neurotoxicology and Risk Assessment. Currently, I am the Director of both the National Institutes of Health [NIH] Collaborative Program of Excellence in Autism, and the National Institutes of Health STAART Center at the University of Rochester. "STAART" is the acronym for the NIH's Autism Research Centers of Excellence, 'Studies to Advance Autism Research and Treatment'.
5. I have published over 50 articles on a variety of topics related to brain damage in general and autism in particular in many peer-reviewed scientific journals, including

Pediatrics, Environmental Health Perspectives, Teratology, Neurotoxicology and Teratology, Developmental Brain Research and The Journal of Comparative Neurology.

6. A copy of my current *curriculum vitae* is attached to this statement.

B. PURPOSE OF STATEMENT

7. This statement responds to the allegation that children have been injured by the ethylmercury content of thimerosal, a preservative contained in many products administered to infants and children, and that exposure to thimerosal via vaccinations leads to pervasive developmental disorders, including autism. I refer in this statement to this hypothesis as "the allegation". I shall use PDD and autism interchangeably in this document.

8. As a research scientist who has studied both the toxic effects of methylmercury in animals, and autism in children and animal models, I believe I am qualified to evaluate the scientific merit of the allegation.

9. My conclusion is that the allegation has no scientific support and is highly improbable.

C. DATA ON WHICH MY CONCLUSIONS ARE BASED

Because I am one of several scientists testifying for the respondent in this case, I am restricting my comments to the areas in which my expertise is greatest. These are a) the symptoms of ethylmercury poisoning versus those of autism b) the stage of brain development when autism is thought to arise, as determined from the known environmental risk factors c) the stage of brain development when autism is thought to arise, as determined from histological studies of the brains of people with autism d) the stage of brain development when autism is thought to arise, as determined from craniofacial anomalies observed in children with autism and other pervasive developmental disorders.

a) **The symptoms of ethylmercury poisoning are different from the symptoms of autism**

10. Bernard, Enayati, Redwood, Roger, and Binstock (2001), have posited that postnatal exposure to ethylmercury in thimerosal-containing vaccines causes autism. The authors claim that the symptoms of autism are also those of "mercury poisoning". This claim is unsupportable. First, experts on autism have pointed out that the "symptoms" of autism used by the authors to find parallels to symptoms of "mercury" poisoning are not the characteristic symptoms used to diagnose the disorder, but include a long list of "symptoms" that occur in all children (e.g., nausea and vomiting, irritability, temper tantrums), or occur in other conditions as well as in some cases of autism (e.g., mental retardation, articulation problems, abnormal gait and posture), (see Nelson and Bauman, 2003).

11. Second, the "symptoms" listed as those of "mercury" poisoning are drawn almost exclusively from reports of pre- or postnatal poisoning with mercury vapor, inorganic mercury, and methylmercury without regard to the fact that no such symptoms have ever been reported for ethylmercury exposure. The most common symptoms of ethylmercury poisoning are muscle weakness, loss of appetite, and dizziness (Zhang, 1984). In fact, of the 35 symptoms of ethylmercury poisoning described by Zhang from a sample of 41 cases, not a single one is even vaguely related to the core symptoms of autism.

12. Third, the paper in *Medical Hypotheses* (an un-refereed journal) repeatedly equates symptoms that are totally unrelated. For example, under Psychiatric disturbances, Bernard et al.(2001) group together "depression, mood swings, flat affect, and impaired face recognition." In fact, the first two symptoms do occur in poisoning by inorganic mercury and mercury vapor, respectively, and the last two are seen in many children with ASDs. However, mood swings and flat affect are not similar symptoms but opposite symptoms, and there is no reason to think that problems with face recognition are related to abnormalities of mood. Further, there are no published studies of facial recognition after exposure to mercury in any of its forms. There are many other examples of this kind of loose interpretation throughout the paper.

13. Little is known about what signs and symptoms might be induced by prenatal exposure to ethylmercury. We do know, however, that postnatal exposure to

ethylmercury, which is claimed to be the cause of autism in this allegation, does not produce the stigmata of autism (Zhang, 1984). The thimerosal–vaccine hypothesis gets around this problem by proposing that some subset of children responds to ethylmercury exposure in a way never before described (thus, the title of the paper, “A novel form of mercury poisoning”). In other words, because the symptoms of ethylmercury poisoning are not similar to those of autism, the authors have tried to construct a new, hypothetical kind of mercury poisoning from symptoms of toxicity of other mercury species and symptoms never reported for any kind of mercury exposure. The hypothesis is not based on facts; instead, the facts are being selected, manipulated, and shaped to fit the hypothesis. The hypothesis is then offered as evidence. But hypotheses are not evidence.

b) The known environmental risk factors for autism all act in the first trimester of pregnancy

14. Epidemiological studies have shown five environmental factors that are correlated with an increased risk of autism. These studies compare the rate of autism in populations exposed to the environmental factor to the rate in the population as a whole. For uniformity, I have calculated the odds ratio for each using the best available data for the population prevalence rate, which is 6.25/1000 for all Pervasive Developmental Disorders (Chakrabarti and Fombonne, 2001).

- Rubella infection of the embryo increases the risk of autism (Chess et al., 1978). The odds ratio is about 11.
- Thalidomide exposure increases the risk more than 40-fold when the injury occurs during days 20-24 post-conception (Miller, 1991; Strömmland et al., 1994).
- Valproic acid: The odds ratio for autism after embryonic exposure to valproic acid - an antiseizure medication- is about 17 (Moore et al., 2000). A more recent paper by the same group suggests that the odds ratio is more than 20 (Rasalam et al., 2005)
- Ethanol: The data for ethanol (an alcohol) exposure is based on small samples, but they suggest an odds ratio of about 20. (Aronson et al., 1997). The

increased risk is only seen in children who actually have Fetal Alcohol Syndrome (Nanson, 1992), indicating that high doses early in the first trimester are necessary for the ASD outcome.

- **Misoprostal:** The most recently-discovered risk factor is misoprostol, a prostaglandin used by poor women in South America to induce abortions. When the conceptus survives, the child frequently has birth defects consistent with an ischemic episode in the sixth week postconception. One of these anomalies is Moebius syndrome (dysfunction of the VIth and VIIIth cranial nerves) (Gonzalez et al., 1993). Moebius syndrome is known to have both teratologic and genetic etiologies, and idiopathic cases have a rate of autism of over 25% (Johansson et al., 2001). Among cases with Moebius syndrome after misoprostol exposure, the rate of autism is increased more than 40-fold (Miller and Ventura, 2001; Bandim et al. 2003).

15. Fortunately, for each of these known environmental risk factors, it is possible to determine the stage of development when exposure to them leads to autism. In the case of thalidomide, each somatic malformation caused by the drug has been linked to a critical period (reviewed in Miller and Strömland, 1999). By examining the malformations in patients with autism, the critical period was determined to be between the 20th and 24th days postconception (Strömland et al., 1994). Several of the same malformations, especially those of the ears, occur in children with autism who were exposed to valproic acid (Williams et al., 2000), thus, valproic acid must have a critical period similar to that of thalidomide for the autism outcome. In the case of misoprostol, abortions are usually attempted in the sixth week postconception, when the mother misses her second menstrual period. The timing was confirmed for all cases of autism by an interview with the mother (Miller and Ventura, 2001). Fetal Alcohol Syndrome is characterised by craniofacial anomalies that overlap with anomalies in the thalidomide and valproate cases of autism, such as epicanthic folds (e.g., Jones and Smith, 1973). Fetal Alcohol Syndrome is thought to arise from exposure during the third to fifth week postconception (Sulik et al., 1986). The epidemiological sample used to identify the increased risk for autism after rubella infection did not include data on time of onset of the rash that heralds

rubella, but the investigators did note that all the children with an autism outcome had multiple symptoms of rubella injury. (Chess and Fernandez, 1980). In a study specifically designed to identify the critical periods for eye defects, deafness, mental retardation, and heart malformations after rubella exposure, Ueda et al. (1979) found that cases with multiple symptoms came mainly from those exposed within the first eight weeks post conception. The same study showed that mothers whose offspring had severe mental retardation had onset of rash in the second to fifth week post-conception. Thus, for all the known environmental risk factors for autism, the critical period is in the first trimester of pregnancy.

16. The early critical periods (the windows of time during which exposure may have consequences) for known environmental risk factors do not prove that autism cannot arise at other times in development. However, the fact that all known environmental risk factors for autism have critical periods early in the first trimester of pregnancy strongly suggests that the period of vulnerability for development of autism is some time during the first trimester of pregnancy. In my opinion, it is therefore improbable that postnatal environmental risks contribute to autism. It is much more likely that other environmental risks, when identified, will be ones that affect embryonic development of the nervous system in the first trimester.

c) Histology of brains of people with autism suggests that the disorder arises in the embryonic period

17. The histology of an injured brain can often provide evidence relevant to the stage of development when the injury occurred. For example, in Rodier, et al., 1996, the brain of a young woman diagnosed with autism is described and pictured. One of the unusual characteristics of this brain was a striking reduction in the number of neurons in the facial nucleus, the cluster of neurons in the brain that control the muscles of facial expression. Did this deficiency arise in the early embryo, around the time when these neurons were born, or might the neurons have formed in normal numbers but died later in life? The comparison of the brain of a control with the brain of the person with autism answers this question. In the control, the area of the large facial nucleus is outlined by many dark-

staining fibers of tracts going up or down the brain stem. In contrast, the tissue of the nucleus, itself, is pale. It is typical in the nervous system that later-forming pathways respect the boundaries of previously-existing structures. In contrast, the abnormal facial nucleus is not only deficient in neuron numbers, but it has no capsule of passing fibers. Instead, bundles of fibers are seen to pass through the area where the nucleus should be. This indicates that the nucleus never existed in this space. That is to say, this loss of neurons occurred in the early embryo.

18. One of the characteristics observed in the histology of many brains donated for autism research is a reduction in the number of Purkinje cells in the cerebellum (Ritvo et al., 1984; Bauman and Kemper, 1985; Bailey et al., 1998). It is known that loss of Purkinje cells in the third trimester or in postnatal life causes a subsequent, corresponding loss of neurons in the inferior olive, one of the nuclei that sends its axons into the cerebellum (Takashima, 1982). Kemper and Bauman (1993) have pointed out that this dying back of neurons in the inferior olive does not occur in the brains of people with autism, and that this means that the missing Purkinje cells must have been absent before late pregnancy. Another phenomenon that accompanies the death of Purkinje cells long after their formation is called "empty baskets". Basket cells are found in close proximity to Purkinje cells, but are born later in development. Their axons wrap around the giant cell bodies of the Purkinje cells, forming a net-like basket of fibers. If a Purkinje cell dies after being wrapped, the result is an "empty basket". Bailey examined the brains of his cases with low Purkinje cell numbers for empty baskets and found none (Bailey et al., 1998). This finding indicates that the reduction in Purkinje cell numbers occurred early in pregnancy, before the basket cells sent out their nets.

e) Craniofacial features of some cases suggest autism arises early in the embryonic period

19. Craniofacial dysmorphologies and neurological dysfunctions of the cranial nerves are common in children with autism (e.g., Steg and Rapoport, 1975, Miles and Hillman, 2000). When children with idiopathic autism (that is, autism that is not associated with one of the known environmental risk factors or with a genetic syndrome with high rates

of autism) are compared to their unaffected siblings, they have significantly higher rates of some anomalies such as low set, posteriorly rotated ears (Rodier et al., 1997). Some of the same anomalies are common in children with autism who were exposed to thalidomide or valproic acid (Strömmland et al., 1994; Williams et al., 2001). Dysmorphic conditions do not arise postnatally. They are congenital anomalies that result from disturbances during embryonic development. It is not logical to propose that a child with autism who has minor malformations evidencing injury in the embryonic period was exposed to some other injury postnatally.

D. CONCLUSION

20. The hypothesis that thimerosal in vaccines causes autism in a subset of susceptible children has been put forward on the basis that the symptoms of autism resemble those of various kinds of mercury poisoning. The similarities claimed by the authors are not convincing, and the symptoms of ethylmercury poisoning are totally unlike those of autism.

21. There is evidence that many cases of autism result from developmental disturbances early in the first trimester of pregnancy, and no evidence of any kind to support a postnatal origin. It is unscientific and illogical to accord any merit to an hypothesis for which there are no supporting data and many lines of negative data. There is no way to stretch or tweak this hypothesis to fit the biological facts.

22. The Institute of Medicine has concluded that "the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism." (IOM, 2004). In addition, they took the unusual step of recommending that future autism research should focus on topics more promising than this one. In reaching those conclusions, they cited many of the points included in this statement. The most direct evidence against the hypothesis is a number of large epidemiological studies that found no association between thimerosal-containing vaccines and autism. Two recent epidemiological studies, which were not available to the IOM in 2004, reinforce the same conclusion (Thompson et al., 2007; Schechter and Grether, 2008). Those are not discussed here because they fall

outside my area of expertise. I mention them because they are new examples of scientific evidence that cannot be interpreted to fit the thimerosal hypothesis.

23. My conclusion is that there is no evidence to support the plaintiffs' allegation, and much evidence against it. As a scientist I have no choice but to agree with the IOM that this hypothesis must be rejected.

Fabricia M. Radwin 02/21/08

E. LITERATURE CITED

Aronson M, Hagberg B, Gillberg C (1997) Attention deficits and autism spectrum problems in children exposed to alcohol during gestation: A follow-up study. *Developmental Medicine and Child Neurology* 39: 583-87.

Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, Rutter M, Lantos, P. (1998) A clinicopathological study of autism. *Brain* 121, 889-905.

Bandim JM, Ventura LO, Miller MT, Almeida HC, Costa AE (2003) Autism and Mobius sequence: an exploratory study of children in northeastern Brazil. *Arquivos de Neuro-Psiquiatria*, 61(2A):181-5.

Bernard S, Enayati A, Redwood L, Roger II, Binstock T (2001) Autism: a novel form of mercury poisoning. *Medical Hypotheses*. 56:462-71.

Chakrabarti S, Fombonne E (2001) Pervasive developmental disorders in preschool children. *JAMA*. 285:3093-3099.

Chess S, Fernandez P (1980) Neurologic damage and behavior disorder in rubella children. *American Annals of Deafness*, 125: 998-1001.

Chess S, Fernandez P, Kor S (1978) Behavioral consequences of congenital rubella. *Journal of Pediatrics*, 9: 699-703.

Gonzalez CII, Vargas FR, Perez ABA, et al. (1993) Limb deficiency with or without Mobius sequence in seven Brazilian children associated with misoprostol use in the first trimester of pregnancy. *American Journal of Medical Genetics*, 47: 59-64.

Institute of Medicine (2004) Immunization Safety Review: Vaccines and Autism. The National Academies Press.

Johansson M, Wentz E, Fernell E, Strömland K, Miller MT, Gillberg C. (2001) Autistic spectrum disorder in Mobius sequence: a comprehensive study of 25 individuals. *Developmental Medicine Child Neurology*, 43:338-345.

- Jones KL, Smith DW (1973) Recognition of the fetal alcohol syndrome in early infancy. *Lancet*, 2:999-1001.
- Kemper TL, Bauman ML (1993) The contribution of neuropathologic studies to the understanding of autism. *Neurology Clinics*, 11(1), 175-187.
- Miller MT (1991) Thalidomide embryopathy: a model for the study of congenital incomitant horizontal strabismus. *Transactions of the American Ophthalmological Society*, 89: 623-74.
- Miller MT, Strömland K (1999) Teratogen update: Thalidomide: A review with a focus on ocular findings and new potential uses. *Teratology*, 60:306-321.
- Miller MT, Ventura L (2001) Moebius syndrome/sequence: a summary of a Brazil study. *Teratology* 63:260.
- Miles JI, Hillman RE (2000) Value of a clinical morphology examination in autism. *American Journal of Medical Genetics*, 91(4): 245-53.
- Moore SJ, Turnpenny P, Quinn A, Glover S, Lloyd DJ, Montgomery T, Dean JCS (2000). A clinical study of 57 children with fetal anticonvulsant syndrome. *Journal of Medical Genetics* 37: 489-97.
- Nanson JL (1992) Autism in fetal alcohol syndrome: A report of six cases. *Alcohol Clinical and Experimental Research*, 16:558-565.
- Nelson KB, Bauman ML (2003) thimerosal and autism? *Pediatrics*, 111:674-679.
- Rasalam AD, Hailey H, Williams JH, Moore SJ, Turnpenny PD, Lloyd DJ, et al. (2005) "Characteristics of fetal anticonvulsant syndrome associated autistic disorder." *Developmental Medicine and Child Neurology*, 47(8): 551-555.
- Ritvo ER, Freeman BJ, Scheibel AB, Duong T, Robinson H, Guthrie D, Ritvo A (1986) Lower Purkinje cell counts in the cerebella of four autistic subjects: Initial findings of the UCLA-NSAC autopsy research report. *American Journal of Psychiatry*, 146:862-866.
- Rodier PM, Bryson SE, and Welch JP (1997) Minor malformations and physical measures in autism: Data from Nova Scotia. *Teratology*, 55:319-325.
- Rodier PM, Ingram JL, Tisdale B, Nelson S, Romano J (1996) An embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei. *Journal of Comparative Neurology*, 370: 247-261.
- Schechter R, Grether JK (2008) Continuing increases in autism reported to California's Developmental Services System: Mercury in retrograde. *Archives of General Psychiatry*, 65:19-24.

- Steg JP, Rapoport JL (1975) Minor physical anomalies in normal, neurotic, learning disabled, and severely disturbed children. *Journal of Autism and Childhood Schizophrenia*, 5:299-307.
- Strömmland K, Nordin V, Miller MT, Akerstrom B, Gillberg C (1994) Autism in thalidomide embryopathy: A population study. *Developmental Medicine and Child Neurology* 36:351-356.
- Sulik KK, Johnston MC, Daft PA, Russell WF, Dehart DB (1986) Fetal alcohol syndrome and DiGeorge anomaly: critical ethanol exposure periods for craniofacial malformations as illustrated in an animal model. *American Journal of Medical Genetics, suppl 2*:97-112.
- Takashima S (1982) Olivocerebellar lesions in infants born prematurely. *Brain Development*, 4: 361-366.
- Thompson WW, Price C, Goodson B, Shay DK, Benson P, Hinrichsen VI, Lewis F, Eriksen E, Ray P, Marcy SM, Dunn J, Jackson LA, Lieu TA, Black S, Stewart G, Weintraub ES, Davis RL, DeStefano F; Vaccine Safety Datalink Team. (2007) Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. *New England Journal of Medicine*, 357:1281-92.
- Williams, PG, J. King, M. Cunningham, M. Stephan, B. Kerr, and J.H. Hersh. (2001) Fetal valproate syndrome and autism. additional evidence of an association. *Developmental Medicine and Child Neurology* 43:202-206.
- Ueda, K, Nishida, Y, Oshima, K, Shepard, TII (1979) Congenital rubella syndrome: Correlations of gestational age at time of maternal rubella with type of defect. *Journal of Pediatrics*, 94: 763-765.
- Zhang, J. (1984) Clinical observations in ethylmercury chloride poisoning. *American Journal of Industrial Medicine*, 5: 151-258.