# In the United States Court of Federal Claims

**OFFICE OF SPECIAL MASTERS**

Filed: July 10, 2017

| | | |
|---|---|---|
| CHASE BOATMON & MAURINA CUPID, *parents of* J.B., *deceased*, | * | PUBLISHED DECISION |
| | * | No. 13-611V |
| Petitioners, | * | Special Master Gowen |
| v. | * | Entitlement Decision; Diphtheria-Tetanus-acellular Pertussis (DTaP) Vaccine; Inactivated Polio Vaccine (IPV); Haemophilus Influenzae (HiB) Vaccine; Pneumococcal Conjugate (PCV) Vaccine; Rotavirus Vaccine; Sudden Infant Death Syndrome (SIDS). |
| SECRETARY OF HEALTH AND HUMAN SERVICES, | * | |
| Respondent. | * | |

Ronald C. Homer & Joseph M. Pepper, Conway, Homer P.C., Boston, MA, for petitioners. Lara A. Englund & Ryan M. Pyles, United States Department of Justice, Washington, DC, for respondent.[1]

## RULING ON ENTITLEMENT[2]

On August 27, 2013, Chase Boatmon and Maurina Cupid ("petitioners"), as the representatives of the estate of their deceased minor child, J.B., filed a petition under the National Vaccine Injury Compensation Program ("Vaccine Act" or the "Program"),[3] 42 U.S.C. § 300aa-10 *et. seq.* (2012). Petitioners allege that as a result of receiving vaccinations for

[1] Mr. Homer is petitioners' attorney of record, while his colleague Mr. Pepper appeared at the entitlement hearing. Similarly, for respondent, Ms. Englund has always been the attorney of record, but Mr. Pyles appeared at the entitlement hearing.

[2] Because this decision contains a reasoned explanation for the action in this case, the undersigned intends to post it on the website of the United States Court of Federal Claims, pursuant to the E-Government Act of 2002, *see* 44 U.S.C. § 3501 note (2012). The court's website is at http://www.uscfc.uscourts.gov/aggregator/sources/7. Before the decision is posted on the court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). "An objecting party must provide the court with a proposed redacted version of the decision." *Id.* If neither party files a motion for redaction within 14 days, the decision will be posted on the court's website. *Id.*

[3] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3705, codified as amended, 42 U.S.C. §§ 300aa-1 to -34 (2012). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

Diphtheria-Tetanus-acellular Pertussis ("DTaP"), inactivated polio ("IPV"), haemophilus influenzae ("HiB"), Pneumococcal Conjugate ("PCV"), and Rotavirus vaccinations on September 2, 2011, J.B. passed away from Sudden Infant Death Syndrome ("SIDS") on September 3, 2011. *See* Petition (ECF No. 1); Amended Petition (ECF No. 15).

After carefully analyzing and weighing all of the evidence and testimony presented in this case in accordance with the applicable legal standards, the undersigned finds that petitioners have met their legal burden. Petitioners have put forth preponderant evidence that the vaccines J.B. received on September 2, 2011 actually caused or substantially contributed to his death from Sudden Infant Death Syndrome. Furthermore, respondent has failed to put forth preponderant evidence that J.B.'s death was in fact caused by factors unrelated to the vaccines. Accordingly, petitioners are entitled to compensation.

## I. BACKGROUND

### A. Procedural History

Petitioners filed a petition for compensation pursuant to the Vaccine Act on behalf of their deceased minor son, J.B., on August 27, 2013. Petition (ECF No. 1). They filed an amended petition on February 6, 2014. Amended Petition (ECF No. 15). Petitioners filed the expert report of Dr. Douglas C. Miller, a neuropathologist, along with the medical literature referenced in his report, on May 20, 2014. Exhibit 13, 14 (ECF No. 21).[4]

On September 9, 2014, respondent filed a Rule 4(c) report advising against compensation. Rule 4(c) Report (ECF No. 28). That same day, he filed an expert report and medical literature referenced therein from Dr. Brent Harris, a pathologist. Exhibit A (ECF No. 29). Respondent also filed an expert report and medical literature from Dr. Christine T. McCusker. Exhibit C (ECF Nos. 30-32). Petitioners filed a supplemental report from Dr. Miller on November 10, 2014. Exhibit 16 (ECF No. 35). Extensive and detailed medical literature was submitted in support of all of the expert reports.[5]

At numerous stages of this case, the undersigned encouraged the parties to pursue the possibility of an informal resolution and/or to consider mediation. *See, e.g.*, Order filed December 9, 2014 (ECF No. 37). The parties ultimately did not settle the case. An entitlement hearing was held on Thursday, August 6, and Friday, August 7, 2015, in Washington, D.C. Dr. Miller testified on behalf of petitioners, and Dr. Harris and Dr. McCusker testified for respondent. The case was well tried and involved detailed expert testimony from both sides. *See*

[4] On October 14, 2014, petitioners refiled the medical literature cited in Dr. Miller's report, highlighting the specific portions being relied upon to support causation. Petitioners' Notice of Refiling Documents (ECF No. 34).

[5] I have read and digested all of the literature submitted in this case and will reference numerous but not all articles in the course of this opinion. However, all articles have been considered in coming to a conclusion in this case. More recent articles, particularly those by the same authors or groups, are referenced more frequently because they incorporate, build upon, and update the earlier literature. Petitioners and Dr. Miller filed Exhibits 13-A through 13-V and Exhibits 14 through 21. Respondent and Dr. Harris filed Exhibits A-1 through A-6. Respondent and Dr. McCusker submitted Exhibits C-1 through C-20 and Exhibits D through G.

Transcript filed on September 9, 2015 (ECF Nos. 50, 52). Petitioners filed their post-hearing brief on December 7, 2015. (ECF No. 61). Respondent filed his post-hearing brief on March 7, 2016. (ECF No. 63). Petitioners filed their reply to respondent's post-hearing brief on March 28, 2016. (ECF No. 64). This matter is now ripe for adjudication.

### B. Standards for Adjudication

The Vaccine Act established the Program to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Rooks v. Sec'y of Health & Human Servs.*, 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

There are two avenues to compensation under the Program. The first is to demonstrate a "Table injury," that is, a specified injury within a specified period of time following administration of a vaccine listed on the Vaccine Injury Table. § 300aa-14(a). A Table injury creates a presumption of causation, which is only defeated if respondent shows that the injury was caused by a factor or factors unrelated to the vaccine. In the present case, petitioners allege that J.B. died suddenly of a cause that remained unexplained after a site investigation and autopsy, often referred to as SIDS, shortly after receiving various vaccines listed on the Table. The Table does not list SIDS occurring in any period of time after any vaccine.

Therefore, petitioners must take the second avenue towards compensation: they must establish an "off-Table injury," meaning that the vaccine(s) were the cause in fact of the vaccinee's injuries. In *Althen*, the Federal Circuit established a three-prong test: petitioners must establish (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. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005).

The legal standard is by a preponderance of the evidence." §300aa-13(a)(1)(a). This does not require "conclusive scientific evidence" or "certainty." *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1322 (Fed. Cir. 2010). Instead, the standard has been interpreted to mean that a fact is more likely than not. *Id.* at 1322 n.2. The Federal Circuit has observed that this preponderance standard enables "the finding of causation in a field bereft of complete and direct proof of how the vaccines affect the human body." *Althen*, 418 F.3d at 1280. Petitioners must establish each *Althen* prong by the preponderance of the evidence. *Caves v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 119, 132 (2011), *aff. per curiam*, 463 Fed. Appx. 932 (Fed. Cir. 2012).

Each *Althen* prong may be satisfied by medical records or a medical opinion. *Althen*, 418 F.3d at 1279; *see also Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006) (noting that the same piece of evidence can support several *Althen* prongs). Petitioners are not required to provide "objective confirmation" by way of "medical

documentation." *Id.* at 1278. Such a requirement would "contravene the plain language of the statute." *Id.* at 1281.

In determining whether a petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating that a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Thus, a special master must weigh and evaluate opposing expert opinions, medical and scientific evidence, and the evidentiary record in deciding whether petitioners have met their burden of proof.

Epidemiological studies, or the lack thereof, are not dispositive of the causation in fact determination. *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1149 (Fed. Cir. 1992). Indeed, petitioners are not required to present medical literature or epidemiological evidence to establish any *Althen* prong. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009). However, the special master can consider [epidemiological evidence] in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury…. Medical literature and epidemiological evidence must be viewed… not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu*, 569 F.3d at 1380.

Under the second *Althen* prong, petitioners need to show that the vaccine(s) was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999). They do not need to show that the vaccine(s) was the "sole" or even the "predominant" cause. *Id.* at 1352. For example, in *Shyface*, the Federal Circuit affirmed that petitioners were entitled to compensation, based on their expert's testimony that the vaccine together with a bacterial infection caused the child's high fever and death (although the expert could not testify that the vaccine was the "sole" or "predominant" cause. 165 F.3d at 1353.

Showing a logical sequence of cause and effect between the vaccine(s) and the injury will tend to show that the injury was not caused by an alternative cause. However, a petitioner is not required to eliminate all possible alternative causes of the injury. *See Walter v. Sec'y of Health & Human Servs.*, 485 F.3d 1146, 1150 (Fed. Cir. 2007) ("the Vaccine Act does not require the petitioner to bear the burden of eliminating alternative causes where the other evidence on causation is sufficient to establish a *prima facie* case"). This standard permits the use of "circumstantial evidence" and accomplishes Congress's goal that "close calls regarding causation are resolved in favor of injured claimants." *Althen*, 165 F.3d at 1280.

Once a petitioner fulfills the *Althen* test, the burden of persuasion shifts to respondent to show that the alleged injury was caused by a factor unrelated to the vaccination. *Knudsen*, 35 F.3d 543 at 548; § 13(a)(1)(B). Respondent has the burden of demonstrating that "a factor unrelated to the vaccination is the more likely or principal cause of the injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury." *Deribeaux v. Sec'y of Health & Human Servs.*, 717 F.3d 1363, 1369 (Fed. Cir. 2013). Section 13(a)(2) specifies that factors unrelated "[do]not include any idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or

condition." Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280; *Knudsen*, 35 F.3d at 551 ("If the evidence (on alternative cause) is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded.

### C. Summary of Relevant Facts

J.B. was born on April 7, 2011, when his mother became pre-eclamptic and underwent a Caesarean section. Exhibit 1 at 10. J.B. was born 4 weeks prematurely at 36 weeks gestation. Exhibit 2 at 3. The mother's medical records report no history of tobacco, alcohol, or illicit drugs. Exhibit 1 at 3. At birth, J.B. was noted to be "well appearing, non-dysmorphic[,] alert and in no acute distress." Exhibit 2 at 9. His Apgar scores[6] were 8 at 1 minute and 9 at 5 minutes. Exhibit 2 at 9. J.B. and his mother are both noted to be African-American. Exhibit 2 at 3, 25.

On April 14, 2011, one week after birth, J.B. received his first Hep B vaccination. Exhibit 2 at 82.[7] At his two-week well baby visit on April 21, 2011, J.B. was "well appearing, alert . . . a healthy appearing 2 [week] old with normal growth and development." *Id.* at 79-81. On June 7, 2011, J.B. – exhibiting a cough and a runny nose – was brought to the emergency room. *Id.* at 73. He underwent a chest x-ray that revealed "no radiographic evidence of acute cardiopulmonary disease." *Id.*

J.B.'s subsequent well-baby visits were scheduled to account for the fact of his being born 4 weeks prematurely. On July 22, 2011, more than three months after J.B.'s birth, he had a two-month well baby visit with his pediatrician, Laura Wright, M.D. Exhibit 3 at 8-10. Dr. Wright's evaluation was thorough and well documented. *Id.* J.B. had no feeding difficulties, slept best at night, slept in his own room, and slept on his back. *Id.* at 8. He was noted to be a "well child, almost 4 months but behind on [vaccinations]" with "normal growth and development." *Id.* at 10. J.B. received DTaP, IPV, PCV, rotavirus, and Hep B vaccinations at this visit. *Id.* at 2, 8.

On September 2, 2011, almost five months after J.B.'s birth, he had his four-month well baby visit with Dr. Wright. Exhibit 3 at 5-7. He was nearly five months post-delivery, although his gestational age was about four months given his early delivery. J.B. was sleeping up to seven hours at a time, on his back, in a crib in his own room. *Id.* at 5. He was described as "healthy appearing and cooperative . . . well-nourished and well developed." *Id.* His chest and lungs were normal with no adventitious[8] sounds. *Id.* at 6.

---

[6] Apgar score is defined as "a numerical expression of the condition of a newborn infant, usually determined at 60 seconds after birth, being the sum of points gained on assessment of the heart rate, respiratory effort, muscle tone, reflex irritability, and color." *Dorland's Illustrated Medical Dictionary* (32d ed. 2012) ("*Dorland's*") at 1682.

[7] Petitioners' expert, Dr. Miller, stated that normally an infant receives the first Hep B vaccination a day after delivery or just before going home. Exhibit 13 at 3. Dr. Miller characterized J.B. receiving the first Hep B vaccination one week after delivery as "a little unusual [but…] likely inconsequential." *Id.*

[8] Adventitious is defined as "accidental or acquired; not natural or hereditary." *Dorland's* at 34.

J.B.'s heart rate was regular with normal heart sounds and no pericardial friction rubs. *Id.* His reflexes were all 2/2 and his red reflex was normal. *Id.* His weight was 16 pounds, 8 ounces. *Id.* at 5. For infants of his age, his weight was stable at the 50th percentile, his height was up at the 50th percentile, and his head circumference was at the 75th percentile. *Id.* Nasal mucosa was normal, turbinates[9] were normal, and nares[10] were patent. Oropharynx was normal. *Id.* at 6. He was recorded as not having a fever, nasal congestion, or cough and history of wheezing. *Id.* at 5. He met numerous 4-month developmental milestones, including "head up 45 degrees, head up 90 degrees, sits – head steady." *Id.* During this visit, J.B. received DTaP, IPV, PCV, rotavirus, and Hep B vaccinations. *Id.* at 6; Exhibit 4 at 1. Dr. Wright completed her records from this visit on September 2, 2011, at 10:45 a.m., suggesting that the appointment had concluded by that time. Exhibit 3 at 7.

J.B.'s father attested that during the well-baby visit, J.B. was "smiling and cooing like normal." Exhibit 11 at 1. However, later that day after J.B. received the vaccinations, he "was not laughing or cooing like he normally did[,] he was not moving as much[, and] he seemed quiet and withdrawn." *Id.* That night, J.B. had a fever and he did not sleep well. *Id.* [11]

J.B.'s mother and father stated that on September 3, 2011, at 4:00 a.m., they gave J.B. Advil,[12] after which he went to bed in a supine position (on his back). Exhibit 8 at 2. When J.B. woke up a few hours later, he was distant, very quiet, and would not eat. Exhibit 11 at 2. He began running a fever again and was given another dose of Advil at approximately 8:00 a.m. *Id.*;

---

[9] Turbinate is defined as "any of the nasal conchae.*" *Dorland's* at 1991.

[10] Nares is defined as "the external orifices of the nose; [also known as] nostrils." *Dorland's* at 1232.

[11] The following factual summary draws from:

- Exhibit 5 – Suffolk, Virginia Department of Fire & Rescue records of responding to the home on September 2, 2011.
- Exhibit 7 – Suffolk, Virginia Police Department records. This includes notes from the police's response to the home on September 3, 2011, and the police department's formal report on their response and a handwritten statement from J.B.'s mother, both completed on September 8, 2011.
- Exhibit 8 – Office of the Chief Medical Examiner, Tidewater District, Norfolk, Virginia, Records. This exhibit contains a summary of a child death reenactment with a doll, performed with J.B.'s parents in their home on September 8, 2011. Exhibit 8 at 3. The autopsy report was completed on November 2, 2011. Exhibit 8 at 1-2; 4-9.
- Exhibit 9 – Suffolk, Virginia Police Department records – photos of a bottle of Advil, taken on September 8, 2011; J.B. following the autopsy, undated; and the crib, bedroom, and exterior of the home, taken on September 3, 2011.

J.B.'s mother and father were not present to testify at the entitlement hearing.

[12] A bottle of children's Advil was taken into evidence. Exhibit 7 at 47. *But see* Exhibit 6 at 2, 5 ("aspirin"); Exhibit 8 at 2 ("infant Tylenol"); Exhibit 8 at 4-6 ("over-the-counter acetaminophen"). To the extent that it makes any difference it would seem most likely that it was the Advil that was given and the other notations were made subsequently without that same attention to this detail that the site investigation utilized.

Exhibit 7 at 11. J.B.'s mother said that J.B. sat up and played with her nephews during the morning. Exhibit 7 at 16.

In the early afternoon, J.B. became fussy and his father put him down for a nap in his bedroom, on the second floor of the house. Exhibit 7 at 3, 16; Exhibit 8 at 2. His father attested that he placed J.B. supine with his head to the right. Exhibit 7 at 5; Exhibit 8 at 3. J.B. seems to have had a pacifier in his mouth. Exhibit 7 at 16. He was placed in the middle of his crib, with a blanket across his midsection. Exhibit 8 at 3. The crib also contained a "little crib pillow – very flat," but no clutter or toys. Exhibit 7 at 5; Exhibit 8 at 3. J.B.'s mother attested that the air conditioning was always set at 76 degrees Fahrenheit. Exhibit 7 at 4. She indicated that J.B. slept on his back and that he could roll over on his own, lift his head, and pull or push himself up. Exhibit 7 at 5.

After putting J.B. down for his nap, his father left the home to get lunch. Exhibit 11 at 2. His mother remained in the home, but "heard [J.B.] fussing in crib" while she was cleaning and on the phone. Exhibit 7 at 16. After some period of time, J.B.'s mother went upstairs and put the pacifier in J.B.'s mouth. *Id.* (noting that J.B. "tend[ed] to cry when he spit the pacifier out"). When she returned, she found J.B. on his right side, with his head turned slightly, and unresponsive. Exhibit 7 at 17; Exhibit 8 at 2-3. She called J.B.'s father and said that J.B. was not breathing. Exhibit 7 at 17; Exhibit 11 at 2. The father told her to call 911 and he headed home. Exhibit 11 at 2.

J.B.'s mother said that "approximately 50 minutes passed" between his father placing J.B. down for a nap and when she found J.B. unresponsive. Exhibit 8 at 2. There was a "10-minute window" between when his mother checked on J.B. and replaced his pacifier, and when she returned to find him unresponsive. Exhibit 5 at 2. She informed the police that his nose and mouth were not covered. Pet. Ex 7 p 5.

J.B.'s mother called 911 at 2:39 p.m. Exhibit 7 at 35. She then attempted CPR. Exhibit 5 at 2; Exhibit 7 at 17. It appears that she removed him from the crib and placed him on his back on the floor. Exhibit 7 at 9-10. Officer Anderson was the first to arrive, at 2:42 p.m. – just 3 minutes and 21 seconds after the call. Exhibit 7 at 7, 9, 11, 35. Upon entering the home and going upstairs, the officer found J.B. lying on the bedroom floor, perpendicular to his crib. *Id.* at 9. J.B. was face up, with his eyes closed, and unresponsive. *Id.* He was still warm, but had no pulse or breath. *Id.* J.B.'s mother was kneeling over him. *Id.* The officer performed chest compressions until EMS arrived. *Id.*

The first responders left with J.B. at 3:02 p.m. and arrived at the emergency department of Harborview Medical Center at 3:08 p.m. Exhibit 7 at 36. J.B. was given oxygen under pressure during transport, but PEA (pulseless electrical activity) was noted on the monitor. Exhibit 5 at 1-2. Efforts at resuscitation were unsuccessful and J.B. was pronounced dead at the hospital, on September 3, 2011, at 4:01 p.m. Exhibit 7 at 10.

On September 5, 2011, a medical examiner, Dr. Jeffrey Gofton, completed an autopsy report for J.B. Exhibit 8 at 4-6. The medical examiner noted that the scene reenactment indicated that J.B. was placed to sleep on his back and was later found on his right side. *Id.* at 6. Scene photographs indicated a crib with soft blankets and a flat soft pillow, but no clutter or toys in the bed. *Id.* It was further noted that J.B. had no known medical problems, with regular infant care and immunizations. *Id.* He had a well-baby check-up on the day prior to his death, during which he received multiple vaccinations. *Id.* He had reportedly been fussy and had an intermittent temperature that seemed to be controlled with Tylenol. *Id.* J.B. was reportedly placed to sleep on his back and later found on his right side. *Id.* The medical examiner stated that J.B.'s lungs exhibited congestion and pulmonary edema.[13] *Id.* However, J.B. had no traumatic injury, congenital abnormalities, or viruses such as influenza. *Id.* Both a cerebral spinal fluid culture and a nasopharyngeal swab for viruses were negative. *Id.* J.B.'s brain weighed 876 grams (normal is 620 plus or minus 71 grams). *Id.* There was no evidence of epidural, subdural, or subarachnoid hemorrhage. *Id.* Serial sectioning showed normal configuration and infantile myelination of the cerebrum. *Id.* The brainstem was normally formed with no focal lesions. *Id.* at 5. Extensive drug testing was performed and was negative. *Id* at 6. The medical examiner, based on the "absence of findings and the reported sleeping position in a child with no anatomic or microscopic significant findings," stated that "the cause of death was SIDS and the manner was "natural." *Id.* The parties agree that the characterization of J.B.'s cause of death as SIDS is appropriate. Joint Prehearing Submission at 2.

The parties' experts in neuropathology – Dr. Miller for petitioners and Dr. Harris for respondent – reviewed 21 slides from J.B.'s autopsy, including two of J.B.'s brain. Exhibit 13 at 4-5; Exhibit A at 5. The first brain slide is a cross-section of pons at the level of the locus coeruleus (the upper pons), and the second slide is of two cingulate gyri with a portion of the adjacent corpus callosum. Exhibit 13 at 5. These brain sections demonstrated no abnormalities. *Id.* However, the medical examiner did not make slides from other parts of the brain, such as the medulla or hippocampus. *Id.* Furthermore, he did not take any photographs of the internal examination. *Id.* The parties' experts agreed that the medical examiner did not collect all of the data necessary to definitively analyze whether J.B. fit the Triple Risk Model of SIDS, introduced in the following section. Tr. 42-43 (testimony of Dr. Miller); Tr. 334 (testimony of Dr. Harris). The experts agreed that they would section considerably more of the brain in a possible SIDS autopsy than the two frontal lobes and one area of the pons that were sectioned in this case. Dr. Harris indicated that usually a SIDS autopsy should include samples of at least ten areas, including the medulla and hippocampus, which can help to show hypoxic ischemic changes as well as epilepsy related changes. Tr. 334. Both experts agreed, however, that in many SIDS cases, brains are not examined with the precision that they would recommend or that Dr. Kinney's group at Harvard did in their studies (introduced in the following section). Tr. 346.

[13] Dr. Miller and Dr. Harris agreed that congestion in the brain and lungs and other organs is a very common and non-specific finding at autopsy from which they would not draw any conclusion. Tr. 103 (Miller); Tr. 332-33 (Harris).

## II. SUMMARY OF THE EVIDENCE

### A. Medical Literature

The parties submitted voluminous literature to explain what is understood about sudden infant death syndrome ("SIDS"), the potential role of inflammatory cytokines generated by vaccines in acting as a necessary trigger, and the epidemiology of SIDS. Both parties submitted various studies from Hannah C. Kinney, M.D., a neuropathologist at Harvard, and others on her team which leads the research and current understanding of SIDS. The later articles tend to build upon and incorporate the earlier articles. Studies by other authors on SIDS and related subjects served to supplement and generally confirm that by Kinney et al.

A review of the literature is critical to the determination of whether petitioners have satisfied the *Althen* prongs (a reliable theory of how vaccines *can* cause death from SIDS, that the vaccines did in J.B.'s particular case, and that there was a medically acceptable temporal relationship between the vaccinations and J.B.'s death). This review is also necessary to determine whether respondent has sufficiently rebutted petitioners' theory by demonstrating that J.B.'s death was caused by factors unrelated to the vaccine.

SIDS is defined as "the sudden death of an infant under one year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, death scene investigation, and review of the clinical history."[14] "Epidemiological studies link SIDS with sleep periods, leading to the premise that SIDS occurs during sleep or transitions between sleep and waking." *Id.*

SIDS is the leading cause of infant mortality in the United States, with an incidence of 0.53 per 1,000 infants.[15] Research has revealed that infants put to sleep in the prone position, i.e., with their heads facing downward, are twice as likely to experience SIDS. *Id.* Other risk factors for SIDS related to the "sleeping environment" have been recognized, including "[being] found face-down, head covered, sleeping on an adult mattress, couch or playpen, soft bedding, [and] bed-sharing." *Id.*

In 1994, Dr. Hannah C. Kinney, Dr. James Filiano, and their colleagues synthesized many neuropathological studies into their proposed Triple Risk Model.[16] This model posits that SIDS occurs when: (1) an infant in a critical development period; (2) possessing an underlying vulnerability; (3) encounters an exogenous stressor. *Id.* The following Venn diagram has been used to illustrate the Triple Risk Model:

---

[14] Filiano, J.J. & H.C. Kinney, *Arcuate Nucleus Hypoplasia in the Sudden Infant Death Syndrome*, 51 J. Neuropathol. Exp. Neurol. 394 (1992), Exhibit 13-A at 394.

[15] Trachtenberg F.L., E.A. Haas, H.C. Kinney, C. Stanley & H.F. Krous, *Risk Factor Changes for Sudden Infant Death Syndrome After Initiation of Back-to-Sleep Campaign*, 129 Pediatrics 630 (2012), Exhibit C-11 at 631.

[16] Filiano, J.J. & H.C. Kinney, *A Perspective on Neuropathologic Findings in Victims of the Sudden Infant Death Syndrome*, 65 Biol. Neonate 194 (1994), Exhibit 13-B at 195 [also filed as Exhibit A-2].


*Id.* at 3, Figure 1. This model emphasizes the intersection of multiple factors in the pathogenesis of SIDS. According to this model, SIDS occurs only when components of all three factors are present simultaneously, which explains why all infants who are placed prone to sleep or who bed share do not die of SIDS.[17]

### 1. First Risk Factor: Critical Development Period

The first factor in the Triple Risk Model of SIDS is the critical development period, which Kinney et al. initially defined as the first year of life.[18] However, their more recent literature tends to define it as the first six months of life.[19] The peak incidence of SIDS deaths has historically occurred between two and four months of age. A study by Trachtenberg, Kinney, and others published in 2012 found slightly more younger and older infants succumbing to SIDS than had been seen in earlier studies. In the groups studied, the percentage of SIDS babies who were five months or more rose from 11.8% in the pre-Back-to-Sleep[20] era, to 17.6% in the 1996-2008 post-Back-to-Sleep era.[21] Kinney and Thach wrote, "Given the wide array of homeostatic functions modulated by the medullary 5-hydroxytrptamine system, sudden death may result from a convergence of defects in protective response to homeostatic stressors during sleep that are modulated by 5-hydroxytrptamine, probably in conjunction with related neurotransmitters."[22]

---

[17] Kinney, H.C. et al., *The Brainstem and Serotonin in the Sudden Infant Death Syndrome*, 4 Annu. Rev. Pathol. Mech. Dis. 517 (2009), Exhibit 13-H at 521.

[18] Filiano & Kinney (1992), Exhibit 13-A at 394.

[19] *See, e.g.*, Kinney et al. (2009), Exhibit 13-H at 521.

[20] The "Back to Sleep" campaign refers to a major public health effort to encourage parents to place their infants on their backs to sleep, particularly during the first year of life as a means of reducing the incidence of SIDS.

[21] Trachtenberg, Kinney, et al. (2012), Exhibit C-11 at 634.

[22] Kinney, H.C. & B. Thach, *The Sudden Infant Death Syndrome*, 361 New England J. of Med. 795 (2009), Exhibit A-4 at 6.

### 2. Second Risk Factor: Vulnerable Infant

After Kinney et al. formulated the Triple Risk Model, the initial research was focused on determining why particular infants were "vulnerable", possibly because of environmental or genetic factors. Exhibit 13-H at 5. Intrinsic risk factors include "male gender, African-American race, poverty, adverse prenatal factors such as maternal smoking or alcohol use during pregnancy, and genetic polymorphisms." *Id.* It was also hypothesized as early as 1987 that most likely SIDS was related to a brainstem abnormality in the neuroregulation of cardiorespiratory control.[23] These intrinsic factors when combined with the vulnerable developmental period of the infant and a critical exogenous factor resulted in sudden infant death. As research progressed over the following decades, the above intrinsic risk factors remained but a significant emphasis was placed on the brainstem hypothesis, based upon the research of Dr. Kinney and others. In 2009, Dr. Kinney explained: "To date the most robust evidence for a neurochemical abnormality comes from research on the medullary 5-HT system,[24] in that approximately 50-70% of infants with SIDS appear to have abnormalities in this system. The medullary 5-HT system, which is considered critical for the modulation and integration of diverse homeostatic functions, is involved in ventilation and gasping, thermoregulation, autonomic control, response to carbon dioxide and oxygen, arousal from sleep, and hypoxia-induced plasticity.[25]

The 5-HT system refers to the serotonin system. "The caudal serotonergic (5-HT) system is a critical component of a medullary "homeostatic network" that regulates protective response to metabolic stressors such as hypoxia, hypercapnia and hyperthermia."[26] "Homeostasis refers to the ability of an organism to maintain a constant internal environment, thereby allowing survival over a wide range of external environmental conditions. It becomes self-sufficient at the moment of birth as the fetus takes the first breath in the extra-uterine world and begins to adjust instantaneously and independently to the myriad of changing metabolic demands. ... Receptor systems that sense deviations in any internal milieu (e.g., oxygen and carbon dioxide, glucose, and temperature levels) have been defined as well as the effector systems that are the final common pathway in mediating adjustments. Major focus has been placed upon the brain as the 'control center' which sets the range at which a particular parameter namely CO2 is maintained, and determines the protective response to deviations from this range namely hypercarbia."[27,28]

---

[23] Kinney et al. (2009), Exhibit 13-H at 519.

[24] 5-HT (5-hydroxytryptamine), also called serotonin, is defined as "a monoamine vasoconstrictor, synthesized in the intestinal chromaffin cells or in central or peripheral neurons and found in high concentrations in many body tissues, including the intestinal mucosa, pineal body, and central nervous system." *Dorland's* at 1699.

[25] Kinney & Thach (2009), Exhibit A-4 at 6.

[26] Kinney, H.C. et al., *The Serotonergic Anatomy of the Developing Human Medulla Oblongata: Implications for Pediatric Disorders of Homeostasis*, 41 J. Chem. Neuroanat. 12 (2011), Exhibit 13-F at 182.

[27] Hypercarbia, also called hypercapnia, is defined as "excess of carbon dioxide in the blood." *Dorland's* at 887.

[28] Kinney et al. (2009), Exhibit 13-F at 183.

The serotonergic system, primarily concentrated in the medulla oblongata, which is called the caudal 5-HT system or the medullary 5-HT system, is now recognized as a key component of the brain's control system of homeostasis. *Id.* Dr. Kinney proposed that deficits in the caudal 5-HT system will lead to imbalances in respiratory, cardiovascular, and/or metabolic regulation – including in response to stress – in the pediatric age range, particularly in the first days and months following birth. *Id.* As noted by the Kinney group in a 2011 article on the serotonergic anatomy, "extensive experimental data implicate the caudal 5-HT system in homeostasis and respiratory and autonomic regulation, including upper airway control, respiration (including via modulation of the pre-Botzinger complex, the putative central rhythm generator of respiration), autoresuscitation, central chemoreceptor responses to hypercapnia and hypoxia, cardiovascular control, pain, motor function, and thermoregulation." *Id.* The article also notes that the medullary 5-HT system "interfaces with the cytokine system which is critical to homeostasis in its mediation of 'protective sickness' behaviors and cellular defenses against tissue damage." *Id.*

Dr. Kinney's team's research on the brainstem focused on a collection of neurons in the ventral medullary surface known as the arcuate nucleus "based upon cytological and positional homologies between the respiratory chemosensitive fields on the ventral medullary surface in cats. Structural underdevelopment of the arcuate nucleus was subsequently observed in SIDS cases."[29] As the research advanced, it was recognized that the "arcuate anomaly was similar to that reported in infants with clinical insensitivity to CO2 and sleep related sudden death." *Id.* By 2009, Dr. Kinney reported, "*Serotonergic neurons at the medullary ventral surface and in the midline (raphe) are now known to be preferentially chemosensitive to CO2* and although they are not the only central chemosensitive neurons they appear to play a critical potentially modulatory role…A small but important population of 5-HT neurons is embedded within the human arcuate nucleus suggesting that the putative dysfunction in chemosensitivity related to the arcuate anomaly specifically involved these embedded 5-HT neurons." *Id.* (emphasis added).

**"**Serotonergic neurons are well-suited to a role as central respiratory chemo-receptors, as they are closely associated with the basilar artery and its largest branches near the ventral surface of the medulla namely they are in a position to directly monitor arterial $PCO_2$.... 5-HT neurons respond intrinsically to increased $PCO_2$[30] with large increases in firing rate; this response is due to a decrease in intracellular pH induced by hypercapnia. On average these neurons increase their firing rate threefold in response to a decrease in pH of 7.4 to 7.2. Chemosensitivity increases during postnatal development, with a blunted response to pH before postnatal date 12 in rats. Physiological delay in chemosensitivity is potentially relevant to SIDS because it indicates that 5-HT neurons may be immature during the critical developmental period, throughout which all infants are susceptible to hypercapnia."[31] Harper and Kinney state the data now suggest that SIDS is associated with a brainstem (medullary) 5-HT deficiency rather than 5-

[29] Kinney et al. (2009), Exhibit 13-H at 522. Kinney defines chemosensitivity as "the ventilator response to a change in carbon dioxide/pH as sensed by tissue chemoreceptors, which are composed of neurons and/or astrocytes." *Id.*

[30] $PCO_2$ is defined as "the partial pressure of carbon dioxide." *Dorland's* at 2120.

[31] Kinney et al. (2009), Exhibit 13-H at 530.

HT overproduction.[32] Of note, the medullary 5-HT profile differed between infants dying of SIDS and those dying with known chronic oxygenation disorders, suggesting that chronic hypoxia does not necessarily play a major role in the pathogenesis of the impairments in the 5-HT tissue markers. *Id.*

Harper & Kinney explained that the insufficient function of the 5-HT system, which is necessary for breathing, leaves an infant vulnerable to a variety of crisis situations. These include external airway obstruction, upper airway obstruction resulting from loss of tone in the upper airway musculature in association with diaphragmatic movements, or importantly of central apnea, which has occupied a central focus of attention. These are also proposed mechanisms underlying the fatal event in SIDS. This failure can result from several components of the breathing process, including impaired sensory transduction or integration of either carbon dioxide or oxygen, or non-recruitment of gasping mechanisms, the final restorative mechanism to low oxygen. In SIDS, a principal concern is the "loss of the wakefulness drive to breathe." *Id.* at 5. The waking state activates processes which maintain breathing, while during sleep those influences are suppressed or not recruited. Thus, impaired central chemosensitivity to excess carbon dioxide or inadequate oxygen contributed to by defects in the medullary serotonin system, in addition to the normal reduction of the function of the 5-HT system during sleep, may play a central role in SIDS, which occurs primarily during sleep. *Id.* at 4-5.

Despite the emphasis on brainstem abnormality or underdevelopment, the other intrinsic risk factors are thought to continue to play an important role in the multi-factorial analysis of SIDS causation. Some of these factors may be related to the medullary 5-HT deficits described above. Several intrinsic risk factors are apparent in J.B.'s case. First, prematurity is defined as less than 37 weeks at birth[33] and J.B. was born at 36 weeks. Male gender, as boys exceed girls in SIDS deaths by a two-to-one ratio, and African-American race have also been called intrinsic risk factors because they are over-represented among SIDS victims.[34] Importantly, maternal smoking and alcohol consumption during pregnancy are considered important risk factors but are not relevant in this case, as J.B.'s mother did not smoke or drink during or after her pregnancy.

Dr. Kinney has hypothesized that males may predominate among SIDS deaths because males tend to be less responsive to the accumulation of carbon dioxide, and in the situation with a defective medullary 5-HT system may be particularly impaired from responding to excess carbon dioxide during sleep. *Id. T*he predominance of males in the occurrence of SIDS appears to be potentially related to the reduction of 5-HT binding in the medullary raphe compared to females dying of SIDS, as well as the report that plasma levels of testosterone, but not estradiol, are significantly higher in both male and female SIDS infants compared to age-matched controls. Several studies in knockout mice and piglets also "underscore gender differences in brainstem-mediated 5-HT function, with females' brains apparently relying less on 5-HT neurons in chemoreception and adapting more readily to the loss of 5-HT function. *Id.*

---

[32] Harper, R.M. & H.C. Kinney, *Potential Mechanisms of Failure in the Sudden Infant Death Syndrome*, 6 Curr. Pediatr. Rev. 39 (2010), Exhibit C-12 at 7.

[33] Trachtenberg, Kinney, et al. (2012), Exhibit C-11 at 631.

[34] Kinney et al. (2009), Exhibit 13-H at 532.

The role of African-American race in SIDS is less defined, other than statistically. Most authors speculate that the statistical predominance of African-American children may represent lower socioeconomic status resulting in inadequate medical care. If that be the case however, J.B.'s race should not be an increased risk factor as he was receiving regular medical care with comprehensive and well-documented well baby visits occurring in July and September. His first set of vaccinations was somewhat late, but the second dose, those received on September 2, 2011, brought him up to date. His growth and functional milestones appeared to be normal. It is also reported that 75% of white infants are placed to sleep in the supine position, while only 53% of black infants are, and that there is greater incidence of bed sharing among black infants than in other groups.[35] J.B. was placed on his back and was in his own crib.

### 3. Third Risk Factor: Exogenous Stressor(s)

The third and last factor is referred to as exogenous stressor[s] present at the time of death.[36] These stressors identified in the literature include "prone sleep position, face-down position, covered face in the supine position, soft bedding, bed sharing, over-bundling, elevated room temperature, and minor infection at the time of death."[37] Virtually every SIDS case includes one or more exogenous stressors, implying that they act as "triggers" for SIDS.[38] Studies also show that often multiple risk factors are present in a given SIDS case. Trachtenberg et al. found that "at least 2 extrinsic risk factors" were present in a majority of 568 cases reviewed. *Id.* at 632.

Dr. Kinney has hypothesized that exogenous stressors "lead to asphyxia, hypoxia, hypercapnia, or thermal imbalance requiring intact brainstem defense systems to protect against lethal consequences."[39] Non-vulnerable infants are generally able to recover from these conditions, but vulnerable infants are less able to recover and succumb to SIDS. *Id.* at 521.

As a result of their research, Dr. Kinney and her team proposed the Triple Risk Model to explain the occurrence of SIDS. Dr. Kinney's group then proposed the "Back to Sleep Campaign" in the early 1990s in which they recommended that babies always be put to sleep on their backs (supine) on a firm mattress, without pillows, blankets, toys, bumpers or other items that could potentially obstruct breathing. The prone or face-down sleeping position was considered to make an infant particularly vulnerable because an infant in the first six months of life with one or more intrinsic defects may re-breathe excess carbon dioxide and lack the corrective arousal mechanisms during sleep that would prevent a fatal outcome. Generally, the accumulation of excess carbon dioxide in the body causes signaling to breathe, thereby exhaling

---

[35] Moon R.Y. et al., American Academy of Pediatrics – Task Force on Sudden Infant Death Syndrome, *SIDS and Other Sleep Related Infant Deaths: Expansion of Recommendations for a Safe Infant Sleeping Environment,* 128 Pediatrics 1030 (2011), available at http://pediatrics.aappublications.org/content/128/5/1030.long.

[36] Trachtenberg, Kinney, et al. (2012), Exhibit C-11 at 631.

[37] Kinney et al. (2009), Exhibit 13-H at 521.

[38] Trachtenberg, Kinney, et al. (2012), Exhibit C-11 at 633.

[39] Kinney et al. (2009), Exhibit 13-H at 520.

carbon dioxide and inhaling room air containing oxygen. During sleep it is thought that excess carbon dioxide normally causes a person to turn the head toward fresh air and become aroused from sleep. When those mechanisms fail, the gasp reflex is triggered, which brings in oxygen and resets the rhythm of breathing. In SIDS, the dominant theory is that all of these mechanisms fail, leading to death.

The Back to Sleep Campaign has succeeded remarkably in reducing the number of SIDS deaths in the United States by approximately 50%.[40] In the U.S., the rate was reduced from more than 1 per 1,000 infants to 0.53 per 1,000, the current rate where it has plateaued. *Id.* However, SIDS remains the leading cause of post neo-natal infant death in the United States, raising some of the questions at issue in this case. *Id.* The emphasis has continued to be on the cardiorespiratory failure explanation of SIDS. Research has indicated that prone sleeping position increases the risk twofold or more. *Id.* They concluded that those not found prone sleeping were subject to alternative SIDS risk factors. *Id.* at 635.

The Trachtenberg article concluded that virtually all SIDS infants have at least one risk factor, and the majority have at least one intrinsic risk factor and two extrinsic factors. *Id.* The article also notes that the American Academy of Pediatrics risk reduction guidelines also include recommendations against side-sleeping and bed-sharing, and suggest a separate but proximate sleeping environment and pacifier use. *Id.* at 636. The data from the Trachtenberg study found a decline in prone position sleeping from 84% in the pre-Back-to-Sleep era to 48.5% in the post-era, but it also found that in the post-era 17.3% of SIDS infants were found on their sides while 22.6% were initially placed on their sides. *Id.* at 634, Table 2. Interestingly, 29% of the SIDS babies in that study were found supine while 41.7% were placed on their backs, suggesting that SIDS is not exclusively caused by prone sleeping. *Id.* at 632.

The Trachtenberg and Kinney articles emphasize the belief in the medical community that SIDS is multifactorial. As Trachtenberg noted, they were only able to evaluate which SIDS risk factors are most common, not which factors raise the odds of SIDS most significantly. *Id.* at 635. The authors suggest that the number of risks is probably underestimated and that "the majority of SIDS infants were subject to at least two extrinsic risk factors, suggesting that SIDS occurs from the simultaneous occurrence of multiple factors, rarely just one." *Id.* Additionally, Dr. Kinney has noted that under the Triple Risk Model, only infants with an underlying brainstem disease process die of SIDS, which explains why all infants who are placed prone to sleep or who bed share do not die of SIDS.[41] She states that SIDS essentially represents the occurrence of "the biologic version of the perfect storm in which the chance combination of multiple events is far more powerful than each individual event alone." *Id.* at 539. She suggests a possible scenario in which a child with the underlying brainstem deficit, during the critical developmental period, is exposed to excess carbon dioxide while he is sleeping. This may be based upon his sleeping position or he may have an issue with the laryngeal chemoreflex stimulated by reflux of gastric contents *or may have a mild infection with fever* causing the laryngeal chemoreflex induced apnea to be inordinately prolonged by mild hyperthermia" *Id.*

[40] Trachtenberg, Kinney, et al. (2012), Exhibit C-11 at 631.

[41] Kinney et al. (2009), Exhibit 13-H at 521.

(emphasis added). In this scenario, "if the infant's ventilator response to the progressive hypoxia and hypercapnia during the apnea is depressed, and if the hypoxic gasping and/or arousal mechanism is abnormal, oxygen lack from uninterrupted apnea results. Ultimately, death occurs *within minutes to hours*." *Id.* (emphasis added).

Respondent filed the article by Trachtenberg et al., which emphasized that they could find no positive correlations between risk factors or risk clusters but it appeared that any combination of risks together increased the odds of SIDS. The fact that most infants have at least two extrinsic risk factors suggests that SIDS occurs as a result of the occurrence of multiple factors and rarely just one.[42] The Kashiwagi article[43] filed by petitioners suggests that vaccines provoke an inflammatory cytokine response similar to that provoked by a mild infection. Petitioners theorize that these cytokines travel to the brainstem and further suppress the function of the already impaired medullary 5-HT system in a subset of SIDS infants.

### a. Cytokines, Mild Infection and Vaccines

Relevant to this case, in a 2009 article in the New England Journal of Medicine, Kinney and Thach stated, "A causal role for mild infection in sudden infant death is suggested by reports that in approximately half of SIDS cases, the infants have a seemingly trivial infection around the time of death, as well as mild tracheobronchial inflammation, altered serum immunoglobulin or cytokine levels and the presence of microbial isolates at autopsy. In infants who die unexpectedly of infection, the given organism may precipitate a lethal cytokine cascade or toxic response."[44] The question arises as to whether the cytokine response stimulated by vaccination can have the same effect as a mild or trivial infection in a baby who presumably has a defect in the medullary 5-HT system.

The role of cytokines stimulated by either mild infection or by vaccination is central to petitioners' theory in this case. Approximately 50% of SIDS babies have been found in multiple studies to have had mild or even "trivial" infections, primarily of the upper respiratory tract at the time of death. In this case, J.B. was documented the prior day as being healthy with patent nares, normal turbinates, and clear chest, but during the 28 hours after the vaccine he was reported to have a fever, which is generated by cytokine signaling. He also was distant, quiet, and would not eat, according to his parents. The case raises the issue of whether inflammatory cytokines stimulated by the innate response to the vaccines triggered the fever and his fussiness, and ultimately suppressed his 5HT system sufficiently so that he could not process the carbon dioxide in his system. The question of whether inflammatory cytokines stimulated by the innate response to the vaccine could have been the trigger that led to his death was central to the testimony and much of the literature submitted by the parties particularly in light of the clear medical evaluation on the day of the vaccination and a fever within hours afterward.

---

[42] Trachtenberg, Kinney, et al. (2012), Exhibit C-11 at 7.

[43] Kashiwagi Y et al., *Production of Inflammatory Cytokines in Response to Diphtheria-Pertussis-Tetanus (DPT), Haemophilus Influenzae Type B (Hib) and 7-Valent Pneumococcal (PC7) Vaccines*, 10 Hum. Vacc. Immunother. 677 (2014), Exhibit 17.

[44] Kinney & Thach (2009), Exhibit A-4 at 2.

As Dr. Kinney and her colleagues explained in 2011: "Cytokines orchestrate immune responses to microbial invasion and other insults and coordinate these responses with those of other physiological systems, including the autonomic nervous system, in the protection of the organism against tissue injury. They also mediate sickness behavior, including fever, anorexia, excessive sleepiness, blunted arousal, deep rest respiration, and lowered heart rate, which is thought to protect the organism during systemic illness by dampening excessive metabolic demands and thereby speeding repair and recovery - a form of homeostasis."[45] "Cytokines determine this sickness behavior by binding to endogenous cytokine receptors on neuronal populations in the hypothalamus and/or brainstem that mediate respiration, autonomic function, satiety, sleep, and arousal." *Id.* at 190. The cytokines which act within the brain in response to tissue injury are produced by astrocytes, and endothelial cells, microglia, *and/or peripheral immune cells* which enter the brain in response to binaural signals of tissue damage." *Id.* (emphasis added). During infection, peripherally produced IL-6 may cross the blood brain barrier and bind to IL-6 receptors on 5 HT neurons that mediate homeostasis in response to the infectious stressor and potentially mediate sickness behavior. *Id.* at 191. The role of pro-inflammatory cytokines in the pathology of SIDS is thought by multiple authors to be a potentially critical factor in tipping the molecular balance in the underdeveloped brainstem leading to death in infants in the vulnerable time period. IL-1β, IL-2, and IL-6 are pro-inflammatory cytokines that have been studied in connection with SIDS leading to theories about their potentially neuro-modulatory role in SIDS babies.

Kadhim et al. described a distinct cytokine profile in a SIDS brain in a study comparing SIDS brains with non-SIDS brains. The non-SIDS brains were from infants who died of known causes, including AIDS, cirrhosis of the liver, mononucleosis, purulent meningitis, and congenital heart disease with post-operative acidosis-shock. He found an over-expression of interleukin 1β in arcuate and dorsal vagal nuclei in all SIDS victims. In arcuate nuclei, high levels of interleukin 1β were detected in 17/17 SIDS brains vs. only 1 of 6 non-SIDS brains.[46] In dorsal vagal nuclei, interleukin 1β was also detected in high levels in 17 of 17 SIDS brains vs. only 2 of 7 non-SIDS brains. *Id.* Kadhim found a "region-specific pattern of cytokine expression in [the arcuate and dorsal vagal nuclei] of SIDS brains compared to non-SIDS brains." *Id.* at 1259. Kadhim theorized: "cytokines could exert neuromodulatory effects. Infectious inflammatory conditions and injury to the brain could up regulate pro inflammatory cytokines and produce functional alteration ... Cytokine/neurotransmitter interactions could therefore modify vital CNS functions." *Id.* Kadhim et al. further concluded that IL-1 causes prolonged apnea and depresses respiration, and that the brain appears to be less effective than the peripheral nervous system in inducing IL-1 antagonists to control IL-1 action.

[45] Kinney et al. (2011), Exhibit 13-F at 189.

[46] Kadhim, H. et al., *Distinct Cytokine Profile in SIDS Brain: A Common Denominator in a Multifactorial Syndrome?*, 61 Neurol. 1256 (2003), Exhibit 13-L at 1256.

In a second study from 2010, Kadhim focused on the expression of IL-2 in 28 autopsied infants who died at less than one year of age.[47] He described IL-2 as major immune-related cytokine that was originally thought to be a T-lymphocyte growth factor but is now recognized to have a wider spectrum of functions, targets and sources. *Id.* The study compared 18 SIDS brains to those of infants who died of diverse severe pathological conditions including infectious, hemodynamic, metabolic or other serious genetic conditions. In the severely ill children (non-SIDS), they found that IL-2 was preferentially expressed in specific neuronal centers within the brainstem (SNT-solitary nucleus tractus and TSNT-spinal trigeminal nucleus/tractus) in 10 of 10 cases of the fatally sick (non-SIDS) children and in the arcuate and dorsal vagal nuclei in 8 of 10. "Examination of the brainstem in the SIDS group showed a topographically similar profile with an equally intense immune reactivity within the very same neuronal circuits; precisely the strongly expressed cytokine labeling of IL-2 in SNTT and/or TSNT was observed in 17 out of 18 cases that constituted the 2nd study group (SIDS). IL-2 was also notable in the arcuate nucleus and dorsal vagus nucleus in 17 cases. These brainstem neuronal centers are known to be intricately implicated in autonomic control of vital homeostatic functions namely cardiorespiratory control mechanisms."[48] The authors concluded that it was not surprising to see the intense IL-2 expression in the infants who were severely ill before they died, but the SIDS victims are generally free from apparent potentially fatal conditions. "The SIDS victims often have preceding mild infectious/inflammatory conditions (like coryza[49]/mild upper respiratory infections, soft stools mild gastroenteritis, *postvaccinal fever*, etc.). Such trivial infections were found to induce a hypertuned immune/inflammatory response including high levels of immune inflammatory cytokines." *Id.* at 122. (emphasis added). Kadhim reviewed the Triple Risk Model, placing his study findings with regard to inflammatory cytokines in that framework; "Such mild infectious inflammatory conditions (extrinsic environmental stressors), if contracted in a vulnerable infant (intrinsic factors including prematurity and gene polymorphisms) during a critical developmental period whereby brainstem command centers undergo rapid maturation could provoke exaggerated immune responses with over expression of cytokines. We believe that this hypertuned immune response is behind the high IL-2 immune-reactivity we detected in situ in the brainstem of these victims." *Id.* at 125. Kadhim also noted that while pro-inflammatory cytokines have immune function, it is noteworthy here that cytokines have *neuro-modulatory effects* whereby they can modify neurotransmission. *Id.*

The role of mild infection was further discussed in an article by Rognum et al.[50] The Rognum group compared three groups of deceased infants. The group of 25 SIDS cases was selected from those subjects in whom no explanation for death was found. A second group died from known infectious causes and the third control group died primarily from violent causes

---

[47] Kadhim, H. et al., *Interleukin-2 as a Neuromodulator Possibly Implicated in the Physiopathology of Sudden Infant Death Syndrome*, 480 Neurosci. Lett. 122 (2010), Exhibit 13-O at 123.

[48] Kadhim et al. (2010), Exhibit 13-O at 124.

[49] Coryza, also known as acute rhinitis, is defined as an "inflammation of the mucous membranes of the nose." *Dorland's* at 423, 1639.

[50] Rognum, I.J., R.L. Haynes, A. Vege, M. Yang, T.O. Rognum & H.C. Kinney, *Interleukin-6 and the Serotonergic System of the Medulla Oblongata in the Sudden Infant Death Syndrome*, 118 Acta Neuropathol. 519 (2009), Exhibit 13-N at 519-30.

such as drowning, suffocation or strangulation. *Id.* at 522. The IL-6 levels were significantly higher in SIDS subjects than in controls. The IL-6 levels in SIDS infants with minor infection were comparable to those infants who succumbed to severe infection. *Id.* at 520.

Rognum et al. wrote: "We previously showed that IL-6 is elevated in the cerebrospinal fluid of SIDS infants and that this elevation may be induced by a peripheral immune reaction. Approximately one half of the SIDS cases we have studied show signs of a mild infection, but IL-6 levels are comparable to those of infants succumbing to severe infection, suggesting an overreaction to the slight infection." *Id.*

According to Rognum: "In addition to its pro-inflammatory properties, IL-6 exerts effects outside the immune system. Non-immune cells including neurons can produce and secrete IL-6 and express its receptor. Of critical relevance to the premise that cytokines interact with central neurons to affect their function, IL-6 is shown to be important in neuronal development in the modulation of neuronal signaling." *Id.* "A major site of 5-HT cell bodies in the human infant brainstem is in the arcuate nucleus, the putative site for central carbon dioxide (CO2) sensitivity in humans and animal models. In this regard the synergistic effect of prone sleeping and infection on SIDS risks may be a set up for CO2 accumulation, as both rebreathing in the face down prone position and increased metabolism due to infection may increase CO2 levels. Death may be triggered if CO2 sensing regions in the brainstem, such as the arcuate nucleus, are compromised and cannot mount an arousal response to protect the infant from the dangerous situation. The arcuate nucleus is of particular interest in the study due to the previous finding by others of high neuronal IL-1β immunoreactivity at this site in SIDS cases compared to controls." *Id.*

Rognum et al. did identify one particular confounder to this theory in that they found that the mean IL-6R (receptor) intensity grade in the arcuate nucleus was significantly higher in the SIDS group than in the control group but the gp130 transducer was significantly higher in the infection group but less so in SIDS relative to the controls. While Rognum et al. acknowledged difficulty in grading the immunosensitivity of IL-6R and gp130 in this study due to its small size as a major limitation in the study, the result led the authors to hypothesize that the increased expression of IL-6R in the arcuate nucleus may be a compensatory mechanism as defective arcuate neurons may require excessive IL-6 stimulation in order to respond to altered carbon dioxide levels and there may be an inability in the SIDS babies to upregulate gp130 to mount an effective response.[51] *Id.* at 528. Nevertheless, the study concluded that abnormal IL-6R expression was found in the arcuate nucleus of SIDS babies 44% of whom had mild infections prior to death and thereby "provides evidence for aberrant interactions in SIDS infants between Il-6 and the arcuate nucleus, a key medullary 5-HT related region involved in protective responses to hypercapnia, potentially induced by the combined effect of prone position and mild infection." *Id.* at 529.

[51] Dr. Miller explained that gp130 is a second messenger in the cell that takes the message that the receptor has bound something and does something with it to take (tell) the cell to do something else. This is a very common mechanism in membrane signaling, that there's a second messenger system that then tells the cell to do something. Tr. p 32.

Rognum et al. concluded: "The key finding in this study is abnormal IL-6R expression in the arcuate nucleus in the SIDS cases, 44% of whom had signs of mild infection immediately prior to death. *Id.* at 528. Rognum further noted that the arcuate nucleus contains 5-HT and glutamatergic neurons that have been shown in animals to be critical to chemosensitivity. It is also the site for several neurotransmitter abnormalities in SIDS, including in 5-HT, muscarinic and kainite receptor binding. It is well documented that CO2 levels are elevated during severe neonatal infection and, interestingly, even mild upper respiratory infection may increase CO2 levels in infants over 3 months of age. Animal studies indicate that the *CO2 elevation can be attributed to a hyper metabolic state induced by proinflammatory cytokines*." *Id.* at 527-28 (emphasis added).

Kashiwagi studied the production of cytokines after vaccination in 61 vaccine recipients with fever and 18 without fever within 24 hours of vaccination. Blood samples were taken within 48 hours of vaccination in both groups. He reviewed the role of the innate immune system in responding to vaccination noting that the activation of the innate immune system including the enhanced production of inflammatory cytokines is indispensable for immunogenicity and these cytokines may be related to the occurrence of adverse events.[52] This group found that cytokine production began about 6 hours after the stimulation by a single or combination of vaccines and *increased for 24 hours, showing the same level afterward. Id.* at 679. They found that higher levels of IL-1β, IL-6, G-CSF[53] and TNF-α were produced with the concurrent stimulation by multiple vaccines than with the single vaccine in PBMC cultures (peripheral blood mononuclear cells - obtained from young infants in this study). *Id.* at 679. Higher levels of IL-6, IL-10, IL 12, G-CSF, IFNγ and TNFα in both the febrile and non-febrile groups were found after vaccination and G-CSF was significantly higher in the febrile group. *Id.* at 680. He noted that innate immune systems are not fully functional at the time of birth. Kashiwagi's group found that TLR (Toll-Like Receptors) stimulated the production of pro-inflammatory cytokines (specifically IL-β, IL-6, and IL-8) which was markedly higher in neonates than in adults. He also found that higher levels of IL-1β were produced in PBMC cultures stimulated with PCV7 than with DPT or Hib. Hib induced higher levels of IL-6 and TNF-α. IL-1β increased in PBMCs stimulated concurrently with Hib/PCV7 and DPT/Hib/PCV7 with similar patterns of TNF-α and G-CSF. However, when blood was drawn 48 hours post-vaccination, IL-1β was not found. *Id.* Dr. Miller theorized that IL-1β rises rapidly and then disappears by 48 hours whereas the other inflammatory cytokines have a longer half-life. Tr. 47

Kashiwagi noted: "All effective vaccines induce the production of cytokines or chemokines, which modulate immunogenicity and are also involved in inducing adverse events, such as systemic febrile illness and immunotoxicity. In this standpoint, IL-6, IL-10, IL-12, G-CSF, IFN-γ, and TNF-α were detected in both febrile and non-febrile groups after vaccination in comparison with those in normal subjects." *Id.* at 683. Inflammatory cytokine profiles after vaccination were similar to the outpatient group infected with the influenza virus. *Id.*

[52] Kashiwagi, et al. (2014), Exhibit 17 at 678.

[53] G-CSF is granulocyte colony stimulating factor *Dorlands* at 767- It is now classified as another cytokine. Tr. 47.

Vege and Rognum reviewed the literature and their own work and noted that "in 1995 they found that half of the SIDS victims had elevated levels of interleukin-6 (IL-6) in their cerebrospinal fluid (csf). The concentrations of IL-6 in SIDS infants were comparable to those we found in infants dying from infectious diseases like meningitis and septicaemia." They concluded that there were two groups of SIDS infants—one with IL-6 levels similar to infants dying of severe infections and another having low levels similar to those dying violent deaths. They hypothesized that one group of SIDS deaths may be attributable to sleep position and another to an uncontrolled inflammatory response to infection, predominantly occurring at night when cortisol levels, another mechanism for controlling inflammatory responses, are low.[54]

Others have studied cytokine expression in animals. Brambilla demonstrated in animal studies that Interleukin 1 (IL-1) inhibited firing of excitatory or wakefulness producing neurons in the dorsal raphe nucleus and enhanced activity of GABAergic or inhibitory neurons and, as such, induces enhancement of NREM sleep.[55]

Respondent submitted an article by Siljehav, Hofstetter et al. which sheds additional light on the possible mechanism involved with apnea in infants occurring in response to infection. These authors wrote: "Our data suggest that PGE2[56] induced by IL-1β as well as hypoxia selectively modulates respiration-related neurons in the rostral ventrolateral medulla, including the preBotzinger Complex via EP3R. Other neuromodulators, including PGE1, have been shown to inhibit preBotC neurons and slow respiration-related rhythm and preBotC lesions may disrupt anoxic gasping and evoke central apneas and ataxic breathing. Moreover, these respiration-related neurons were recently shown to be critical for adequate response to hypoxia, maintaining brainstem homeostasis with gasping and autoresuscitation and thus restoring oxygen levels. PGE2-induced depression of this vital brainstem neuronal network, e.g., during an infectious response, could result in gasping and autoresuscitation failure and ultimately death."[57] The model of the IL-1β induced respiratory depression and autoresuscitation failure via a PGE2 –mediated pathway was described. "During a systemic immune response, the proinflammatory cytokine IL-1ß is released into the peripheral blood stream. It binds to its receptor (IL-1R) located on endothelial cells of the blood brain barrier. Activation of IL-1R induces the synthesis of PGH2 from arachidonic acid via COX-2 and the synthesis of PGE2 from PGH2 via the rate limiting enzyme mPGES-1. PGE2 is released into the brain parenchyma and binds to the EP3R located in respiratory control regions of the brainstem, e.g., nucleus tractus solitarius and rostral ventrolateral medulla. This results in depression of central respiration-related neurons and

---

[54] Vege, A & T. Rognum, *Sudden Infant Death Syndrome, Infection, and Inflammatory Responses*, 42 FEMS Immunol. Med. Microbiol. 3 (2004), Exhibit 13-Q at 5 and 8.

[55] Brambilla, D. et al., *Interleukin-1 Inhibits Firing of Serotonergic Neurons in the Dorsal Raphe Nucleus and Enhances GABAergic Inhibitory Post-Synaptic Potentials*, 26 Eur. J. Neurosci. 1862 (2007), Exhibit 13-M at 1862.

[56] PGE2 is a symbol for a prostaglandin. *Dorland's* at 1529. Prostaglandins are "any of a group of components derived from unsaturated 20-carbon fatty acids, primarily arachidonic acid, via the cyclooxygenase pathway; they are potent mediators of numerous different physiologic processes." *Dorland's* at 1528.

[57] Siljehav, V. et al., *mPGES-1 and Prostaglandin E2: Vital Role in Inflammation, Hypoxic Response, and Survival*, 72 Pediat. Res. 460 (2012), Exhibit C-9 at 9897.

breathing, which may fatally decrease the ability to gasp and autoresuscitation during hypoxic events." *Id.* at 9898.

Stoltenberg[58] experimented on piglets and concluded IL-1 stimulates the release of beta endorphin and indicated that his group had shown that the level of beta-endorphin in cerebral spinal fluid correlates strongly with the duration of apnea. Furthermore IL-1β stimulates GABA transmission and hence increases the inhibitory postsynaptic function by opening of chloride delective channels, and this will reduce the activity in the central respiratory neurons and may produce hypoxia. He concluded that intravenous and intrathecal injections of interleukin 1β in piglets' prolonged apnea and modified autoresuscitation. Such a mechanism may play a role in depressing respiration in some infants dying of sudden infant death syndrome. *Id.* at 427.

In a study looking at the role of vaccination in producing apnea, bradycardia and oxygen desaturations in pre-term infants who received first DPT (whether whole cell or acellular pertussis, inactivated polio and Haemophilus influenza B), Lee found elevations in apnea, bradycardia and desaturations defined as cessation of respiration for 20 seconds, with a heart rate less than 100 and oxygen saturation less than 85%. Almost half had adverse cardiorespiratory events in the 72 hours post-vaccination which was statistically significantly higher than the control group which did not receive a vaccination in the prior 72 hours.[59]

Schulzke also studied apnea and bradycardia in pre-term infants, not on oxygen or respiratory support but in the NICU when they received pentavalent or hexavalent vaccines. Rate of increased apnea and bradycardia (defined the same as by Lee) was 13% in otherwise stable infants. Infants received ventilatory support and recovered. Events occurred between 8 and 24 hours after vaccination with onset of fever between 6 and 24 hours post immunization. [60]

### B. SIDS Epidemiology

Although epidemiology is not required to demonstrate entitlement to compensation in the Vaccine Program, the parties submitted multiple articles, primarily from European studies, which looked at the question of the possible relationship between vaccination and the incidence of SIDS, as well as several articles that reported on cases. Articles by Venneman[61], Jonville Bera, Traversa, VonKries, Goldman, and Kuhnert studied the question of vaccine causation in SIDS by various methodologies all of which described their own limitations. Others by Ottaviani and

---

[58] Stoltenberg, L. et al., *Changes in Apnea and Autoresuscitation in Piglets After Intravenous and Intrathecal Interleukin-1β Injection*, 22 J. Perinat. Med. 421 (1994), Exhibit 13-J.

[59] Lee et al., *Frequency of apnea, bradycardia, and desaturations following first diphtheria-pertussis invactivated polio-Haemophilus influenzae type B immunization in hospitalized preterm infants,* BMC Pediatrics (2006), Exhibit 20 at 3-4.

[60] Schulzke, *Apnea and bradycardia in preterm infants following immunization with pentavalent or hexavalent vaccines,* European Journal of Pediatrics (2005), Exhibit 21 at 432-35.

[61] Vennemann M.M. et al., *Sudden Infant Death Syndrome: No Increased Risk After Immunization*, 25 Vaccine 336 (2007), Exhibit C-17.

Zinka discussed individual cases of unexplained deaths occurring in close temporal proximity to receipt of vaccinations.

Goldman looked at VAERS data from 1990 to 2010 for hospitalizations and deaths after vaccinations and found a statistically significant positive correlation between mortality and receipt of five to eight vaccines compared to one to four.[62] (J.B. received 7 counting DTaP as three as the study did). Traversa conducted a large study using data from the Italian health system where vaccines are offered for free and the belief is that 95% of children are vaccinated. The study found a statistically significant relative risk for death in the first seven days after vaccination for the first hexavalent vaccine (six vaccines) but not after subsequent doses.[63]

Kuhnert did a review of studies from Germany, England, and New Zealand and critiqued the case control methodology through the use of the self-controlled case series method (SCCS). It concluded that the re-analysis using the latter method showed that the risk of SIDS was neither increased or decreased in SIDS cases or controls during the early post-vaccination periods but did "provide more detailed insights into the methodological pitfalls of such analyses using conventional case control methods."[64] Dr. McCusker testified that the Kuhnert study looked at three different studies and applied 39 statistical tests to them. She read the study as concluding that despite the application of multiple statistical post hoc tests, they still did not see anything. Tr. 236.

Other papers submitted in evidence included Zinka[65] reporting on six deaths in Germany within 48 hours of receipt of hexavalent vaccines. Kries[66] reported on a slight elevation in day one in the first year of life after one particular hexavalent vaccine but a significant increase in deaths in the second year of life after receipt of that vaccine. Ottaviani[67] did a detailed case study of one young child who died three hours after receipt of a hexavalent vaccine at 3 months of age. He did a detailed autopsy identifying bilateral hypoplasia of the arcuate nucleus. He concluded that this death could be consistent with the Triple Risk Model or be one of the SIDS

---

[62] Goldman, G.S. and N.Z. Miller, *Relative Trends in Hospitalizations and Mortality Among Infants by the Number of Vaccine Doses and Age, based on the Vaccine Adverse Event Reporting System (VAERS): 1990-2010*, 31 Hum. Exp. Toxicol. 1012 (2012), Exhibit 19 at 1016, Table 4.

[63] Traversa, G. et al., *Sudden Unexpected Deaths and Vaccinations During the First Two Years of Life in Italy: A Case Study*, 6 PLoS One 1 (2011), Exhibit 13-U at 4.

[64] Kuhnert R. et al., *Reanalyses of Case Control Studies Examining the Temporal Association Between Sudden Infant Death and Vaccination*, 30 Vaccine 2349 (2012), Exhibit C-20 at 2355.

[65] Zinka, B. et al., *Unexplained Cases of Sudden Infant Death Syndrome Shortly After Hexavalent Vaccination*, 24 Vaccines 5779 (2006), Exhibit 13-S.

[66] Kries, R. et al., *Sudden and Unexpected Deaths After the Administration of Hexavalent Vaccines (Diphtheria, Tetanus, Pertussis, Poliomyelitis, Hepatitis B, Haemophilus Influenza Type B): Is There a Signal?*, 164 Eur. J. Pediatr. 61 (2005), Exhibit 13-R.

[67] Ottoviani, G. et al., *Sudden Infant Death Syndrome (SIDS) Shortly After Hexavalent Vaccination: Another Pathology in Suspected SIDS?*, 448 Virchows Arch. 100 (2006), Exhibit 13-T at 4.

"grey zone" cases in which it is difficult to establish if the pathological findings were sufficient to cause death.

Each of the studies contained considerable acknowledgment of its own methodological deficiencies that may have affected the results. In different papers, these included inclusion without autopsies, small samples, comparing SIDS victims to living children rather than vaccinated SIDS to unvaccinated SIDS, as well as having no control group or having potential underreporting as in VAERS. The Kuhnert paper which analyzed three other case control studies including Venneman, said, "The small number of cases is a problem with the three case control studies, particularly in view of the short time periods under investigation. This problem is illustrated by the very broad confidence intervals of estimates that are only related to the events of the first few days."[68]

Dr. Miller criticized several of the studies for failing to use cases that were verified by autopsy, that the Vennemann study compared a new hexavalent vaccine to older vaccines rather than asking the question as to whether vaccines regardless of new or old could be associated with SIDS, and used data based on the number of vaccines sold rather than administered. Tr. 70-74. He noted that the IOM concluded that the evidence that it reviewed was insufficient to accept or reject causation. Tr. 387. In his report, Dr. Miller explained why it is difficult to do reliable epidemiological studies of SIDS. He said, "[I]f the risk for SIDS is present only in those infants who are already vulnerable because of a pre-existing brainstem abnormality, then no retrospective (or prospective) epidemiological study not grounded in a thorough neuropathological examination of all of the supposed SIDS cases would be likely to identify that putative causal relationship." Exhibit 13 at 5. He observed that J.B. would be one of those not counted as he did not have a complete neuropathological autopsy. *Id.* at 6.

Dr. McCusker criticized some studies as case reports or having no control group. She looked to Kuhnert which incorporated Vennemann to argue that there was no significant finding that SIDS occurred more often than chance. Tr. 228.

The Vaccine Program does not require epidemiological evidence and the studies presented contained multiple methodological flaws, and did not tend to shed much light on the question at issue, that is, whether the death of the child in this case was caused or triggered by the vaccinations received the day before. Thus the studies were read and considered and credited to show that vaccines are generally safe, but were specifically unpersuasive as to whether they are on rare occasions the exogenous factor resulting in the perfect storm in a child with a defective arcuate nucleus or other 5HT structure during the vulnerable period of life. They were also unpersuasive to reject causation as they frequently showed some temporal correlation to the receipt of vaccines even if those correlations were not found to be statistically significant.

[68] Kuhnert et al. (2012), Exhibit C-20 at 2355.

## C. Expert Opinions

### 1. Petitioners' Expert Douglas C. Miller

Dr. Douglas C. Miller earned his bachelor's degree from Williams College and his medical degree from the University of Miami School of Medicine in 1978.[69] He received a Ph.D. in Physiology and Biophysics from the University of Miami in 1980. *Id.* Dr. Miller was a resident at Massachusetts General Hospital from 1980-1984, focusing in the areas of anatomic pathology and neuropathology. *Id.* He currently serves as a clinical professor of pathology and anatomical sciences, as well as the program director of pathology residency, at the University of Missouri School of Medicine. *Id.* at 3. He also serves as an associate medical examiner for Boone, Callaway, and Greene Counties in Missouri. *Id.*; Tr. 10. Dr. Miller has been a full-time faculty member at the medical schools at Robert Wood Johnson in New Jersey, New York University, and the University of Missouri. He has published over 150 articles in medical journals and is the author of a textbook on neuropathology.

#### i. *Althen* Prong One: Medical Theory

Dr. Miller, consistent with the dominant literature in the field, proposed the Triple Risk Model of SIDS as the framework for his theory of causation.[70] Tr. 19. As explained above, this model first provides that SIDS can occur only when an infant is in a critical developmental period (the first year of life). Tr. 20. Second, SIDS can occur only to an infant who is inherently vulnerable in some way. *Id.* Third, the infant must encounter an exogenous stressor. *Id.*

Dr. Miller explained the normal physiological process for handling carbon dioxide and stimulating breathing. He said if the carbon dioxide levels rise above a normal threshold to an abnormal threshold, a normal brainstem's response – in this age group – is mediated by the arcuate nuclei alone. The excess carbon dioxide stimulates other neuronal systems to alert the cervical spinal cord motor neurons to tell the diaphragm and other muscles of respiration to contract, at the same time signaling up through other mechanisms in the basal forebrain, underneath the lower part of the frontal lobes, to wake up. In general, there is arousal and there is deeper breathing to blow off the carbon dioxide, and if it is position-related, the infant would also move so that homeostasis is restored. Tr. 29. He explained that this process is dependent on serotonin, an excitatory neurotransmitter, which stimulates the cells to which it signals to fire more rapidly to increase breathing or arousal. Tr. 28. That is in contrast to GABA, which is inhibitory and balances the excitatory effect of serotonin. *Id.*

Dr. Miller explained that the majority opinion in the medical community is based principally but not exclusively on work done by Dr. Hannah C. Kinney, in a series of papers that stretch back more than 25 or 30 years and has been verified by other people. She has shown that "the medulla, the lowest part of the brainstem, in infants who have died of SIDS and have been autopsied and have had the appropriate examinations is defective. In particular, it has a defect in

[69] Curriculum Vitae of Dr. Douglas C. Miller, Exhibit 14 at 1.
[70] Kinney, H.C. et al., *Medullary Serotonergic Network Deficiency in the Sudden Infant Death Syndrome: Review of a 15-Year Study of a Single Dataset*, 60 J. Neuropathol. Exp. Neurol. 228 (2001), Exhibit 13-C.

a set of nuclei [or] groups of neurons, which use, as a neuro-transmitter a molecule called serotonin … which is also known as 5-hydroxytryptophan and which is abbreviated as 5-HT." Tr. 19. He further explained that Dr. Kinney and others have shown various deficits in infants, but the ones who die of SIDS have in common deficits in either the number of 5-HT neurons or in receptors for serotonin on those neurons or various other associated abnormalities. All of these suggest that the infants who die of SIDS usually die in their sleep and usually after an episode of apnea – that is, the cessation of breathing with elevated carbon dioxide in the blood to which they fail to respond normally. They fail to respond because the 5-HT system is the system which, in that age group, allows for arousal and increased breathing to respond to that kind of a danger. Since they fail to respond, they do not wake up, they do not breathe, and they die. Tr. 20.

Dr. Miller theorized, consistently with the research of Dr. Kinney and others, that many SIDS infants have "abnormalities of the medullary serotonergic synaptic systems governing respiration and arousal from apnea." *Id.* at 6. He said that "we have data that at least 70 percent of infants who ultimately die of SIDS have a defective 5-HT system which is way over half and thus statistically likely that [J.B.] was one of those." Tr. 62. Dr. Miller said, "It's really a neurochemical question. These molecules (cytokines) are provoked by an immune response, an innate immune response, originally in the periphery, but their effect in terms of SIDS is a neurochemical effect, affecting synaptic transmission and neuronal activity of the 5-HT system and maybe the GABA system in the medulla, and that's a neurochemical synaptic effect." Tr. 61. He stressed that the role of the cytokines in SIDS was in their capacity to modify normal neurologic function rather than being purely immune in nature. He assumed that J.B. was an immunologically normal child, who when given a vaccination would have had an appropriate immune response, including the production of cytokines such as the ones identified by Kashiwagi et al. Therefore, he would expect the level of cytokines to be transiently increased after vaccination. Tr. 62. "These cytokines would have been circulating in his body after vaccination and we have direct evidence that there was some cytokine-central nervous system interaction in that he had fever. Then there is a logical chain of events that says cytokines depressed the 5-HT system in a defective medulla leading to SIDS during sleep." Tr. 62-63.

Dr. Miller stated that research is still identifying all of the exogenous stressors for SIDS. Tr. 44. He opined that one very well-recognized exogenous stressor for SIDS is mild infection. Tr. 45. Some of the estimates indicate that 40 - 50% of SIDS victims have had a very recent or current mild upper respiratory infection (URI) at the time of death. Tr. 45. He said that it is explicit in the literature from Dr. Kinney's laboratory and others that what happens with mild infections is that the response to the infection involves the production of certain cytokines and that those cytokines can act on the central nervous system. He presented a theory: that a mild upper respiratory infection can act as a neurochemical stressor by prompting the upregulation of cytokines, which he theorizes are detrimental in two ways. He said that an infection could cause fever, an extrinsic risk factor, and can cause elevated IL-1β levels, which would further depress a defective medullary 5-HT system. The system would then be incapable of responding to excess carbon dioxide, resulting in death. Tr. 46.

Dr. Miller cited several studies, including ones discussed above by Rognum, Kashiwagi, Kadhim, Brambilla, Stoltenberg, and Froen, that addressed the issue of cytokine stimulation and the function of cytokines entering the central nervous system. From these studies, Dr. Miller concluded that either mild URIs or vaccinations upregulate the production of cytokines, and these inflammatory cytokines, can "shut down" a structurally vulnerable 5-HT system and completely prevent it from restoring an infant's normal breathing. Tr. 35. In other words, the cytokines and the structural defect in the serotonin system acting in concert during a vulnerable period have the cumulative effect of causing SIDS by making the baby incapable of responding to excess carbon dioxide.

Dr. Miller noted that Kashiwagi found similar cytokine profiles in the recently-vaccinated population and those suffering from influenza, and further that the cytokine profiles were similar in post-vaccination babies whether they had a fever or not. Tr. 49. He explained that cells that are injured by infection initially produce an innate immune response. The cells of the innate immune system release cytokines which signal further activation of the adaptive immune system to respond to the foreign antigen. He said that there is a wide range of things that the cytokines produce, but the initial production is certainly peripheral where there is infection. Tr. 50. He testified that there is a whole lot of evidence that cytokines, produced peripherally, interact with the central nervous system and the easiest one to understand is the way fever is produced. He explained that fever is mediated by the central nervous system and specifically by the hypothalamus in the brain. The hypothalamus sets our body temperatures. It causes us to shiver if we are in the cold and need to warm up, or to sweat when we are overheated. Tr. 50-51. He further explained that if the fever was generated in response to an infection outside of the brain, such as in the case of a URI, there would be no inflammation in the brain as the brain is not infected, but there is still an interaction with the hypothalamus in the brain caused by cytokine signaling that causes fever in response to an infection outside of the brain. Tr. 51-52. Dr. Miller stated that he was not aware of any literature describing URI as a *mechanical* exogenous stressor and that in his professional experience conducting autopsies, he had never seen a URI "obstruction of the airway" that would be sufficient on its own to cause death. Tr. 46.

Dr. Miller stated that vaccinations can be an extrinsic risk factor in SIDS, as they prompt the upregulation of cytokines that, among other things, produce fever. Tr. 62-63. He testified that, based on the literature, there is a scientifically-plausible mechanism for vaccinations acting as the extrinsic risk factor in SIDS in much the same way as a mild infection. He explained that when you get a vaccination or a whole group of them at once, as J.B. did, it evokes a response which includes the production of cytokines, and that among those cytokines are IL-6, TNFα, and IL-1β. The physiological studies have shown that these can raise body temperature by producing fever, which is a risk factor, and they can inhibit the activity of 5-HT neurons in the medulla causing prolonged apneas and interference with autoresuscitation. Tr. 54, 62-63. When the vaccines are administered in the presence of the defects in the medulla, during the critical developmental period, they are likely to have a similar effect as mild infection that may cause a failure of the medullary response system and ultimately a death. Tr. 54.

Dr. Miller stated that mild upper respiratory tract infection is widely recognized to be an exogenous stressor under the Triple Risk Model. However, he acknowledged that there is not wide recognition, or a generally accepted theory, that vaccinations are an exogenous stressor. He stated that the Institute of Medicine concluded "the evidence is insufficient to say that there is an effect or there isn't an effect." Tr. 55. The Kinney research team has not studied the relationship between vaccination and SIDS. Tr. 60. Dr. Miller pointed to "multiple reports of similar cases of SIDS following various neonatal or infant vaccinations, mostly stressing the close temporal relationships between vaccination, increased cytokine production, and death from apparent SIDS as seen with this case."[71] He said that these individual cases and small case series show a "suspicious association between the timing of vaccination and the timing of SIDS deaths." Tr. at 55.

Summarizing his theory and review of the literature, Dr, Miller testified that the papers cited, including Kadhim, Kashiwagi, Rognum, Stoltenberg, and Froen, "verify the importance of the 5-HT system and its interactions with the GABA system in the medulla in terms of response to apnea or other respiratory-related insults." Tr. 34. Second, "they showed that there's an altered cytokine profile in SIDS cases versus non-SIDS cases, dying of other things, like drowning or trauma." *Id.* Third is the specific information on IL-1β, in that it inhibits the 5-HT system. *Id.* Therefore, in the context of SIDS, this suggests that if there is an elevated level of IL-1β to which the 5-HT neurons are exposed in an infant who already has too little 5-HT activity because of a defective brainstem, this additional cytokine effect would shut down the system such that it would not respond to other external stressors such as prone sleeping, nicotine, infection or fever. Tr. 34-35.

Dr. Miller addressed this analysis in terms of the cytokine reaction generated by vaccines. He said that we know that when a child gets a vaccine or a whole group of vaccines all at once, as occurred in this case, it evokes a response which includes the production of cytokines; that among those cytokines are IL-6, TNFα, and IL-1β. Those levels go up in the blood. We know that IL-1β can inhibit the activity of the 5-HT neurons in the medulla. If you take an infant who has a defective medulla with a defective 5-HT system already, you put in a stress situation with elevated carbon dioxide or low oxygen, and there is a vaccination which further shuts down the 5-HT system, and you can get a complete failure of response and therefore a death. He concluded that the mechanism is plausible. Tr. 54.

### ii. *Althen* Prong Two: Logical Sequence of Cause and Effect

Dr. Miller then applied his theory to J.B.'s specific case. As an initial matter, he agreed with the decision to classify J.B.'s death as SIDS. Exhibit 13 at 1. Under the Triple Risk Model, Dr. Miller opined that J.B. was in the critical developmental period. Tr. 44. Statistically, he was inherently vulnerable. Dr. Miller opined that Kinney et al. have found that a significant proportion – up to 70% – of SIDS infants have abnormalities in the arcuate nuclei and other sections of the medulla. Exhibit 13 at 3. Dr. Miller said that there is also a Japanese study in

[71] Vege & Rognum (2004), Exhibit 13-Q; Kries et al. (2005), Exhibit 13-R; Zinka et al. (2006), Exhibit 13-S; Ottoviani et al. (2006), Exhibit 13-T; Traversa et al. (2011), Exhibit 13-U; Institute of Medicine, *Adverse Effects of Pertussis and Rubella Vaccines* (1991), Exhibit 13-V.

which that number went as high as 90 percent. Tr. 38. He testified that it is statistically most likely that J.B. also had this medullary 5 HT defect based on the Kinney data and other studies, even though it was not confirmed because the medical examiner did not sample that section of the brain. Exhibit 13 at 4-6; Tr. 37-38. Dr. McCusker agreed that "according to the Triple Risk theory, the brain problem must exist [in J.B.'s case]." Tr. 206.

A great many autopsies of SIDS infants outside of the research context do not section all of the necessary areas of the brain or view them histopathologically, which is typical of medical examiner autopsies. Tr. 16. Respondent's expert pathologist, Dr. Harris, acknowledged that based on Dr. Kinney's research, the majority of SIDS babies and up to 70% in some of her studies had an abnormality of the 5-HT system. Tr. 346. However, "[d]etection of these abnormalities requires special immune-histochemical research techniques not generally available for a 'routine' autopsy." *Id.* Dr. Miller testified that even in some autopsies where no structural abnormality was found in Dr. Kinney's research, when the full histochemistry was performed, there were still receptor binding deficits, such as in the IL-6 and gp130 studies. Tr. 41-42. Unfortunately, the types of tools she used including autoradiography and immunohistochemistry are not generally available for autopsies. Tr. 42-43.

Dr. Miller discussed the logical sequence of cause and effect between vaccines administered on September 2, and J.B.'s death on September 3. He opined that the vaccines acted as a critical external stressor in this case. He noted that J.B. was a "healthy infant… developing normally." Exhibit 13 at 4. He was "immunologically normal." Tr. 62. Therefore, after receiving vaccinations, his body mounted an innate immune response including the production of cytokines. Exhibit 13 at 6; Exhibit 16 at 1; Tr. 63. Those cytokines circulated in J.B.'s body, specifically into the central nervous system. Exhibit 13 at 6; Tr. 63. These peripheral cytokines interacted with the hypothalamus to provoke fever the night after the vaccinations, and the following day (before J.B.'s death). Exhibit 13 at 6; Exhibit 16 at 1; Tr. 62-64. "Those cytokines then acted in the brainstem which was already deficient in serotoninergic drive for respiratory effort, leading to an apneic episode from which he did not recover, i.e., SIDS." Exhibit 13 at 6; *see also* Tr. 62 (the cytokines "depress[ed the] 5-HT system in a defective medulla, leading to SIDS during sleep").

He opined that there was "no other demonstrable inciting event" for J.B.'s death. Exhibit 13 at 1. There was no evidence of the fever being related to anything other than J.B.'s vaccinations. Tr. 66. The autopsy did not identify any other infectious processes. Tr. 66.[72]

Dr. Miller was asked whether the pillow in J.B.'s crib increased the risk of SIDS. Tr. 87. Dr. Miller was not sure whether J.B.'s head was on the pillow. *Id.* He said, "If the pillow was by his feet, I don't think it's a risk factor." *Id.* A review of the investigation files indicates that there was no evidence as to whether or not his head was on the pillow. The only relevant evidence was that it was "a little crib pillow-very flat" and that his mother told the police that his nose or mouth were not covered when she found him about ten minutes after replacing his pacifier. Exhibit 7 at 5.

[72] Dr. Miller noted that there was bacterial growth and food particles in J.B.'s lungs and epithelial cells in the upper airways. He opined that this was not evidence of a separate infectious process. He agreed with the medical examiner that these were terminal or resuscitative events. Tr. 17-18; 66; 352-53.

On cross-examination, Dr. Miller stated that J.B. was placed on his back but was found on his side, which demonstrates that he was able to "move around." Tr. 92. However, J.B. did not pass away until "something else intervened." Tr. 85. Based on his theory and the temporal association, Dr. Miller opined that the vaccines were the intervening factor that caused J.B.'s death. Tr. 85; Exhibit 7 at 5. He said that he looks at SIDS cases individually and that it was his diagnosis that the vaccines contributed substantially to the death of J.B. in this case. Tr. 106-08.

#### iii. *Althen* Prong Three: Timing

With regard to timing, Dr. Miller stated several reports "have noted an elevated risk for SIDS within the first 48 hours following immunization, although this is not statistically significant." Exhibit 13 at 5. He stated that J.B. died within this 48-hour "window of elevated risk" following vaccination. *Id.*

Dr. Miller also stated that the available evidence is that foreign antigens, like those contained in vaccinations, activate the production of cytokines "within hours" and that production "peaks within 2 to at most 4 days." Exhibit 16 at 1. Thus, a vulnerable infant who receives vaccinations is most likely to suffer a fatal event if one is to occur "within the first 48 hours to at most 4 days." *Id.* Dr. Miller opined that J.B.'s death was "well within this vulnerable period." *Id.*

### 2. Respondent's Expert Dr. Christine McCusker

Dr. Christine McCusker earned a Masters in Molecular Virology in 1988, followed by an M.D. in 1993, at McMaster University, in Hamilton, Ontario. Exhibit D at 1. Her residency training was in pediatrics, at Montreal Children's Hospital, McGill University, from 1993-1996. *Id.* at 2. She was then a clinical fellow in allergy and immunology at McGill University from 1996-1999. *Id.* Dr. McCusker is board certified in pediatrics. *Id.* She is currently the division director of pediatric allergy, immunology, and dermatology at the Montreal Children's Hospital at McGill University Health Center and is the director of the Clinical Immunology Lab. Tr. 122. She has a wet lab that studies developmental immunology, which has peer-reviewed funding. *Id.* She also runs a clinical research program that uses databases to follow patients with primary immunodeficiency. *Id.* In addition, she sees pediatric patients at McGill Children's emergency room and at several allergy, immunology, and general pediatrics clinics. Tr. 124. Dr. McCusker also teaches medical students in the areas of immunology, dermatology, and malignant hematology. *Id.*

#### i. *Althen* Prong One: Response to Petitioners' Medical Theory

Like petitioners' expert Dr. Miller, Dr. McCusker accepted Dr. Kinney's formulation of the Triple Risk Model. Dr. McCusker agreed with Dr. Miller on the critical development period, and that an infant may be "vulnerable" because of a brain defect, premature birth, male gender, and/ or African American race. Dr. McCusker disagreed with Dr. Miller's opinion that upper respiratory infection, and by extension, vaccines, act as *neurochemical* exogenous stressors within the Triple Risk Model.

Dr. McCusker spent considerable time explaining why upper respiratory infection and other exogenous stressors, such as "being placed or found in a prone/ side-sleep position, found face down, head covered, sleeping on an adult mattress, couch, or playpen, soft bedding, bed-sharing, and signs of upper respiratory tract infection," are *mechanical*. Specifically, each one impedes an infant's ability to exhale carbon dioxide and inhale fresh oxygen, thereby increasing the risk of SIDS. Tr. 127-28.[73]

She opined that the prone sleep position is more widely recognized as an exogenous stressor for SIDS, but that the side-sleep position poses just as much risk. Tr. 131. She stated that breathing depends on "drop[ping] the diaphragm down and creat[ing] a negative airspace, [in which] the air comes rushing in." Tr. 130. An infant's body is not fully developed, so it uses "more than just the diaphragm" and "a lot of abdominal muscle to breathe." *Id.* An infant lying supine with the head back breathes most easily. *Id.* In contrast, an infant in either the prone or side-sleep position has more difficulty dropping the diaphragm and exhaling carbon dioxide. *Id.* Dr. McCusker also opined that the side-sleep position compresses "at least half your rib cage." Tr. 132. She stated that an infant's rib cage is "soft" and "very pliable." Therefore, it does not take much to influence the infant's ability to exchange air. *Id.* She also noted that an infant's breath is much more shallow and rapid than an adult's, and therefore the diffusion of exhaled carbon dioxide is less than in adults and rebreathing is more likely. *Id.* Theoretically, this means that an infant is at greater risk of re-inhaling expelled carbon dioxide. *Id.* Dr. McCusker acknowledged that the Back to Sleep Campaign previously advised parents to avoid all risk factors for SIDS, and that early research emphasized avoiding prone sleeping. *Id.* at 132-33. However, she said more recent studies looking "a little bit more closely" indicate that "prone and side-sleeping have equal risk." Tr. 134. She also stated that an infant learns to roll from the supine position to the side or prone position, but "usually not until somewhere between four and six months." Tr. 134-35. She did acknowledge, however, that the American Academy of Pediatrics does say that once a child is able to roll from his back to his side or to prone, then the parent should not disturb them. They should just have nothing else in the crib that could obstruct breathing. Tr. 135.

She also stated that gastroesophageal reflux is an exogenous stressor. Tr. 137. Specifically, an infant's airway and esophagus are linked at the back of the throat. *Id.* An infant may regurgitate and inhale at the same time, and therefore stop breathing momentarily. *Id.* at 138. If the infant neither swallows nor expels the food, his breathing will become obstructed and he will not recover. *Id.*

Dr. McCusker stated that bundling is an exogenous stressor and suggested several possible reasons why. *Id.* at 135. First, she opined that bundling decreases an infant's arousal, which helps the infant go back to sleep, but may increase the incidence of SIDS. *Id.* at 136. Second, a bundled infant may be less able to roll out of the prone or side-sleeping position. *Id.* Third, bundling may be an exogenous risk factor by leading to hyperthermia. *Id.* It should be noted that there is no evidence of bundling in this case, as J.B.'s father said he placed him on his back with a blanket across the midsection, but there was no indication that he was wrapped or bundled.

[73] Trachtenberg, Kinney, et al. (2012), Exhibit C-11.

Dr. Miller stated that hyperthermia was a term encompassing both high ambient temperature and fever. But Dr. McCusker disagreed. She testified that hyperthermia was high ambient temperature, and *hyperpyrexia* was fever. She stated that older literature listed both hyperthermia and hyperpyrexia as exogenous risk factors for SIDS. Tr. at 201, 287. However, she opined that newer literature, such as an article by Trachtenberg, lists hyperthermia as a risk factor for SIDS, but not fever. Tr. at 201, 287, 290. She agreed with this distinction. She reasoned that an infant experiencing hyperthermia tries to cool himself down. Tr. 289. To do so, the infant takes short, shallow breaths, which increase CO2 levels, which trigger the pathway to SIDS. Tr. 288, 295. She cited an article by Harper and Kinney, which provides that "vasodilation associated with overheating makes compensation for low blood pressure more difficult."[74] Dr. McCusker opined that fever is *not* a risk factor for SIDS. Specifically, she said in fever the body fasciculates or shivers – it makes small muscle movements that create friction, which generates heat inside the body. *Id.* at 184. The body cannot make these movements during deep REM sleep. Therefore, it stays in NREM sleep. *Id.* at 184-85. She opined that an infant generating or maintaining a fever, who does not descend into REM sleep, is less susceptible to SIDS. *Id.* at 202. It should be noted that nowhere in the submitted literature was an explicit distinction made between hyperthermia and hyperpyrexia, including in Trachtenberg or the Harper & Kinney article. Dr. McCusker is correct that in a 1992 article by Dr. Kinney, she mentioned "infection, fever and hyperthermia" as exogenous stressors.[75] Later articles generally reference hyperthermia and overheating. However, in a 2009 article, Dr. Kinney described a SIDS scenario in which in part she describes "an infant may be slightly febrile due to an otherwise trivial upper respiratory tract infection (3) as a consequence, the apnea component of the LCR is inordinately prolonged by mild hyperthermia,"[76] This reference would appear to suggest that the term hyperthermia may be more broadly inclusive.

Unlike Dr. Miller, Dr. McCusker characterized mild upper respiratory infection as a purely mechanical extrinsic risk factor for SIDS. Tr. at 127-28. She opined that an infant is accustomed to breathing through the nose, which enables uninterrupted bottle or breast-feeding. *Id.* at 138-39. When the nose is congested, she said, the infant still exerts significant effort to breathe through the nose, which elevates carbon dioxide. *Id.* at 139. If and when the infant finally resorts to breathing through the mouth, that is less effective and also increases the risk of respiratory distress. *Id.* at 140-43.

Dr. McCusker then spoke about cytokines. She asserted that cytokines serve a variety of positive functions in the healthy human brain. *Id.* at 145-58.[77] Researchers initially theorized that cytokines found in the brain, including IL-6, IL-1$\beta$, and tumor necrosis factor-alpha (TNF-alpha), had traveled there through the cerebrospinal fluid, to respond to inflammation in the brain. *Id.* at 151-52. However, research beginning in the late 1990s indicates that the brain itself

[74] Harper & Kinney (2010), Exhibit C-12 at 3.

[75] Filiano & Kinney (1992), Exhibit 13-A at 401.

[76] Kinney et al. (2009), Exhibit 13-H at 539.

[77] Besedovsky, H.O. and A. del Ray, *Central and Peripheral Cytokines Mediate Immune-Brain Connectivity*, 36 Neurochem Res. 1 (2011), Exhibit C-3.

produces cytokines. *Id.* at 152. Dr. McCusker cited articles reporting that inflammatory cytokines such as IL-6 and IL-1$\beta$ regulate pain sensitivity, memory consolidation, stress, fever, and sleep. *Id.* at 152-56.[78] Ron-Harel wrote, "Pro-inflammatory cytokines are abundantly expressed in healthy brain and are involved in the regulation of many physiological functions such as pain sensitivity, memory consolidation and neural plasticity. Elevation in brain cytokine levels is considered part of the adaptive response to external stimuli. Exposure to acute psychological stressors by induction of adrenalin, noradrenalin and dopamine induces an increase in brain proinflammatory cytokines which modulate the neuroendocrine and behavioral response to the stressor. *Id.* at 3. She also cited an article by Moidunny et al. suggesting that cytokines including IL-6 may play a neuroprotective role in the brain after stroke or head trauma. *Id.* at 157.[79] Moidunny was studying the role of IL-6 in reducing glutamate excitotoxicity in stroke and head trauma with the goal of further research to identify additional pharmacological protection with IL-6 from glutamate neurotoxicity in these patients. Moidunny does not discuss SIDS or the role of peripheral cytokines in this article.

Dr. McCusker also cited to an article by Chen Miller, which discusses the role of Tryptophan Hydroxylase 2 which is a rate limiting enzyme in 5-HT biosynthesis. The article discusses advances in understanding Tryptophan Hydroxylase TPH and TPH2 which are critical for the initiation of the synthesis of 5-HT (serotonin) which modulates the stress response by interacting with the hormonal hypothalamic pituitary adrenal axis and neuronal sympathetic nervous system. The TPH2 mRNA expression is abundant in the raphe nuclei or regions containing raphe nuclei such as the pons and medulla, while it is detectable in a number of other regions including the cortex, hypothalamus, thalamus, hippocampus, amygdala and cerebellum. TPH2 gene expression is sensitive to stressful events including hemorrhage and hypoxia and involves neuronal and hormonal mechanisms. The article hypothesizes about the role of TPH2 and serotonin in response to stimulating events such as hypotensive hemorrhage, hypoxia and adverse events experienced in early life or as an adult, and a possible role in such conditions as PTSD but it was not clear how this paper directly addresses the issue of respiratory depression in SIDS. [80]

Dr. McCusker argued that the various animal studies cited by Dr. Miller were not relevant to cytokines' effect in infant brains *in vivo*. *Id.* at 162-87. First, she stated that the Brambilla article,[81] which showed that IL-1$\beta$ depressed serotonin in rats' brain tissue, was not

---

[78] Ron-Harel, N. et al., *Brain Homeostasis is Maintained by "Danger" Signals Stimulating a Supportive Immune Response Within the Brain's Borders*, Brain Behav. Immun. (2011), Exhibit C-1; Su, Y. et al., *Predator Exposure-Induced Cerebral Interleukins are Modulated Heterogeneously in Behavioral Asymmetry*, 135 Immunol. Let. 158 (2011), Exhibit C-4; Kinney et al. (2011), Exhibit 13-F.

[79] Moidunny, S. et al., *Interleukin-6-Type Cytokines in Neuroprotection and Neuromodulation: Oncostatin M, but not Leukemia Inhibitory Factor, Requires Neuronal Adenosine A1 Receptor Function*, 114 J. Neurochem. 1667 (2010), Exhibit C-2.

[80] Chen, G.L. & G.M. Miller, *Advances in Tryptophan Hydroxylase-2 Gene Expression Regulation: New Insights into Serotonin-Stress Interaction and Clinical Implications*, 159B Am. J. Med. Genet. B. Neuropsychiatr. Genet. 152 (2012), Exhibit C-15.

[81] Brambilla, D. et al., *Interleukin-1 Inhibits Firing of Serotonergic Neurons in the Dorsal Raphe Nucleus and Enhances GABAergic Inhibitory Post-Synaptic Potentials*, 26 Eur. J. Neurosci. 1862 (2007), Exhibit 13-M.

relevant to sleeping infants. *Id.* at 185. Specifically, the Brambilla study submerged rats' brain tissue in "super-physiologic doses" of IL-1*β* for an extended period of time; and kept it isolated in petri dishes, which would not reflect what happens to a vulnerable infant in a "crisis situation." *Id.* at 186-87.

Similarly, Dr. McCusker opined that the Stoltenberg and Froen articles,[82] which reported that very young piglets did not recover from apnea as quickly when they received super-physiological doses of cytokines, had limited significance. *Id.* at 162-63. The articles reported this effect only in piglets younger than fifteen days old; in a previous study, cytokines did not have any effect on older piglets. *Id.* at 163. Dr. McCusker opined that pigs' and infants' respiratory systems develop at similar paces; therefore, piglets younger than fifteen days old could be compared only to infants under one month old. *Id.* at 164. Furthermore, she argued that Froen induced extremely high cytokine levels that would not occur naturally in infants. *Id.* at 171. On rebuttal, Dr. Miller responded to this criticism, by saying that pigs' *brains* are very different from human brains. Pigs are born with much more myelin than adult brains; they are much more mature than our brains. The piglets are walking and do things early in piglet life that humans take up to a year or more to do. Thus, this model is not an irrelevant model for a 4-month-old in terms of brain development. He noted correctly that what Stoltenberg and Froen were looking at was *brain physiolog*y or pathophysiology. They were not looking at respiratory development in terms of pulmonary or bronchial development or vascular or cardiac development. They were looking at the responsive neurons in the brain. Tr. 358.

Dr. McCusker also argued that studies of cytokine levels in human brains were only observational, and did not support Dr. Miller's theory. She stated that the Rognum article[83] found similar IL-6 levels in SIDS infants *with* and *without* minor infections. She argued that if infection upregulates cytokine levels, the data between these two groups should be different. *Id.* at 173-74.

Dr. McCusker opined that cytokines play a protective role. Specifically, they maintain homeostasis in the body. She stated that cytokines carry messages (e.g., that an infant's breathing is disrupted) to receptor cells, which contain gp130 molecules, which are supposed to respond to those messages (e.g., by prompting the infant to arouse or gasp). *Id.* at 174-77. Dr. McCusker noted that the Rognum article reported that SIDS brains showed increased binding of IL-6 to neurons in the arcuate nucleus, but no corresponding increase in expression of gp130 (a "signal transducer" for the 5-HT system).[84] She said that if the lack of a corresponding increase in gp130 is physiologically important, which "is a big if," it would imply that the increased IL-6 would not be doing anything. Tr. 175

---

[82] Stoltenberg et al. (1994), Exhibit 13-J; Froen, J.F. et al., *Adverse Effects of Nicotine and Interleukin-1β on Autoresuscitation After Apnea in Piglets: Implications for Sudden Infant Death Syndrome*, Pediatrics (April 2000), Exhibit 13-K.

[83] Rognum, Kinney et al. (2009), Exhibit 13-N; Kadhim et al. (2010), Exhibit 13-O.

[84] Rognum, Kinney et al. (2009), Exhibit 13-N.

As Dr. Miller mentioned, Rognum suggested that IL-6 may have "aberrant interactions" with the arcuate nucleus, leading to SIDS. However, Rognum also suggested another theory: that the "increased expression of the IL-6R in the arcuate nucleus *may be a compensatory mechanism* as defective arcuate neurons may require excessive IL-6 stimulation in order to respond to altered CO2 levels." *Id.* at 528 (emphasis added). Kinney cited this theory, writing: "The expression of IL-6 is elevated in the arcuate nucleus in SIDS infants, which may reflect a compensatory mechanism whereby defective arcuate 5-HT neurons require excessive cytokine stimulation to respond to infection-induced hypercapnia."[85] Dr. McCusker adopted and elaborated on this theory suggesting that IL-6 mounts a protective response. Tr. 157. She cited an article by Moidunny, which states that some IL-6 cytokines have "neuroprotective properties" and that IL-6 requires gp130 receptor subunits to be activated for signaling.[86] When a stressor – such as inadequate oxygen or hypoxia - occurs, the cytokines bind to the 5-HT system, which expresses gp130 molecules to prompt a response – such as prompting the body to turn over or gasp. Tr. 155-56, 161, 175-77, 241. Dr. McCusker opined that these responses can be "quite rapid, within hours or days." Tr. 180-81. Based on these findings, Dr. McCusker suggested that SIDS infants have potentially protective IL-6 molecules in the brain, but in SIDS infants hey fail to prompt the upregulation of gp130 molecules. Thus the IL-6 is ineffective. Tr. 176

Dr. McCusker stated that neither the Kinney team nor the AAP lists vaccinations as a risk factor for SIDS. *Id.* at 144. Dr. Miller testified to a conversation that he had with Dr. Kinney who told him that she did not want to study vaccines because she did not want to testify and did not want to be involved in vaccine controversies. Tr. 60. Dr. McCusker acknowledged that medical literature has reported a temporal association between vaccination and infant death in certain cases. Specifically, the Ottaviani study reported that a three-month-old white female infant received a hexavalent vaccine, lost consciousness one hour later, did not recover upon resuscitation, and passed away a few hours later.[87] Dr. McCusker highlighted that Ottaviani suggested the case might fall into a "SIDS 'gray zone'" because it was "difficult to establish whether the pathological findings [were] sufficiently severe to have caused the death." *Id.* Dr. McCusker noted that Ottaviani published another study of five infants displaying those same pathological abnormalities; however, that study did not mention vaccinations.[88] Therefore, she suggested that the vaccination in the first Ottaviani case was temporally associated with, but did not cause, that infant's death despite the fact that the author stated that in this case the sudden death in a child with arcuate hypoplasia could have been triggered by the hexavalent vaccine or could have been a gray zone case where it is difficult to determine if the pathological findings were sufficient to cause the death. Tr. at 103. It should be noted that the gray zone study focused on the neuropathology and histopathology of five specific SIDS victims to identify the possible brainstem abnormalities. The victims were chosen for study with no reference to vaccines or other specific causal pattern. The case report involving the child who died three

[85] Kinney et al. (2011), Exhibit 13-F at 195.

[86] Moidunny et al. (2010), Exhibit C-2 at 1668.

[87] Ottoviani et al. (2006), Exhibit 13-T at 101-02.

[88] Ottoviani G. et al., *Sudden Infant Death Syndrome "Gray Zone" Disclosed Only by a Study of the Brainstem on Serial Sections*, 33 J. Perinat. Med. 165 (2005), Exhibit C-16 at 6.

hours after receipt of the hexavalent vaccine was published subsequently to the gray zone study and mentions it as the group's prior work. It does hypothesize that the death could have been triggered by the vaccination or fall into the gray zone category.[89]

Dr. McCusker's comments in her report about the literature submitted by petitioners caused some concern, in that they could be read as misleading. Exhibit C at 7-8. Dr. McCusker stated that in the study by Rognum et al., "although [in SIDS infants] there was increased intensity staining for IL-6R, it was not different from those dying of infectious causes." Exhibit C at 7 (discussing Exhibit 13-N). However, Dr. McCusker did not note that at most the SIDS infants had mild infections, which would not be expected to cause elevated cytokines in the brain, while the other group had severe infections which *would* be expected to cause elevated cytokines in the brain and that "the mean IL-6R intensity grade in the arcuate nucleus was significantly higher in the SIDS group than in the control group."[90] [the control group died of "primarily violent causes."] *Id.* at 521.

Of greater concern was Dr. McCusker's characterization of the article by Kadhim et al. Exhibit C at 7-8 (discussing Exhibit 13-O). She stated: Kadhim et al. "examined IL-2 levels in SIDS versus non-SIDS brains and showed no difference in expression in IL-2 and they hypothesize that IL-2, like the cytokines IL-1β, TNFα, and IL-6, may be expressed in normally functioning brains of infants." Exhibit C at 7-8. Kadhim et al. actually stated; "SIDS victims often have preceding mild infectious/ inflammatory conditions (like coryza/ mild upper respiratory infections, soft stools/ mild gastroenteritis, post-vaccinal fever, etc.)"[91] They compared the brains of SIDS infants to those of infants who died of *severe* infectious/ inflammatory conditions. *Id.* at 123. They found that IL-2 levels were unexpectedly comparable in the two groups. *Id.* Kadhim said, "the comparable (equally intense) expression of IL-2 in SIDS infants was rather unexpected as SIDS victims have no obvious or detectable serious health conditions before death and that autopsies show no obvious cause for their demise. (as per definition). However, this high expression in SIDS would corroborate the tenet that SIDS victims experience hyperimmune reactions with 'exaggerated cytokine response to the often reported preceding mild/trivial infectious/inflammatory conditions. Upregulated cytokines exert serious effects on many biological systems including the turnover, release, and transmission of neurotransmitters; cytokines therefore act as neuro-modulators that could modify neural, neuroimmune, and neuroendocrine functions, and can modify synaptic transmissions." *Id.* at 125. The authors further concluded, "Thus various biological stressors such as infectious inflammatory, ischemic or anoxic, and hyperimmune conditions, and metabolic disorders induce IL-2 which is preferentially expressed in vital brainstem neuronal centers. IL-2 and other subsequently triggered cytokines in downstream immune inflammatory mediators interact with neurotransmitters and/or their receptors and modify their function. The resulting neuronal molecular disequilibrium tips the delicate molecular balance causing dysfunction in those vital

[89] Ottoviani et al. (2006), Exhibit 13-T at 103.

[90] Rognum, Kinney et al. (2009), Exhibit 13-N at 521.

[91] Kadhim et al. (2010), Exhibit 13-O at 122.

brainstem centers in producing disturbed homeostasis with potentially drastic effects on target organs systems and eventual death." *Id.*

Dr. McCusker reviewed the epidemiological papers submitted and noted that an article by Kuhnert found a *decreased* incidence of SIDS in days 1-3 after vaccination, then *increased* incidences of SIDS in days 4-7, 8-14, and 15-21. Tr. 229-35.[92] Furthermore, she stated that other studies did not find *any* temporal association between vaccination and SIDS. First, an article by Jonville-Bera et al. did not find a heightened risk of SIDS in French infants vaccinated at three months old.[93] Second, Toro et al. found that the incidence of SIDS in two-month-old children in Hungary decreased when that country instituted vaccinations at that age. *Id.* at 7.[94] Third, Vennemann et al. did not find an increased risk of SIDS with vaccination.[95] In Dr. McCusker's opinion, "large studies, designed to unmask rare events, have shown no link between vaccination and SIDS and have at least in some studies demonstrated a vaccine protective effect for SIDS." Exhibit C at 7.

At trial, Dr. McCusker added that the Kries study cited by petitioners did not support their case. Specifically, SIDS is defined as a syndrome that only affects children "under one year of age."[96] However, Kries et al. did not find an association between vaccination and death in children under one year old. They found an increased incidence of SIDS only in children vaccinated during the *second* year of life. *Id.* Therefore, she said this study does not support petitioners' theory about vaccination and SIDS. Tr. at 257.

#### ii. *Althen* Prong Two: Response to Petitioners' Opinion of a Logical Sequence of Cause and Effect

Dr. McCusker stated that there was "no evidence" that vaccinations contributed to J.B.'s death from SIDS on September 3, 2011. Exhibit C at 8; Tr. 126. She did not dispute that J.B. was in the critical development period. She agreed that "according to the triple-risk theory, the brain problem must exist" for an infant to succumb to SIDS. Tr. 206.

She agreed that vaccines "increase cytokine circulation." Tr. 195. She also stated that Kashiwagi et al. showed that 24-48 hours after vaccination, a child will have elevated cytokines, whether or not he has a fever. Tr. 199. "Cytokine elevation in this model is independent of fever." *Id.* Dr. McCusker stated that J.B. had a fever, and because he was generally healthy and had no signs of upper respiratory infection, the fever could be attributed only to his vaccinations. Tr. 204-05. The fever was "an indication that [J.B.] was responding… to the vaccine." Tr. 238.

---

[92] Kuhnert et al. (2012), Exhibit C-20.

[93] Jonville-Bera A., et al., *Sudden Unexpected Death in Infants Under 3 Months of Age and Vaccination Status – A Case Control Study*, 51 Br. J. Clin. Pharmacol. 271 (2001), Exhibit C-18.

[94] Toro K. et al., *Change in Immunization Schedule and Sudden Infant Death Syndrome in Hungary*, 42 FEMS Immunol. and Med. Microbiol. 119 (2004), Exhibit C-19.

[95] Vennemann et al. (2007), Exhibit C-17.

[96] Kries et al. (2005), Exhibit 13-R at 1.

She stated that J.B. had a fever on September 3, 2011, but after he was given Advil that morning at approximately 8:00 a.m., his fever resolved. Exhibit C at 4; Tr. 204-05, 237. She also stated that a non-steroidal would last for eight hours. Tr. 192. She stated that "if IL-1β mediated respiratory depression [occurred] in the case of J.B., the Advil he was given would have acted to counter this effect, suggesting that this mechanism was not involved in his death from SIDS." Exhibit C at 5, 8.

Her theory was that J.B. 'was put down for his nap, he rolled over, he started rebreathing, and he died of a sudden infant death due to hypercapnia… independent of any cytokines." Tr. 206. She opined that there were several recognized exogenous stressors in J.B.'s case: formula feeding, side sleeping, soft bedding, and a pillow under his head. Exhibit C at 5; *also* Tr. 128-29. In her report, Dr. McCusker stated that J.B. "was found on his side with his face down on a pillow." Exhibit C at 4 (citing Exhibit 7 at 6). (The sixth page of this exhibit is a confirmation of faxing the record.) However, the preceding page is a handwritten scene investigation form. It states that J.B.'s crib had a "little crib pillow." Exhibit 7 at 5. J.B. was found "on side with head downward." *Id.* The form also indicates that neither J.B.'s nose nor his mouth was covered. *Id.*

At the hearing, Dr. McCusker first testified that J.B.'s "face was downward according to the reports." Tr. 128. On cross-examination, she could not identify where in the record it said that his face was down on a pillow. Tr. 265. She thought "he was found with his head down. There was a pillow in the bed, which is clear from the photos. So, it would be easy to hypothesize that he was at least found face down in the general vicinity of a pillow, and one would wonder what the pillow was doing in the bed if it wasn't for under his head." Tr. 266. She noted that the photos of the crib showed a pillow on one end of the bed and diapers and wipes on the other end. Tr. 266 (discussing Exhibit 9 at 8-9). She opined that J.B.'s head would have been on the end of the bed where the pillow was. Tr. 266-67. Dr. McCusker acknowledged, however, that she did not know whether J.B. was actually found with his head on the pillow. Tr. 267. She also agreed that J.B.'s crib was taken down shortly after his death, after which law enforcement and J.B.'s parents participated in a death scene reenactment. Tr. 267-68. That reenactment does not mention the pillow or any other elements that were in the crib. Tr. 268.

The undersigned asked Dr. McCusker about the "mechanical effect" of the sleep position she assumed that J.B. was found in. Tr. 269. Dr. McCusker stated that side-sleeping, a pillow under the head, "the lack of tight bed sheets," and the "disarray" in the crib all together present "the same risk factors as prone" sleeping. Tr. 269-72. The undersigned commented that these facts were not completely clear from the record. Tr. 272.

#### iii. *Althen* Prong Three: Response to Petitioners' Timing Argument

Dr. McCusker stated that she understood Dr. Miller's testimony to be that "the upregulation of the serotonin through the TPH2 and 1433 system… would not be an instantaneous event and that it would take time and presumably more than 24 hours' time." Tr. 180. She stated that "the production of increasing cortisol that occurs following a stimulus and

upregulation through IL-6 is actually quite rapid, within hours, not days." Tr. 181.[97] But she also stated that Kashiwagi et al. showed that a child will have elevated cytokine levels in the blood 24-48 hours after vaccination. Tr. 198.

### 3. Respondent's Expert Dr. Brent Harris

Dr. Brent A. Harris earned a Masters in Biology from Hahnemann University in 1988. Exhibit A at 1. He then earned a M.D. and a Ph.D. in Pharmacology from Georgetown University in 1995. *Id.* He then obtained post-doctoral training at Stanford Medical School, where he was a resident in Anatomic Pathology from 1995-1999, chief resident from 1997-1998, and a neuropathology fellow from 1997-1999. *Id.* Dr. Harris is board certified in anatomic pathology and neuropathology and is a Fellow of the College of American Pathologists. *Id.* He is currently an Attending Pathologist, Associate Professor in Neurology and Pathology, and Director of Neuropathology at Georgetown University Medical Center. *Id.* He also serves as a Neuropathology Consultant for the Chief Medical Examiner, the National Institutes of Health, Howard University Hospital, the Washington, DC Veterans Administration Hospital, and the American International Pathology Laboratory. *Id.*

#### i. *Althen* Prong One: Response to Petitioners' Theory

Dr. Harris agreed with the other experts that the Triple Risk Model is a generally accepted and reliable model of SIDS. Tr. 345. He could not say whether all extrinsic risk factors are mechanical or whether some of them may be neurochemical. *Id.* at 346. However, he testified that he would want to see conclusive proof before he would list vaccines as a risk factor in a medical report that he wrote. Tr. 348. He was aware of studies finding that vaccinations induce the production of cytokines in the brain, but not of any studies finding that those cytokines have a detrimental effect. Exhibit A at 6.

#### ii. *Althen* Prong Two: Response to Petitioners' Opinion of a Logical Sequence of Cause and Effect

Dr. Harris agreed with the characterization of J.B.'s death as SIDS and that under the Triple Risk Model, J.B. was in the critical development period. Exhibit A at 6. It cannot be confirmed whether J.B. had a brain defect rendering him "vulnerable" because the autopsy did not sample that section of the brain. Exhibit A at 6.

Dr. Harris opined that if vaccinations are found to be an exogenous stressor, they "certainly cannot be proven in J.B.'s death." Exhibit A at 6. He stated that there were "no pathologic findings in the brain or other organs in this case that indicate a vaccine-related death." Exhibit A at 7; *see also* Tr. 328. J.B.'s brain was found to have metabolic glia, which are not fully understood. Exhibit A at 6-7. Dr. Harris also opined: Induction of cytokines after

[97] This may not be an accurate characterization of Dr. Miller's opinion. A review of the transcript did not find a clear statement from Dr. Miller about the timing of cytokine production. But in his expert report, Dr. Miller actually opined that cytokine production would *begin* "within hours" and would *peak* "within 2 to at most 4 days." *See* section above (citing Exhibit 16 at 1).

vaccination is a recognized physiological response involved in the immune process. The primary immune surveillance cells in the brain are microglia.These cells when activated by circulating molecules or direct invasion in the brain by organisms change their morphology and produce a host of cytokines in response. Over-activation of these cells in J.B.'s brain is a non-specific finding that could be related to the prior day's vaccination and/ or infection." Exhibit A at 6. Dr. Harris testified that the "circulating molecules" that activate microglia can be either lipopolysaccharides from bacteria or "circulating cytokines," although this is not completely understood. Tr. 342.

#### iii. *Althen* Prong Three: Response to Petitioners' Timing Argument

Dr. Harris agreed with Dr. McCusker's opinion that cytokine signaling "doesn't happen immediately but happens over a period of time." Tr. 343. He did not otherwise address the timing for the cytokine response or whether it fit the case of J.B.

## III. ANALYSIS

### A. Summary of the Arguments

The parties agree that the sole issue to be resolved is "whether the vaccines that J.B. received on September 2, 2011 caused or substantially contributed to his death." Joint Prehearing Submission at 2. Pursuant to *Althen,* petitioners must show by a preponderance of the evidence a reasonable theory as to how the vaccine could cause the harm at issue, a logical but not scientifically certain explanation of how it did, and show the timing was appropriate given the theory of causation. The Federal Circuit has observed that this preponderance standard enables "the finding of causation in a field bereft of complete and direct proof of how the vaccines affect the human body." *Althen v. Sec'y of Health & Human Servs.,* 418 F.3d 1274, 1280 (Fed. Cir. 2005). The standard permits the use of "circumstantial evidence" and accomplishes Congress's goal that "close calls regarding causation are resolved in favor of injured claimants." *Id.* (citing *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 549 (Fed. Cir. 1994) ("to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program")).

To address the issue in the case, several questions must be addressed. The specific questions for decision are whether inflammatory cytokines generated by a mild infection are likely the critical exogenous stressor in many cases of SIDS when mild infection is also present. The second question is whether the same cytokines are stimulated by the innate immune response to vaccines and whether they are likely to be the exogenous stressor in some SIDS cases, particularly, as in this case, when the child was thoroughly examined by a physician the day before he died and found to be completely healthy, and there was no evidence of viral infection by nasal swab at autopsy.

Petitioners' theory is essentially that a high percentage of SIDS infants, almost 50% in most studies, have no history of a serious illness in the days and weeks prior to death, but have a mild infection or fever at the time of death. In most instances, the mild infection was an upper

respiratory infection, although one author listed post-vaccinal fever among the conditions.[98] In this case, J.B., a nearly five-month-old African American boy, who had been born at 36 weeks, died of unknown causes while napping in the early afternoon one day after receiving his scheduled four-month vaccines. He had a well-documented physical examination the prior day, performed by an M.D. pediatrician who had performed a similar examination about five weeks prior. J.B. was documented to be healthy, with no signs or symptoms of illness. He had patent nasal passages and clear lungs, and he was progressing well in terms of growth and milestones. His pediatrician noted that he was able to raise his head, hold it steady and roll over. In the 28-hour period following vaccination, at 4 a.m. and again at 8 a.m., his mother noticed that he had a mild fever and gave him children's Advil. He seemed to be fine and playing normally during the morning, but was fussy and started running a fever again in the early afternoon. Exhibit 8 at 2. His father then put him in his crib for a nap. He was put in the crib on his back, with a blanket over his midsection. He was using a pacifier. There was a small, flat, crib pillow in the bed. The air conditioning in the house was set at 76 degrees. His mother checked on him and replaced his pacifier during his nap. She came back about ten minutes later, noticed that he had rolled onto his side with his head tilted slightly downward, and he was not breathing. There is no evidence that his breathing passages were in any way obstructed or that his face was down in the bed or pillow when his mother found him. She called 911. Police and emergency medical personnel responded within minutes. J.B. was transported to the hospital when he could not be revived on scene. He was pronounced dead at the hospital.

Under the first leg of the Triple Risk Model, petitioners theorize that J.B. likely had a defective or under-developed serotonin system in the arcuate nucleus or other medullary area, which unfortunately was not examined or sectioned at autopsy. He was clearly within the vulnerable risk period for SIDS in that he was between four and five months old and, given his pre-maturity, only about four months based on dates of conception. He had several intrinsic risk factors in that he was born at 36 weeks, he was male and he was African American, all of which groups are overrepresented among SIDS deaths – blacks more than whites and Hispanics, boys more than girls, and preterm babies more than term babies. As noted above, at birth, J.B. had Apgar scores of 8 at one minute and 9 at five minutes. He had grown to 16 pounds and was well within the average ranges for height, weight and head circumference. He appeared to be meeting expected milestones as documented by his pediatrician. He was receiving good medical care and did not appear to be affected by issues associated with poverty, which is often speculated to account for the overrepresentation of African American babies in the SIDS statistics. He was a boy and it has been suggested, as noted above, that boys are more dependent than girls on an effective serotonin system for sensing the accumulation of carbon dioxide and responding appropriately to clear it.

Also, J.B. was put to bed on his back. At J.B.'s two last appointments, Dr. Wright noted that he slept on his back. The available evidence indicates that he rolled onto his side but was not prone. His mother described in the police reenactment that he had turned to his right side and his head was turned slightly downward. Nothing in the notes of the reenactment indicated that the baby's mouth or nose were in or close to the bedding, and in her police interview his mother noted that his nose and mouth were not covered. His father indicated that he had a fever when he was put down for his nap.

[98] Kadhim et al. (2010), Exhibit 13-O at 122.

Thus, petitioners theorize that he did have a fever during the night, early morning and before his nap. Dr. Miller testified that the fever documents the effect of inflammatory cytokines, likely IL-1 and/or IL-6 signaling from the periphery to the hypothalamus to cause the fever. They also theorize that the fever elevates body temperature, which is another risk factor for SIDS. According to petitioners' theory, because J.B. had no evidence of illness or infection prior to vaccination, it is therefore highly likely that the fever was generated by the vaccines, which likely caused a cascade of cytokines to cross the blood brain barrier and further suppress the function of the already underdeveloped medullary serotonin system during sleep. This caused his death to occur within about 28 hours of the administration of the four-month vaccines.

Respondent disagrees, saying that J.B. was premature, an African American boy, and was side sleeping, all of which are risk factors for SIDS. Citing the principle of Occam's Razor, he argues that it is unnecessary to consider anything beside these known risk factors and that the proximate timing to the administration of the vaccines can be explained by coincidence given that the peak time period of the occurrence of SIDS deaths coincides with the timing of the two month and four month vaccine administration schedules. He further argues that there has not been epidemiology to substantiate a causal relationship between vaccines and SIDS. Dr. McCusker argued that the role of mild infection in relation to SIDS deaths is one of obstructing airways rather than one of chemosensitivity, and she discussed her experience of suctioning the noses of infants brought into the emergency room with upper respiratory infections.

Dr. Miller and Dr. Harris agreed that an ideal autopsy would have sectioned the ventral medulla and that that was not done in this case. They also agreed that the type of histological examination that was done by Dr. Kinney and others would be unlikely to be done in a standard autopsy. Tr. 339. They agreed that there is not definitive proof of defective medullary structures.

### B. *Althen* Prong One

After extensive review of the literature in the field of SIDS causation and listening to the testimony of the experts in this case, I think it is clear that the Triple Risk Model is broadly accepted as the general structure for understanding SIDS, even if the lack of comprehensive autopsies do not allow the medical profession to say that SIDS always has a deficient medullary serotonin system, as demonstrated in up to 75% of the cases examined by Dr. Kinney and her group.[99] She has said that "the most compelling hypothesis is that SIDS is related to a brainstem abnormality in the neuroregulation of cardiorespiratory control."[100] She further observed, "according to the Triple Risk Model, *only* infants with an underlying brainstem disease process die of SIDS, which explains why all infants who are placed prone to sleep or who bed share do not die of SIDS. They do not have the underlying vulnerability." *Id.* at 521. Dr. Miller opined that it is likely that J.B. had this defect based on the data from these studies. Tr. 37. Dr. McCusker agreed, "according to the triple-risk theory that the brain problem must exist." Tr. 206. The "brain problem" described in the triple-risk literature is that in the respiratory control center in the medulla. As such, it is reasonable to conclude that the petitioners have shown by a

[99] Kinney & Thach (2009), Exhibit A-4 at 6.

[100] Kinney et al. (2009), Exhibit 13-H at 519.

preponderance of the evidence that an infant who has died of unknown causes, and in whom autopsy has ruled out other causes, had the inherent brainstem vulnerability. I do conclude that J.B. did.

There is also no disagreement that the Back to Sleep Campaign convincingly demonstrated the danger of prone sleeping. By persuading parents to place babies on their backs to sleep during the vulnerable risk period, the campaign brought about an approximate 50% reduction in the rate of SIDS. Side-sleeping has also been recognized as having an elevated relative risk for SIDS, but the reason for this is not entirely clear. Dr. McCusker stated at some length her understanding of the mechanics of breathing in an infant. Essentially, she explained that the diaphragm drops down creating negative pressure within the lung relative to the atmosphere, at which point air rushes in. She suggested that the stomach muscles which the baby uses to help drop the diaphragm are compressed, as are the soft ribs in infants who are prone or side-sleeping, which reduces the gas exchange. Tr. 129-32. Dr. Miller disagreed with her explanation of respiratory physiology in that he did not find persuasive the notion that side-sleeping in a four-month-old is going to inhibit the ability to have inspiratory motion in the diaphragm, which creates the negative pressure in the lungs. Rather, he said the literature in SIDS has emphasized the pocket of air and re-inhaled carbon dioxide. Tr. 354.

The policy statement by the American Academy of Pediatrics, which was repeatedly referenced by Dr. McCusker but not marked as an exhibit, says that the risk of side-sleeping is similar in magnitude to prone sleeping (2.0 vs. 2.6).[101] The statement appears to focus on the risk of turning if the infant is placed on his side. "The risk of SIDS is exceptionally high for infants who are placed on their sides and found on their stomach. The side sleep position is inherently unstable, and the probability of an infant rolling to the prone position from the side sleep position is significantly greater than rolling prone from the back." *Id.* at 7. Interestingly, the same report addresses the issue of children who are able to roll over, which it notes generally occurs at 4-to-6 months of age, and that as they age it is more likely that they will roll. The Academy recommends, "If the infant can roll from supine to prone and from prone to supine, the infant can then be allowed to remain in the sleep position that he or she assumes." *Id.* at 8.

In this case, J.B. was placed supine and he rolled to his side, but not prone. It would appear from this policy statement that the greatest concern with side sleeping is when the infant is placed on its side and can easily roll to the prone position. The fact that the Academy recommends allowing the baby to remain in the position to which he rolls after being placed supine suggests that it is likely that a baby who can roll probably also has developed the ability to raise and turn his head.

All of the experts in this case appeared to agree that at least the predominant thinking in medicine as to the cause of SIDS is explained by the Triple Risk Model. Although as Dr. Harris testified we do not know with certainty that the medullary serotonergic network deficiency is always present because a great many autopsies, such as the one in this case, are not adequate to

[101] Moon R.Y. et al., American Academy of Pediatrics – Task Force on Sudden Infant Death Syndrome, *SIDS and Other Sleep Related Infant Deaths: Expansion of Recommendations for a Safe Infant Sleeping Environment,* 128 Pediatrics 1030 (2011), available at http://pediatrics.aappublications.org/content/128/5/1030.long.

document that deficiency, it was also recognized that as Dr. Kinney stated in a 2009 paper, "only infants with an underlying brainstem disease process die of SIDS."[102] Dr. McCusker agreed that according to the triple risk theory the brain problem must exist. Tr. 206. There has also not been significant debate about the statistical relevance of the other intrinsic risk factors. The success of the Back to Sleep Campaign in educating the public about the danger of prone sleeping has been remarkable in reducing SIDS deaths by half. But the other half still occur. The question remains as to what extrinsic risk factors come to play at that "fatal intersection of vulnerability, critical period and stressor."[103] The literature strongly suggests that SIDS is likely to be multi-factorial. Some cases are likely to be caused by continued prone sleeping, but others are likely caused by other factors. Mild infections, often described as "trivial" infections, appear to be a factor as they have been reported to be present in nearly 50% of SIDS deaths, raising the question of what it is about mild, otherwise non-life threatening infections that appear to interact with the impaired medullary serotonin system during the vulnerable period to cause the "perfect storm" that results in an unexplained death of a child?

Dr. Miller, relying on multiple pieces of research described in the SIDS literature, opined that it is likely that the cytokine signaling triggered in the immune system by mild infection interacts with the underdeveloped 5-HT system in the brainstem, during sleep when the excitatory function of serotonin is reduced, to further suppress the function of the brainstem to cause a cardio-respiratory crisis. The further issue raised is whether, in the absence of a mild infection, can the multiple vaccines administered together – in this case the day before – trigger the same cytokines as does a mild infection with the same fatal result? Dr. Miller concluded that they do.

Petitioners refer to the significant number of SIDS deaths that document the co-occurrence of mild or trivial infections which appear to stimulate a cytokine response similar to that generated by severe infections with adverse or repressive effects on the 5-HT system for chemosensitive response to hypercarbia, leading to failure to arouse and failure to initiate a gasping reflex and ultimately death. Petitioners are not the first to suggest this theory. Dr. Kinney has written, "A causal role for mild infection in sudden infant death is suggested by reports that in approximately half of SIDS cases, the infants have a seemingly trivial infection around the time of death, as well as mild tracheobronchial inflammation and altered serum immunoglobulin or cytokine levels and the presence of microbial isolates at autopsy. In infants who die unexpectedly of infection, the given organism may precipitate *a lethal cytokine cascade or toxic response*."[104] Another article by her group explained the likely mechanism: "During infection, peripherally produced IL-6 may cross the blood brain barrier and bind to IL-6 receptors on 5-HT neurons that mediate homeostasis in response to the infectious stressor and potentially mediate sickness behavior. …We found ubiquitous expression of IL-6 receptors and gp130 neurons in all regions in the infant medulla, including those effector nuclei critical to respiratory and autonomic control, and those that contain 5-HT source neurons. Serotonergic

[102] Kinney et al. (2009), Exhibit 13-H at 521.

[103] Filiano & Kinney (1994), Exhibit 13-B at 197 [also filed as Exhibit A-2].

[104] Kinney & Thach (2009), Exhibit A-4 at 2 (emphasis added).

neurons in the caudal 5-HT system, including in the raphe obscurus and arcuate nucleus, express IL-6Rs on somata and processes, indicating the site of IL-6/5 HT interaction."[105]

Various authors have identified the presence of IL-1β, IL-6, and IL-2, which are all pro-inflammatory cytokines, in elevated levels in the infant medulla in SIDS. Stoltenberg studied the effects of injection of IL-1β in piglets, and theorizes that in addition to cytokines being transported to the brain by retrograde axonal transport, his findings suggested an equally important alternative route in the immune-stimulation of the brain, inducing hypoxia and sudden infant death. He said that it has been shown that IL-1β is internalized by blood brain barrier endothelial cells, which implies that this cytokine passes through the blood brain barrier at the endothelial rather than the ependymal or blood cerebrospinal fluid part of the brain barrier. He found in his experiments with piglets that IL-1 stimulates the release of β-endorphin and the level of β-endorphin in CSF correlates strongly with the duration of apnea. Further, he found that "IL-1β stimulates GABA-transmission and hence increases the inhibitory postsynaptic function by opening of chloride-delective channels, and this will reduce the activity in the central respiratory neurons and may produce hypoxia."[106] Dr. McCusker referred to an article by Besedovsky for the proposition that cytokines are produced in the brain, suggesting that cytokines active in the brain necessarily originate in the brain. However, on review of the article, Besedovsky also noted that some cytokines such as IL-1 and IL-6 are produced both peripherally and within the brain.[107] He postulated that tripartite synapses possess the cellular and molecular components to function as a "relay system" capable of receiving and integrating peripheral immune signals with central neural signals. *Id.* at 5.

One of the best understood functions of cytokines in the case of infection and vaccination is the triggering of fever. When this occurs, cytokines from the periphery at the site of the infection travel to the brain, in particular to the hypothalamus, which then causes fever. As J.B. had a fever in the day following vaccination after having a completely clear medical examination the day before, Dr. McCusker agreed with Dr. Miller that in order for fever to have occurred there had to be a hypothalamic signal, which is mediated by endogenous pyrogens, i.e. IL-6 or TNFα. Tr. 286. The literature also recognizes IL-1 and others which are known pyrogens as well. She also agreed that in the absence of an infection, the only thing we can attribute the fever to is the vaccine. Tr. 205.

After identifying a plausible mechanism for the means of activation of cytokines in the medullary brainstem from a peripheral source, the next key question is why does mild or trivial infection appear to occur in conjunction with SIDS? It is not the infection itself which causes death, as by its mild nature it is not life threatening. Whether the infection is mild or severe, it triggers the innate immune response, which in turn triggers the release of cytokines. As Dr. McCusker explained, cytokines are small molecules that are released by different cell types originally described in immune cells. They are viewed primarily as communication molecules,

---

[105] Kinney et al. (2011), Exhibit 13-F at 191.

[106] Stoltenberg et al. (1994), Exhibit 13-J at 427.

[107] Besedovsky, H.O. and A. del Ray, *Central and Peripheral Cytokines Mediate Immune-Brain Connectivity*, 36 Neurochem Res. 1 (2011), Exhibit C-3 at 1.

because they are released by one cell and bind to another through a series of signaling steps. Tr. 145. Dr. Miller explained that cytokines are messenger molecules that have a lot of different effects which were first identified as products of the innate immune system, but are seen elsewhere as well, including the brain. IL-6 binds with 5-HT and IL-1 has been shown in animals to inhibit 5-HT firing. Tr. 30. There was no disagreement between the experts or in the literature that cytokines are released by the innate immune response to infection, whether it be mild or severe.

The Siljehav-Hofstetter article filed by respondent provides an additional theoretical basis for the role of cytokines in SIDS. The authors found that IL-1β stimulates a prostaglandin (PGE2) with receptors in the rostral ventrolateral medulla. They explained that once stimulated by IL-1β, PGE2 induced depression of this vital brainstem neuronal network, e.g., during an infectious response, that could result in gasping and autoresuscitation failure and ultimately death."[108]

Dr. Miller found further support in the work of Kadhim, who found overexpression of IL-1β in the arcuate nuclei in 17 of 17 SIDS brains studied, but only in 1 of 6 non-SIDS brains.[109] Kadhim noted that cytokines could exert neuromodulatory effects in the ascending reticular activating system, which is involved in the arousal reflex. He noted that IL-1 causes prolonged apneas and depresses respiration and the brain appears to be less effective than the periphery in inducing IL-1 antagonist to terminate IL-1β actions. He hypothesized that the particular pattern of neuronal cytokine he detected might therefore overturn a subtle equilibrium in a molecular chain involving vital brain centers, causing SIDS. *Id.* at 1259.

In a second study involving SIDS brains, Kadhim's group noted that SIDS victims often have preceding mild infections and that cytokines have neuromodulatory effects whereby they can modify neurotransmission. In this study, they compared the brainstems of SIDS victims to those of infants who died of diverse severe pathological conditions, mainly infectious, hemodynamic, metabolic, severe congenital, or other serious conditions. They found that IL-2, another inflammatory cytokine, was preferentially expressed in specific neuronal centers within the brainstem. In this study, they found equally intense immune reactivity within the arcuate and dorsal vagal nuclei in fatally sick infants, as with SIDS victims who had no obvious or detectable serious health condition before death. They hypothesized that a hyperimmune response to mild infection in the SIDS babies may result in a molecular disequilibrium which tips the delicate molecular balance, causing dysfunction in those vital brainstem centers and producing disturbed homeostasis with potentially drastic effects on target organs/systems and eventual death.[110]

[108] Siljehav (2012), Exhibit C-9 at 9897.

[109] Kadhim et al. (2003), Exhibit 13-L at 1256.

[110] Kadhim et al. (2010), Exhibit 13-O at 122-26.

Brambilla also provided some support for this theory by demonstrating in animals that IL-1 inhibited firing of neurons that promoted wakefulness in the dorsal raphe nucleus and enhanced activity of GABAergic neurons which are inhibitory and induce enhancement of NREM sleep.[111]

Rognum further compared brains of SIDS victims to those of babies who died of severe infections and to another group who died from drowning, suffocation, strangulation, or other violent causes. They found that the SIDS babies had higher cytokines in the medullary brainstem than did those who died of violent causes but their levels were not as high as those that died of infectious causes. In a small section of their study, the Rognum group found elevations of IL-6R in the arcuate nucleus in the SIDS and infection groups relative to the controls. However, they found that the gp130, which is necessary for IL-6 to function, did not rise as high above the controls as did the infection group, although it was higher than in those dying violent deaths. This caused them to speculate that the IL-6R might be reactive to an excess carbon dioxide crisis rather than its cause. Thus significant evidence has been produced to show that cytokines are abundantly present in the medullary brainstem of SIDS infants relative to those dying of other causes which strongly suggests a hyperimmune response to mild infection in these children well out of proportion to the mild or trivial infection that they had. The presence of these cytokines also appears likely to suppress the 5-HT response to the accumulate of carbon dioxide in the body and the ultimate failure of the respiratory response system.

The next important question is whether the vaccines can play the same cytokine generating role as mild infection in a child who does not have an infection. If, as his father described, the child developed symptoms such as a fever, crankiness and not being himself, signs of cytokine activation, and had no evidence of infection, could one or more of the seven vaccines he received the day before have generated a cytokine cascade that caused him to be unable to respond to elevated carbon dioxide in his system, whether it was produced by rebreathing or metabolically? Dr. Miller's thesis was that the main role for mild inflammation as a risk factor for SIDS is thought to be in elevating cytokines. He said that is explicit in multiple articles that have been submitted. Then, if vaccines produce the same cytokine responses as very mild upper respiratory infections, which is what is demonstrated by Kashiwagi, it would seem logical to impute both having the same effect on the central nervous system. Tr. 370.

Indeed, Kashiwagi conducted testing with multiple vaccines and studied the cytokine response. He found that there was a more significant response in children who received three or four vaccines at one time than in those who received fewer, and he found that higher IL-1β production was noted in young infants, but decreased at around 2 years or older.[112]

He also examined the cytokine profiles in 61 serum samples obtained from recipients who exhibited febrile illness within 24 hours of being vaccinated and 18 serum samples from recipients without febrile illness. The samples were taken within 48 hours of vaccination in both groups. These were compared to each other and to cytokine profiles of ten normal subjects

[111] Kinney et al. (2009), Exhibit 13-H.

[112] Kashiwagi et al. (2014), Exhibit 17 at 680.

without vaccination. "Higher levels of IL-6, IL-10, IL-12, G-CSF,[113] and IFN-α were detected in both the febrile and non-febrile vaccination subjects in comparison with those in normal subjects." *Id.* at 680.

The Lee and Schulzke studies of multiple vaccine administration to premature infants, referenced above, found an elevation in the rate of apnea, bradycardia, and, in the Lee study, oxygen desaturations (Schulzke did not look at desaturations). Both authors hypothesized that the adverse events may be related to the immune response to the vaccines, particularly as Lee found there was no difference in the rate of adverse events between whole cell pertussis and acellular pertussis. [114] Schulzke noted that the adverse events occurred within 6 to 24 hours of vaccination.[115] While not studying SIDS, these studies focused on premature infants in a controlled environment – a hospital – where the mechanism that is hypothesized to occur in SIDS could be rapidly recognized, addressed, and treated. It seems quite likely that the same sequence occurring post-administration of multiple vaccines may be what occurs in the uncontrolled environment of the home when the child and often the parents are sleeping, or at least not in the same room with the child when the combination of events leading to the fatal sequence occurs.

Dr. Miller's theory, consistent with many of the articles in the literature, is that SIDS is multifactorial. Multiple factors come together at the fatal moment that causes the perfect storm leading to death. He theorizes that the cytokines triggered by the vaccines in the initial innate immune response to the vaccines travel to their receptors in the arcuate nucleus and suppress the serotonin function in a child whose functionality in that area is already impaired by an underdeveloped or defective 5-HT system while he is asleep, which further reduces 5-HT function. The input of the cytokines stimulated by the vaccines causes the lack of response to elevation of carbon dioxide that converts a recoverable event to a fatal one. Whether the vaccine generated cytokines cause additional metabolic activity generating fever and additional production of carbon dioxide, or whether they caused the neurons in the brainstem to be unable to respond to rebreathed or accumulated carbon dioxide, it is probable that they played an important role in causing the death of this infant.

Dr. McCusker disagreed. She argued that the presence of the various intrinsic risk factors together with a flat pillow in the bed and side-sleeping to which the child turned after being placed supine was sufficient to explain the death. She argued that the role of mild infection was that it caused obstruction in the nasal passages in infants who are "obligate nose breathers" (Tr. 138) and mucous in the nose would obstruct the breathing of the child sufficient to cause death. She referred to infants she sees in the emergency room with upper respiratory tract infections who need to be suctioned which then brings down their carbon dioxide level. Tr. 139-40. Dr. Miller disagreed. He stated that he had never seen a SIDS autopsy where the death was

[113] G-CSF is an abbreviation for granulocyte colony stimulating factor. It is another cytokine which mobilizes and recruits neutrophils to the site of inflammation from the marginal pool. Kashiwagi et al. (2014), Exhibit 17 at 693.

[114] Lee, J. et al., *Frequency of Apnea, Bradycardia, and Desaturations Following First Diphtheria-Tetanus-Pertussis-Inactivated Polio-Haemophilus Influenzae Type B Immunization in Hospitalized Preterm Infants*, 6 BMC Pediatr. 20 (2006), Exhibit 20.

[115] Schulzke (2005), Exhibit 21 at 3.

attributed to nasal passage obstruction by mucous and that he had never seen any literature to support that concept. Tr. 355.

The literature certainly suggests that Dr. McCusker's interpretation of the role of mild infection was too limited in that she ignored the entire concept of brainstem chemosensitivity in response to carbon dioxide accumulation. Dr. Kinney wrote, "Serotonergic neurons at the medullary ventral surface and in the midline (raphe) are now known to be preferentially chemosensitive to CO2 and although they are not the only central chemosensitive neurons they appear to play a critical potentially modulatory role. … A small but important population of 5 HTE neurons is embedded within the human arcuate nucleus suggesting that the putative dysfunction in chemosensitivity related to the arcuate anomaly specifically involved these embedded 5 HT neurons."[116] In an article in the New England Journal of Medicine, Kinney wrote, "the arousal from sleep that is triggered by abnormal levels of carbon dioxide and oxygen is essential for the initiation of protective airway responses. … Arousal involves a progressive activation of specific subcortical to cortical brain structures and consists of ascending and descending components that mediate cortical and subcortical arousal respectively."[117] The importance of the chemosensitive role in the stimulation of breathing, arousal, and ultimately gasping in response to the accumulation of excess carbon dioxide appears critical to all of the triple risk hypotheses. A stuffy nose does not explain the inability of the neurons in the arcuate nucleus to modulate breathing rhythm and respond to excess carbon dioxide by initiating breathing, particularly when there was no evidence of mucous congestion in the nose the day before at the medical exam, in the report of the parents, or at the autopsy. The role of cytokines stimulated by vaccines administered approximately 28 hours before seems much more likely to play a critical role, similar to that of mild infection in causing the ultimate convergence of the multiple factors leading to death. The inhibition of the 5-HT response, beyond its initially impaired level with which the child had lived to that date, seems more likely to be caused by the cytokine response to the multiple vaccines than to a stuffy nose or the side-sleeping position to which he had turned, particularly when there was no evidence of nasal congestion or of the breathing passages being obstructed. Exhibit 7 at 5. In fact the evidence was to the contrary.

Dr. McCusker, citing to the Imeri article[118] on sleep in general, also testified that fever would tend to push the child out of REM sleep and into NREM, which she argued would make him more arousable. A review of the Imeri article, which discusses the immune system and sleep in general, and not specifically in infants, does indeed discuss the role of fever and the generation of shivering in NREM sleep and that during the course of most infections there is an increase in the amount of time spent in NREM sleep and a decrease in the amount of REM sleep. *Id.* However, it also discusses the role of IL-1 and the generation of GABAergic inhibitory cytokines. *Id.* at 205. Imeri also acknowledged the role of peripherally generated cytokines in the regulation of sleep. Imeri concluded that at present we know little about these mechanisms

[116] Kinney et al. (2009), Exhibit 13-H at 522.

[117] Kinney & Thach (2009), Exhibit A-4 at 5.

[118] Imeri L. & M.R. Opp, *How (and Why) the Immune System Makes Us Sleep*, 10 Nat. Rev. Neurosci. 199 (2009), Exhibit C-6 at 201.

by which cytokines inhibit REM sleep and argued that it is important because REM sleep is disrupted in many pathologies that involve altered cytokine concentrations. *Id.*

Dr. Miller hypothesized two roles for fever – overheating and travel of cytokines to the brain in the mechanism of SIDS. Dr. McCusker agreed with cytokine signaling as relevant to the production of fever but disagreed that fever was the equivalent of hyperthermia in the SIDS literature. On the witness stand she drew a sharp distinction between environmental hyperthermia and overheating secondary to fever, which she called hyperpyrexia. The literature was unclear on this point. But the significant importance of fever to this case was in demonstrating the travel of peripheral cytokines stimulated by the vaccines across the blood brain barrier to the hypothalamus. Fever is the most obvious manifestation of the signaling of cytokines from the peripheral location of the vaccinations to the brain. The SIDS literature suggests that production of inflammatory cytokines IL-6, IL-10, IL-12, and IFNγ in response to DPT, Hib, and PCV7 were detected in both febrile and non-febrile groups, with febrile illness appearing 12-16 hours post vaccination.[119] NREM sleep is also implicated in SIDS. A distinctive feature of 5-HT neurons is that they exhibit differential firing rates according to the level of arousal, with increased firing during waking, decreased firing during NREM, and almost complete absence of firing during REM. Given the relationship of the firing of raphe 5-HT neurons to arousal, the medullary 5-HT system is postulated to modulate and integrate homeostatic function according to the level of arousal.[120] Thus, particularly in the deeper levels of NREM sleep, the 5-HT system is also functioning at lower levels, potentially contributing to the multi-factorial causal picture.

After review of all of the above, I have concluded that petitioners have presented a reasonable and reliable theory of vaccine causation involving the role of inflammatory cytokines acting as an extrinsic stressor in a baby with a brainstem deficit during the vulnerable time period. It is particularly important to note that the literature indicates that SIDS is likely caused by a multi-factorial process. Dr. Kinney wrote in the New England Journal of Medicine in 2009, "Current evidence suggests that SIDS involves a convergence of stressors that probably results in the asphyxia of a vulnerable infant who has defective cardiorespiratory or arousal defense systems during a critical developmental period when immature defense mechanisms are not fully integrated. Thus our current understanding of the pathogenesis of SIDS reflects the simultaneous juxtaposition of multiple events that, when taken individually, are far less powerful than the result of their chance combination."[121] In another 2009 article she wrote; "We now conceptualize SIDS as the biologic version of the perfect storm, in which the simultaneous and chance combination of multiple events is far more powerful than any individual event alone."[122]

[119] Kashiwagi et al. (2014), Exhibit 17 at 680.

[120] Kinney, H.C., *Brainstem Mechanisms Underlying the Sudden Infant Death Syndrome: Evidence from Human Pathologic Studies*, 51 Dev. Psychobiol. 223 (2009), Exhibit 13-E at 226.

[121] Kinney & Thach (2009), Exhibit A-4 at 7.

[122] Kinney et al. (2009), Exhibit 13-H at 539.

I have concluded that the petitioners have demonstrated by a preponderance of the evidence that the vaccines can and likely did play a critical role in this child's death by stimulating the production of inflammatory cytokines that suppressed the respiratory response system and caused the vulnerable infant to be unable to respond in the normal way to the accumulation of carbon dioxide in his system. Accordingly, petitioners have satisfied the requirement of *Althen* Prong One by presenting a reasonable explanation of how the vaccine could cause or substantially contribute to the child's death.

### C. *Althen* Prong Two

*Althen* Prong Two requires the demonstration of a logical cause and effect as to how the vaccine caused the harm, in this case the sudden unexplained death of J.B. Under *Althen* Prong Two, petitioners must prove that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Capizzano*, 440 F.3d at 1324 (quoting *Althen*, 418 F.3d at 1278).

Dr. Miller testified that it was his diagnosis that J.B. died of SIDS and that the vaccines were a substantial contributing factor to his death. Tr. 126. Having accepted the theory of a causal role of vaccine stimulated cytokines as an exogenous factor converging with the first two prongs of the Triple Risk Model, the question of logical cause and effect requires a review of the likely mechanism and comparing it to the operative facts of the case. Kashiwagi in particular found that cytokines began to be produced 6 hours after stimulation and increased until 24 hours, showing the same level thereafter. Higher levels of IL-1B, IL-6, G-CSF, and TNFα were produced in that study by the concurrent stimulation of three vaccines than by one alone.[123] J.B. received seven vaccines at his 4 to 5 month well baby visit with his pediatrician on September 2, 2011. He was carefully examined and documented to be in entirely good health the day before. Overnight, he developed a mild fever, consistent with cytokine signaling from the vaccination site to the brain. In the early afternoon of September 3, he died during his nap.

Dr. Miller discussed the logical sequence of cause and effect explaining how he believed the vaccines acted as an exogenous stressor which caused J.B. to succumb to SIDS. He noted that J.B. was a "healthy infant… developing normally." Exhibit 13 at 4. He was "immunologically normal." Tr. 61. Therefore, after receiving vaccinations, his body mounted an innate immune response including the production of cytokines. Exhibit 13 at 6; Exhibit 16 at 1; Tr. 62. Those cytokines circulated in J.B.'s body, going to the central nervous system. Exhibit 13 at 6; Tr. 62. These peripheral cytokines interacted with the hypothalamus to provoke fever the night after the vaccinations and during the following day (before J.B.'s death). Exhibit 13 at 6; Exhibit 16 at 1; Tr. 62-64. "Those cytokines then acted in the brainstem which was already deficient in serotoninergic drive for respiratory effort, leading to an apneic episode from which he did not recover, i.e., SIDS." Exhibit 13 at 6; *see also* Tr. 62 (the cytokines "depress[ed the] 5-HT system in a defective medulla, leading to SIDS during sleep").

[123] Exhibit 17 at 679.

He opined that there was "no other demonstrable inciting event" for J.B.'s death. Exhibit 13 at 1. There was no evidence of the fever being related to anything other than J.B.'s vaccinations. Tr. 66. The autopsy did not identify any other infectious processes. Tr. 66.[124]

On cross-examination, Dr. Miller stated that J.B. was placed on his back but was found on his side, which demonstrates that he was able to "move around." Tr. 92. However, J.B. did not pass away until "something else intervened." Tr. 85. Based on his theory and the temporal association, Dr. Miller opined that the vaccines were the intervening factor that caused J.B.'s death. Tr. 85.

An innate immune response to either mild infection or to a vaccine is likely to be fast and begins the process of immune attack of a foreign antigen. Part of that response is the triggering of cytokines to signal further response in the immune system. The triggering of the innate immune system by vaccination is necessary and fundamental to producing the adaptive response and immune memory which vaccines are designed to produce. After review and consideration of all of the testimony and the literature submitted, I have concluded that Dr. Miller has presented a reasonable and persuasive theory that the cytokine cascade triggered by the innate response to the vaccine antigens is similar to the cytokine response to a mild infection, and that the inflammatory cytokines had an immune modulatory effect on J.B.'s impaired medullary 5-HT system causing a prolonged apneic event resulting in his death. As such, the progression from vaccination to an unexplained death within approximately 28 hours is logical.

This logical progression is also consistent with reports of at least mildly elevated SIDS deaths in some studies such as Traversa, which found a 2.0 relationship in the first 7 days.[125] Goldman reported a statistically significant increase in deaths when 5 to 8 vaccines were administered simultaneously as opposed to 1 to 4.[126] Ottaviani[127] and Zinka[128] reported on SIDS deaths within 48 hours of receiving vaccinations. Other studies, such as Kuhnert[129], found neither a protective effect nor elevated risk, but Kuhnert noted that the small number of cases is a problem with the three case control studies he reviewed, particularly in view of the short time periods under investigation. According to Kuhnert, this problem was illustrated by the very broad confidence intervals of estimates that were related to the first few days. *Id.* at 2355.

[124] Dr. Miller noted that there were bacterial growth and food particles in J.B.'s lungs and epithelial cells in the upper airways. He opined that this was not evidence of a separate infectious process. He agreed with the medical examiner that these were terminal or resuscitative sequelae. Tr. 17-18; 66; 352-53.

[125] Traversa et al. (2011), Exhibit 13-U at 8.

[126] Goldman & Miller (2012), Exhibit 19 at 1016.

[127]Ottoviani et al. (2006), Exhibit 13-T.

[128] Zinka et al. (2006), Exhibit 13-S.

[129] Kuhnert et al. (2012), Exhibit C-20.

The statistical prevalence of boys, African Americans and premature babies among the victims of SIDS also seems to be clear and causes their inclusion as intrinsic risk factors. I think it is reasonable to question in this case whether the influence of prematurity would still be a likely factor, given that he had nearly reached the age of five months and appeared to be developing very well. It is also reasonable to question whether the statistical prevalence of African Americans should be a significant factor, as it is often speculated that this may be a function of socioeconomic status and poor medical care. This child appeared to have been living in a two-parent household, with attentive parents, was well-nourished, and was receiving good medical care. The role of his male gender may well have been important, as Dr. Kinney has reported a greater reduction in 5-HT-1A in the medullary raphe in males compared to females dying of SIDS.[130]

Given that Dr. Miller's thesis and that of much of the literature for the Triple Risk Model is that SIDS results from the convergence of multiple factors, it seems likely that his male gender may well have been a contributing intrinsic factor that may have amplified the effect of the cytokine response to the vaccines on the day that he died. But, his gender, his race, and his prematurity – all intrinsic factors – do not explain his death without the interaction with a critical extrinsic factor, which I have concluded was likely the cytokines triggered by the vaccines which depressed his 5-HT system sufficiently that he did not respond when carbon dioxide became elevated in his system.

The evidence for J.B.'s death occurring as a result of his having turned to his side without a causal input from another significant extrinsic factor such as the vaccine stimulated cytokines suppressing his response system is weak in this case. As noted above, the Academy of Pediatrics recommends leaving a child in the assumed position when he has rolled from his back presumably because it is also likely that he can push up and lift his head by the time he can roll. This capability was documented in J.B's case by his pediatrician. Although there was a flat pillow and a light blanket in the bed, J.B.'s mother told the police investigators that his head was not covered and that his head was turned downward only slightly. The scene investigation noted her report that J.B.'s mouth and nose were not covered. Exhibit 7 at 5. It was described that he had been put to sleep in the middle of the bed. Thus, there is no evidence in this case that the baby's breathing passages were obstructed or that he was breathing into an air pocket. The possibility of rebreathing carbon dioxide in that position cannot be ruled out, but seems less likely based upon this evidence derived from the extensive interviews and the site re-enactment performed by the responding police. Thus, even if the side- sleeping position did cause some rebreathing of carbon dioxide, I have concluded from the evidence that it is most likely that the cytokines stimulated by the vaccines caused suppression of the already impaired medullary serotonin system with the consequent failure to chemically sense elevated carbon dioxide, which caused the ultimate failure to arouse and to breathe normally thus substantially contributing to the death of J.B

The emphasis of the Triple Risk Model on prone sleeping has had a powerful impact in reducing SIDS deaths by approximately 50%. But there remains a significant number of SIDS deaths each year, some of which are likely related to continued prone-sleeping and some to side-sleeping. But the co-occurrence of mild infection in the statistics in nearly 50% of cases raises a

[130] Kinney et al. (2009), Exhibit 13-H at 532.

significant issue about the operative extrinsic risk factor or factors in the remaining cases, including many that are found supine. In this case, an apparently perfectly healthy child was found dead a day after vaccination, having had a mild fever in the interim without evidence of infection. He was not prone sleeping but had turned to his side, with no evidence that his breathing passages were in any way impaired. Significant literature introduced demonstrates that the triggering of inflammatory cytokines in response to vaccines is similar to that raised in response to mild infection. J.B.'s post-vaccinal fever provided confirmation of responsive cytokine activity. The cause and effect between the vaccines, the cytokines triggered by the vaccines, and their co-occurrence with other intrinsic and/or extrinsic risk factors in the presence of a defective or underdeveloped brainstem seems likely to have produced the perfect storm that resulted in J.B.'s death. Thus, I am persuaded that petitioners have proved prong two.

### D. *Althen* Prong Three

Under *Althen* prong three, petitioners must provide "preponderant proof that the onset of symptoms occurred within a timeframe for which, given the understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *De Bazan*, 539 F.3d at 1352. The acceptable temporal association will vary according to the particular medical theory advanced in the case. *See Pafford*, 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. *See, e.g.*, *Veryzer v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 344, 356 (2011) (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that petitioner must posit a medical theory causally connecting the vaccine and injury").

Dr. Miller stated that the available evidence is that foreign antigens, like those contained in vaccinations, activate the production of cytokines "within hours" and that production "peaks within 2 to at most 4 days." Exhibit 16 at 1. Thus, a vulnerable infant who receives vaccinations is most likely to suffer a fatal event if one is to occur "within the first 48 hours to at most 4 days." Exhibit 13 at 5. Dr. Miller opined that J.B.'s death was "well within this vulnerable period." *Id.*

In this case, the timing of the innate immune response to the multiple scheduled vaccinations that J.B. received on September 2, to his death the following afternoon appears entirely appropriate for an innate immune response in the vulnerable risk period for SIDS. It is also consistent with reports of at least mildly elevated SIDS deaths in some studies and reports of deaths that occur within the first several days after the vaccination. In this case, one day post-vaccination is appropriate timing, in that inflammatory cytokines stimulated during the innate immune response to the vaccine antigens are likely to be active in close proximity to the stimulating event. As Dr. Miller stated, an adverse event that can be caused by the inflammatory cytokine response to vaccine antigens would be likely to occur within a few days of the vaccination. The cytokine response has been shown by Kashiwagi[131] to occur within 6 to 24 hours of the vaccination, and the very essence of the innate immune response is one that occurs rapidly after the invasion by a foreign antigen. As noted above, that rapid innate immune response is necessary to initiate the ultimate adaptive immune response necessary to achieve the

[131] Kashiwagi et al. (2014), Exhibit 17 at 679.

design purpose of vaccination. The close temporal relationship of the child's death to the receipt of seven vaccines is reasonable and consistent with the theory of neuro-modulation in the arcuate nucleus by the cytokine response to the vaccines. Accordingly, I am persuaded that prong three of *Althen* has been satisfied.

## IV. CONCLUSION

In this case, I have concluded that petitioners have presented sufficient evidence and testimony to entitle them to compensation in the Vaccine Program. I have not concluded that vaccines present a substantial risk of SIDS. In fact, the evidence is to the contrary. The vast majority of vaccine recipients do not succumb to SIDS. Under the multi-factorial analysis of the Triple Risk Model, it is theorized that the ultimate fatal event may occur when multiple factors converge during this vulnerable period to cause death when one stressor acting alone may not have. As Dr. Kinney wrote, "Current evidence suggests that SIDS involves a convergence of stressors that probably results in the asphyxia of a vulnerable infant who has defective cardiorespiratory or arousal defense systems during a critical developmental period when immature defense mechanisms are not fully integrated. The convergence of these factors appears to be far more powerful than any one taken individually."[132] Thus, even if J.B. were rebreathing some carbon dioxide on this occasion, it was likely the combination with the cytokines that caused depression of the 5-HT system that caused his death by blunting the normal chemosensitive response to excess carbon dioxide. The multi-factorial analysis, including vaccines as an extrinsic risk factor, meets the *Shyface* standard that the vaccine need not be the sole or even predominant factor but must be a "but for cause" and a substantial factor in causing the death. *Shyface*, 165 F.3d at 1352. In this case, I have concluded, after review of the evidence, that it is more likely than not that the vaccines played a substantial causal role in the death of J.B. without the effect of which he would not have died. The role of inflammatory cytokines as neuro-modulators in the infant medulla has been well described and is likely the reason for a significant number of SIDS deaths occurring in conjunction with mild infection. I have concluded that it is more likely than not that the vaccine-stimulated cytokines had the same effect in this vulnerable infant during sleep.

**Accordingly, petitioners are entitled to compensation. A separate damages order will issue.**

**IT IS SO ORDERED.**

**s/ Thomas L. Gowen**
Thomas L. Gowen
Special Master

[132] Kinney et al. (2009), Exhibit 13-H at 539.