IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

IN RE: ZOLOFT (SERTRALINE HYDROCLORIDE) PRODUCTS LIABILITY LITIGATION	:	**MDL No. 2342** **12-md-2342**
THIS DOCUMENT APPLIES TO: ***ALL ACTIONS***	:	

MEMORANDUM OPINION

Rufe, J. **August 12, 2014**

Zoloft (sertraline hydrocloride) is a prescription antidepressant, commonly used to treat depression, anxiety, and other mental health conditions.[1] Plaintiffs in this multi-district litigation allege that Zoloft, when taken during pregnancy, causes birth defects in the children born to exposed mothers. The Plaintiffs' Steering Committee ("PSC") proposes to offer the testimony of various expert witnesses on the issue of general causation. These include Dr. Sadler, Dr. Cabrera, and Dr. Levin. Before the Court is Defendants' Motion to exclude the testimony of these three experts. Pfizer does not challenge the qualifications of the experts. The Court has reviewed the expert reports, as well as Defendants' rebuttal expert reports and the briefs of the parties, and held a *Daubert* hearing at which testimony and evidence were presented in support of each position.

[1] Zoloft is one of a class of drugs known as selective serotonin reuptake inhibitors (SSRIs). Serotonin is a neurotransmitter produced endogenously by humans and other animals. The SSRIs do not contain serotonin; rather, they alter the availability of the serotonin produced by the body.

I. STANDARD OF REVIEW

Federal Rule of Evidence 702 reads:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
> (b) the testimony is based on sufficient facts or data;
> (c) the testimony is the product of reliable principles and methods; and
> (d) the expert has reliably applied the principles and methods to the facts of the case.

The Third Circuit has distilled this rule to two essential inquiries: 1) is the proffered expert qualified to express an expert opinion; and 2) is the expert opinion reliable?[2] Here, the challenge is to the reliability of the experts' opinion, not their expertise in their respective fields.

Under the Third Circuit's framework, the focus of the Court's inquiry must be on the experts' methods, not their conclusions. Therefore, the fact that Plaintiffs' experts and Defendants' experts reach different conclusions does not factor into the Court's assessment of the reliability of their methods. The experts must use good grounds to reach their conclusions, but not necessarily the best grounds or unflawed methods.[3]

Expert evidence must be relevant and reliable to be admissible. The Court must consider: 1) whether the expert's theory can be tested; 2) whether studies have been subject to peer review and publication; 3) the potential for error in a technique used; and 4) the degree to which a technique or theory (but not necessarily a conclusion) is generally accepted in the scientific community.[4] The burden is on Plaintiffs to demonstrate that their experts used reliable scientific methods to reach their opinions.

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[2] *In re TMI Litig.*, 193 F.3d 613, 664 (3d Cir. 1999).

[3] *Holbrook v. Lykes Bros. S.S. Co.*, 80 F.3d 777, 784 (3d Cir. 1996); *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 745 (3d Cir. 1994).

[4] *Id.* at 593-94.

II. DISCUSSION

Drs. Sadler, Cabrera, and Levin have been retained by the PSC to opine as to whether: (1) there is a plausible biological mechanism by which Zoloft could cause the injuries at issue in this litigation; and (2) Zoloft causes the birth defects at issue when taken by pregnant women, in clinically appropriate doses, during the first trimester of pregnancy.

A. Opinions Regarding Plausible Biological Mechanisms

Biological plausibility is one of the criteria scientists need to address in opining as to whether an association between a substance and an adverse outcome reflects a causal relationship (i.e. whether the substance is a teratogen), and the PSC has asked three experts to address this criteria.[5] All three experts opine that there is at least one plausible biological mechanism by which SSRIs generally, and Zoloft particularly, may alter embryonic development. In their expert reports, they set forth the basis for their opinions regarding the plausible biological mechanism of injury.

1. *Dr. Cabrera*

Dr. Cabrera is a teratologist, with a Ph.D. in Medical Sciences, whose research focuses on identifying agents that may cause or prevent birth defects. He has conducted *in vitro* and *in vivo* animal studies, most often using mouse models. His research focuses on the impact of immunizations and anti-epileptic medications on developing embryos. He has never performed studies of Zoloft or other SSRIs, but has reviewed relevant publications in connection with this litigation.[6]

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[5] The causation criteria are commonly known as the Bradford-Hill criteria. See further discussion beginning on page 12, *infra*.

[6] Pfizer argues that these experts improperly assume they can generalize from research on one SSRI to other SSRIs (i.e. that there is a class effect). Although the Court found that an assumption of a class effect was unwarranted in the context of human epidemiology (see Memorandum Opinion and Order dated June 27, 2014, Doc. No. 979), and the Court notes that the SSRIs have different chemical structures, and differ in how they are absorbed,

Dr. Cabrera opines that serotonin is an important signaling molecule for organ development in a developing embryo, regulating "cell proliferation, migration, differentiation, and gene expression. . . processes [] fundamental to creating a normally formed embryo."[7] He further opines that SSRI exposure "alters normal serotonin signaling pathways,"[8] and that "[t]here exists a biologically plausible mechanism of teratogenic action (MOA). . . [A]lteration of serotonin signaling by SSRIs, including sertraline, can impact embryonic development resulting in several different congenital malformations, involving various body and organ systems. . . ."[9] Thus SSRIs, including Zoloft, are "capable of causing birth defects."[10]

In forming his opinion for this litigation, Dr. Cabrera reviewed some of the relevant scientific literature on Zoloft, with a particular focus upon Pfizer's pre-clinical animal reproductive toxicity studies data on rodents and rabbits, the only whole animal studies of which he is aware.[11] Pfizer's studies were conducted in the 1980s and presented to the FDA in the application for approval of Zoloft. In his report and testimony, Dr. Cabrera discussed and critiqued Pfizer's studies. For example, he testified that although Pfizer noted an increase in pup deaths in Zoloft-exposed rats (especially at the high doses), when Pfizer looked at the timing of exposure, it concluded that the vulnerability for pup death was late in gestation (days 16 to 21), not during organogenesis.[12] When Dr. Cabrera reanalyzed the data, combining all groups exposed prior to day 15 of gestation, he found a nearly statistically significant increase in pup

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distributed, metabolized, and eliminated, for the purpose of this opinion, the Court will assume, without deciding, that the SSRIs have a similar impact on the serotonin levels of embryos *in vitro*.

[7] Cabrera Report at 19.

[8] Cabrera Report at 20.

[9] Cabrera Report at 13.

[10] Cabrera Report at 43.

[11] Cabrera N. T., 4/8/14 Tr. at 95:14-17.

[12] Cabrera N.T., 4/7/14 Tr. at 196:4-9.

death in that combined group as well.[13] He concluded that the studies suggest a teratogenic effect, but were underpowered to test this effect,[14] particularly with regard to birth defects, and opines that it is "questionable whether any reasoned interpretation could be derived from these studies."[15]

Dr. Cabrera also reviewed *in vitro* studies testing the importance of serotonin pathways in embryonic development and the impact of disruptions to those pathways on various organs and systems. He concluded that there is a plausible mechanism of action by which Zoloft may impact embryonic development and produce the birth defects at issue in this litigation.

Pfizer argues that Dr. Cabrera has never tested his hypothesis about Zoloft, noting that although "in his non-litigation work he conducts and publishes peer-reviewed animal studies regarding medications and birth defects. . . Dr. Cabrera has performed no studies of Zoloft, or any other SSRI, to test any aspect of his hypothesis." While hypothesis testing is indisputably a requirement for scientifically reliable opinions, the Court does not agree that Dr. Cabrera must perform his own studies in order to form a reliable opinion. It is acceptable to rely on the hypothesis testing of others, so long as one addresses both supportive and contrary evidence in reaching one's opinion. In his analysis of the Pfizer animal studies, Dr. Cabrera demonstrates that he has done just that: he did not ignore the findings of those studies from which conclusions at odds with his opinion were drawn; rather he analyzed those studies and explained why those studies did not alter or undermine his own opinion regarding a plausible biological mechanism of injury.

[13] Cabrera N.T.. 4/7/14 Tr. at 193:23-194:8.

[14] Cabrera N.T., 4/7/14 Tr. at 189:22-190:10.

[15] Cabrera Report at 35.

2. *Dr. Sadler*

Dr. Sadler is an embryologist and teratologist with a Ph.D. in anatomy and embryology, who studies the mechanisms of normal and abnormal development in embryos, generally using an *in vitro* whole embryo culture system he co-developed. In an *in vitro* whole embryo study, an embryo is removed from an animal's uterus by caesarian section, with the yolk sac and membranes intact, and the embryo is placed in a prepared laboratory vessel where it can be maintained for 24-48 hours. The embryo is then directly exposed to the medication of interest and observed for one to two days. One advantage of conducting such studies is the ability to introduce a medication at levels which would be lethal if given to a pregnant animal. Disadvantages include the short time frame in which the embryo can be observed and the lack of maternal metabolism in the system.

Much of Dr. Sadler's research has focused upon the association between maternal use of folic acid and a reduction in neural tube defects. He has also extensively studied the impact of diabetes on fetal development. In addition, he has conducted *in vitro* studies of the potential role of serotonin in prenatal craniofacial and cardiac development. He has been retired from active research for approximately 12 years.

Dr. Sadler opines, in relevant part, that serotonin has a known critical role "in cell signaling and a high degree of biological plausibility for the mechanism of injury."[16] Dr. Sadler's report explains why he believes serotonin disruption, through SSRI exposure, is a plausible biological mechanism of injury for a range of birth defects, including heart defects, craniofacial defects, craniosynostosis, neural tube defects, gastrulation, omphalocele, and limb defects. He explains that serotonin is a signaling molecule which regulates fundamental developmental

[16] Sadler Report at 4.

phenomena, including cell proliferation, migration, differentiation, and gene expression, and that these key processes play essential roles in embryological development. Because SSRIs alter cellular concentrations of serotonin, Dr. Sadler believes SSRI exposure may result in a variety of "laterality" (left/right) birth defects, including heart defects, cleft lip and palate, neural tube defect, and limb defects.

Pfizer points out certain difficulties in drawing conclusions about biological mechanisms from *in vitro* studies. For example, when a medication is administered to a pregnant mammal (including a human), the maternal system absorbs, distributes, metabolizes, and eliminates the medication, which effects the embryonic exposure; in an *in vitro* system, the embryo is directly exposed to the drug of interest. Pfizer also notes that when researchers study embryos *in vitro*, rather than live animals, medication can be administered at concentrations which would be lethal to a pregnant animal. While the Court recognizes these limitations to the *in vitro* methodology Dr. Sadler relies upon, the Court does not find that these limitations are methodological *flaws* which render Dr. Sadler's opinion on plausible biological mechanism of injury inadmissible, and the Court is confident that these limitations can be effectively addressed on cross-examination.

3. *Dr. Levin*

Dr. Levin is a molecular developmental biologist with a doctorate in genetics. His relevant research focuses upon mechanisms that govern the patterning of the embryo (e.g., genetic and molecular mechanisms that dictate the asymmetrical positioning of the heart and other organs). He has studied the role of cell signaling mechanisms in embryonic patterning, "with a specific focus on the role of serotonin and voltage gradients [ion channel activity] in this process."[17] Currently, he is working on using ion channel activity to induce limb and eye

[17] Levin Report at 2.

regeneration in injured animals, with the goal of using similar techniques in injured humans at some point in the future.

Dr. Levin's opinion is based primarily upon studies conducted using non-mammals, such as xenopodes (frogs), chickens, and zebrafish. He explained that that for certain developmental processes, such as the development of left-right asymmetry in organ placement, frogs are better models than rats or mice because of their embryonic body architecture.

Dr. Levin opines that serotonin is a "profoundly important medium for cell to cell communication during embryogenesis," and "there are at least three obvious and distinct routes by which SSRI, including Zoloft, exposure can affect embryonic development, causing malformations of the brain and central nervous system, mispatterning of the limbs, heart, and face, and mispositioning of the visceral organs."[18] Specifically, he opines that SSRIs disrupt serotonin levels, ion channels, and intracellular calcium levels, all of which are important to embryonic development, and particularly to normal left-right patterning in embryos (laterality). In his studies on serotonin signaling, he uses SSRIs to study the impact of disruptions in serotonin. However, when he studies ion channels in embryos (which he believes are key to proper development of the brain, face, heart, and appendages), he does not use SSRIs to disrupt the channels, but relies on other drugs.[19]

Dr. Levin's report summarizes the basis for his opinions. He explains how the serotonin transporter works, how Zoloft and other SSRIs affect the transporter, by design, and why this may lead to a variety of birth defects. He points to a study conducted on frog embryos, in which the serotonin pathway was perturbed by treatment with SSRIs, resulting in laterality defects of

[18] Levin Report at 3.

[19] Levin Report at 2.

the heart, gut, or gallbladder, although not the specific types of defects at issue in this litigation.[20] The report does not indicate the dose at which this effect was seen. He does not report seeing evidence of other defects he hypothesizes may be associated with SSRI exposure, such as neural tube defects, limb defects, or even defects within the heart (e.g. septal defects), in this study, but he does cite other studies which demonstrate, for example, that manipulating serotonin levels in mouse embryos impacts craniofacial components.[21]

Pfizer argues that Dr. Levin's opinions regarding plausible biological mechanisms are not reliable because he has not demonstrated that blocking serotonin receptors causes laterality defects. However, the Court finds that Dr. Levin sufficiently supported his opinion that serotonin plays an essential role in embryonic patterning in some species.[22] In his published research he has used several SSRIs to perturb embryonic serotonin in frogs,[23] and it is undisputed that Zoloft impacts embryonic serotonin levels. Therefore, the Court will not exclude Dr. Levin's opinions regarding disruptions in serotonin signaling as a plausible biological mechanism of injury. Any limitations in the research used to support his opinion can be addressed through cross-examination and the presentation of contrary evidence.

Pfizer also argues that Dr. Levin has pointed to no studies demonstrating that Zoloft (or any other SSRI) alters ion or calcium signaling in developing embryos at relevant doses, and that his opinion on these proposed channels are no more than untested hypotheses. Pfizer notes that the two studies on which Dr. Levin relies for his hypothesis regarding calcium signaling were conducted on human cancer cells and canine kidney cells (not embryos),[24] which were exposed

[20] Levin Report at 16-17.

[21] Levin Report at 24.

[22] Levin N.T., 4/10/14 Tr. at 29:20-30:19; 82:7-13; 84:23-85:13.

[23] Levin N.T., 4/10/14 Tr. at 31:22-24.

[24] Levin Dep. at 303:22-304:7.

to concentrations of Zoloft well above therapeutic concentrations. The study he cites in support of his hypothesis regarding ion channels used cultured adult human brain cells exposed to Zoloft, and Zoloft concentrations in neural cells are much higher than concentrations elsewhere in the body. While the Court recognizes that these studies may be informative to Dr. Levin, especially in conjunction with research findings indicating that ion and calcium channels may play an essential role in the embryonic development of some species (although, in his deposition, Dr. Levin agreed that "the field is currently in disarray with respect to an understanding of the role of ion flows in determining left-right patterning")[25] the Court agrees with Pfizer that, at this time, Dr. Levin can only hypothesize as to whether Zoloft exposure will significantly disrupt ion and calcium channels in embryonic cells. The Court cannot allow an expert to testify to an untested hypothesis, as such an opinion does not meet the evidentiary requirement of reliability, and therefore the Court will exclude Dr. Levin's testimony to the extent that he opines as to these alternative pathways, and limit him to discussing SSRIs' "well established effect on the serotonin transporter."[26]

For the reasons set forth above, the Court will not exclude the opinions of these experts to the extent that they opine as to plausible biological mechanisms of injury, except that Dr. Levin will not be allowed to testify regarding ion and calcium channels.

B. Opinions Regarding Teratogenicity and Human Causation

In addition to opining as to plausible biological mechanisms, the experts retained by the PSC have all opined regarding human causation, i.e. that Zoloft can cause birth defects in the children born to pregnant women who take Zoloft in the first trimester of pregnancy. Specifically, Dr. Cabrera opines:

[25] Levin Dep. at 307:16-19.

[26] Defendant's Brief, Doc. No. 692-1 at 26.

> SSRIs, as a class, including Zoloft (sertraline) are teratogens, both in animals and in humans, when ingested during pregnancy. The teratogenicity of SSRIs, including sertraline, has been amply demonstrated in animal studies, as well as in a number of human epidemiological and registry studies. There exists a biologically plausible mechanism of teratogenic action (MOA). . . [A]lteration of serotonin signaling by SSRIs, including sertraline, can impact embryonic development resulting in several different congenital malformations, involving various body and organ systems. . . ."[27]

Dr. Sadler's opinion is summarized in his report as follows:

> In summary, it is my opinion, stated to a reasonable degree of scientific certainty, that maternal ingestion of Zoloft, especially during the first trimester of gestation, disrupts serotonin concentrations and cell signaling, which are critical to normal development of the embryo, resulting in birth defects to multiple organ systems, including cardiac, nervous, craniofacial, skeletal, gastrointestinal and genitourinary. The foundation for my opinions stated herein is based upon my background, training, and experience as an embryologist, as well as . . . research, literature, and documents regarding SSRIs and Zoloft, known critical roles of [serotonin] in cell signaling and a high degree of biological plausibility for the mechanism of injury.[28]

And Dr. Levin also opines that Zoloft may cause birth defects in human babies born to exposed mothers:

> maternal exposure to SSRIs like Zoloft during pregnancy can and does cause or substantially contribute to important defects in embryonic development, and the alteration of serotonergic and bioelectrical signaling by these drugs have high biological plausibility for mechanism of injury to numerous body organs and systems. . ."[29]

To meet the *Daubert* standard, the experts must demonstrate that these opinions are based on methods and procedures of science, not speculation or subjective belief, and they must possess a reasonable degree of scientific certainty regarding their causation opinions.[30] The parties agree that to reach conclusions regarding whether a substance is a human teratogen, scientists must apply Wilson's principles of teratology and the Bradford-Hill criteria.

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[27] Cabrera Report at 13.

[28] Sadler report at 4.

[29] Levin Report at 4.

[30] *See Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 590 (1993).

Wilson's principles of teratology require scientists to consider the following when evaluating a potential teratogen: 1) the genotype of the embryo or the mother, which may interact with the adverse environmental factors; 2) susceptibility to injury will vary with the developmental stage at the time of exposure, with injury most likely during certain critical periods; 3) teratogenic agents act in specific ways on the developing embryos; 4) the route and degree of embryonic exposure, including the characteristics of the agent, the degree of maternal exposure, the rate of systemic absorption and placental transfer, etc, are relevant; 5) the four manifestations of deviant development are death, malformation, growth retardation and functional defect; [31] and 6) adverse events will increase in frequency degree as the dose increases, from a dosage at which there are will be no observable adverse effects to a dose producing 100% lethality.[32]

Scientists use the Bradford-Hill criteria to analyze whether an observed association between a medication and an outcome reflects a causal relationship.[33] The criteria include: 1) the strength of the association between the exposure and the adverse outcomes of interest; 2) replication of findings; 3) the temporal relationship between the exposure and the outcome; 4) the dose-response relationship (looking for correlations between dose and adverse outcome, and identifying the lowest dose that produces the adverse developmental effect);[34] 5) the biological plausibility of or mechanism for such an association; 6) alternative explanations for the association; 7) the specificity of the association (*i.e.*, does an outcome have only one cause, or

[31] Wilson's principles include as adverse outcomes death or growth retardation, as well as malformation; findings regarding death and growth retardation may be relevant and useful to scientists in forming hypotheses about birth defects (malformations), but death and growth retardation are not themselves the outcomes at issue in this case.

[32] PSC Brief, Doc. No. 712 at 8-9.

[33] PSC Brief, Doc. No. 712 at 10.

[34] Cabrera N.T., 4/7/14 Tr. at 133:22-134:5.

several? does genetic susceptibility play a role?); and 8) the consistency with other scientific knowledge.

Although the Bradford-Hill criteria are used to infer causation from associations in many scientific fields, and their application is not limited to the science of identifying teratogens, there is substantial overlap between the Bradford-Hill criteria and Wilson's principles of teratology, so the Court will generally discuss them together.

Pfizer has moved to exclude the experts opinions on human causation, arguing that they were not based on sufficient facts or data (i.e., they are speculative or subjective) and that they are not the product of reliable scientific principles and methods. Although the Court has found that the experts at issue have offered scientifically reliable opinions on biological plausibility, that is but one of the Bradford-Hill criteria. Therefore, the Court must examine the extent to which their opinions on human causation address the other Bradford-Hill criteria.

A. Failure to Address Inconsistent Epidemiological Data

The Bradford-Hill criteria ask first whether there is evidence of a strong, well-replicated association between the variables of interest (here, Zoloft exposure and birth defects). When one is interested in human causation, the most relevant evidence will come from human epidemiological studies. Pfizer challenges the methodology these experts used to reach their litigation opinions on human causation, contending that the experts rely primarily on *in vitro* and *in vivo* studies of animals for their opinions regarding human causation, when such studies are only "third tier" and "second tier" evidence that a drug causes birth defects in humans, and "first tier" evidence, from human epidemiological studies, does not support their conclusions.[35] Pfizer

[35] Def. Brief, Doc. No. 692-1 at 1. The Court notes that this is not an entirely accurate way to look at the evidence, as *in vitro* and *in vivo* animal studies are useful tools for testing some causation criteria (e.g. biological mechanisms, dose responses), while epidemiological studies are better suited to testing other criteria (e.g., the strength of association between a medication exposure and an outcome in humans).

argues that, applying generally accepted scientific principles, the experts cannot reliably reach opinions on human causation without supporting epidemiological research. Pfizer notes that Zoloft has been commonly prescribed for over twenty years, so there is a substantial body of epidemiological research on use in pregnancy, and Pfizer argues that much of that research is inconsistent with the opinions of these experts.

Several courts have held that positive human epidemiological studies are required to reach reliable conclusions as to whether an agent is teratogenic in humans, and causation opinions based primarily upon *in vitro* and live animal studies are unreliable and do not meet the *Daubert* standard.[36] The Court agrees that reliable expert opinions about human causation generally should be supported by positive and replicated epidemiological studies, but reaches a narrower holding here. Specifically, the Court holds that when epidemiological studies are equivocal or inconsistent with a causation opinion, experts asserting causation opinions must thoroughly analyze the strengths and weaknesses of the epidemiological research and explain why that body of research does not contradict or undermine their opinion.

In Dr. Cabrera's report, he indicates that he applied Wilson's principles of teratology, considering genetic susceptibility, timing of exposure, the biological mechanism of action, the various manifestations of deviant development (including death and growth retardation, as well as malformations), and the dose response, which he described in his testimony as the lowest dose that produces the development effect.[37] Dr. Cabrera cited animal research, generally conducted on rabbits and rats or mice, noting that where genetic, cellular, and tissue processes are conserved between species, one can hypothesize from animal studies "what is expected to occur

[36] *Wade-Greaux v. Whitehall Laboratories, Inc.*, 874 F. Supp. 1441, (D.V.I. 1994); *see also, Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311 (9th Cir. 1995); *Raynor v. Merrell Pharm. Inc.*, 104 F.3d 1371, 1375 (D.D.C. 1997).

[37] Cabrera N.T., 4/7/14 Tr. at 133:22-134:5.

in humans."[38] Dr. Cabrera did briefly address human epidemiological evidence in his expert report, noting that, as a teratologist, he does commonly review the human epidemiological literature, although he is not a specialist in the field of epidemiology. He testified that he reviewed many epidemiological studies, although his report selectively cited six epidemiological studies, four of which used overlapping data sets from the Danish National Birth Registry.[39] He did not discuss the strength of any associations detected, potential confounders or biases, or replication of findings, and he did not discuss, explain, or analyze studies reaching contrary conclusions to his own.

Dr. Sadler offers an opinion that Zoloft exposure in pregnant woman may cause many different birth defects, but Plaintiffs acknowledge that in "extrapolat[ing] from animals to humans, Dr. Sadler relied upon the mechanism of action of the drug."[40] His discussion of human epidemiology studies is extremely limited. He notes that his opinion "is buttressed in part by epidemiological data,"[41] and cites eleven epidemiological studies in his report, including multiple studies which found no statistically significant association between Zoloft use and birth defects. Perhaps acknowledging that the epidemiological data he cited provides insufficient support for his opinion, he goes on to hypothesize that the epidemiological studies may underestimate the true impact of Zoloft, as some birth defects might result in spontaneous abortion or termination of a pregnancy.

Dr. Levin does not cite any human epidemiology studies as a basis for his opinion. In fact, Dr. Levin testified that although he has reviewed some human epidemiology studies of

[38] Cabrera Report at 17.

[39] Cabrera N.T., 4/8/14 Tr. at 54:4-17.

[40] PSC's Post-Daubert Hearing Brief, Doc. No. 831 at 17.

[41] Sadler Report at 8.

SSRI exposure in pregnant humans, he does not have the expertise to analyze those studies and his opinions are not based upon the epidemiological research.[42] His report states that "[k]nowledge on the interactions of SSRIs like Zoloft with fundamental genetic and physiological pathways thus allows one to make reasonable scientific conclusions regarding how these compounds will affect human development.[43]

Zoloft has been on the market and used during pregnancy for approximately twenty years, and a great deal of epidemiological research has been conducted and published.[44] Therefore, the Court holds that any litigation experts on human causation in this MDL must address the epidemiological research.[45] Where that body of research does not support the conclusions drawn by the experts, the experts must endeavor to reconcile the inconsistent epidemiological data with their opinions. Here, the experts have given scant attention to the epidemiology research in their reports, and have failed to reconcile inconsistent epidemiological evidence with their opinions on human causation. Only Dr. Sadler makes any effort to reconcile the inconsistent epidemiological research with his opinion, and he provides only an untested hypothesis. The experts' failure to reconcile inconsistent epidemiological research with their opinions regarding human causation is a significant methodological flaw, undermining their reliability under *Daubert*.

[42] Levin N.T., 4/10/14 Tr. at 58:2-12.

[43] Levin Report at 6.

[44] The PSC indicates that at least 104 studies have been published. PSC Brief, Doc. No. 712 at 11.

[45] The Court notes that Drs. Cabrera, Sadler, and Levin were retained for their expertise on biological mechanisms, and although they each reviewed the epidemiological literature, it was Dr. Bérard who was retained for her expertise in that field. Had the Court found Dr. Bérard's methodology was sound, they would have been justified in relying upon her report as evidence in support of their own human causation opinions. However, without Dr. Bérard's opinion to rely upon, the Court must examine whether each of these experts adequately addressed the epidemiological evidence in forming their opinions on human causation.

B. Concerns about Extrapolating from *In Vitro* and *In Vivo* Animal Studies to Humans

The experts at issue have offered opinions about human causation in this case, based largely on *in vitro* or *in vivo* animal studies. As noted above, courts caution against direct extrapolation from cellular and animal studies to humans, because where sound epidemiological data do not exist, or the epidemiological research produces results inconsistent with the animal research, "the rate of error is likely to be quite high."[46] In one such case, the court explained:

> [t]he notion that one can accurately extrapolate from animal data to humans to prove causation without supportive epidemiological studies is scientifically invalid because it is inconsistent with several universally accepted and tested scientific principles. The principle of species specificity has been tested and demonstrates that different species can react differently to the same agent… [Moreover], at some dosage, virtually any substance is teratogenic in an animal species. Finally, the phenomenon that different routes of administration affect the teratogenic impact of an agent has been repeatedly tested and confirmed.[47]

In this section, the Court will discuss specific issues with the experts' extrapolations in this case.

1. *Failure to Consider the Dose Response (No Teratogenic Effect Found at Clinical Doses)*

Nearly any substance can be teratogenic at some concentration. Dose response refers to correlations between dosage and outcome, the minimum dose at which adverse effects are seen, and the dose at which a substance is lethal. According to both Wilson's principles and the Bradford-Hill criteria, scientists drawing conclusions about teratogenicity and causation should consider the evidence regarding the dose response. Because high doses of a medication are often administered in *in vitro* and live animal studies, it is especially important for scientists relying upon such studies to carefully consider the dose-response relationship.[48]

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[46] *See, e.g., Raynor*, 104 F.3d at 1375.

[47] *Wade-Greaux* at 1480.

[48] *In re Accutane Prod. Liab. Litig.*, 511 F. Supp. 2d 1288, 1292 (M.D. Fla. 2007), quoting Michael D. Green, et al., *Reference Guide on Epidemiology*, in *Reference Manual on Scientific Evidence*, 333, 392 (FJC 2d Ed. 2000)r.

Because researchers can expose animals and *in vitro* embryos to extremely high doses of a drug, *in vitro* and *in vivo* animal studies can be useful in examining the dose response. When researchers study embryos *in vitro*, rather than live animals, medication can be administered at concentrations which would be lethal to a pregnant animal. For example, in one *in vitro* study on mouse embryos, Dr. Sadler exposed the embryos to varying concentrations of Zoloft, and found no adverse effects on the embryos at typical doses, high doses, or even doses which were 2.5 times the dose that would be lethal to a pregnant mouse. At a concentration of Zoloft five times the level that would have been lethal to a pregnant mouse, he observed an increased risk of craniofacial defects, but no other defects.[49] In his testimony, Dr. Sadler noted that the lower doses, which did not block serotonin uptake *completely*, did not produce any malformations.[50] He does not point to any evidence that Zoloft, used in typical or maximum recommended clinical doses, would block serotonin uptake completely in a pregnant woman. Thus, Dr. Sadler fails to reconcile his study results with his conclusion that Zoloft, used at all conventional doses, will significantly increase the likelihood of a number of congenital malformations in humans.

Even in live animal studies, in which lethal doses cannot be administered, the doses administered to some study groups may be well in excess of the maximum recommended human concentration. For example, the label for Celexa (another SSRI) indicates that defects occurred when pregnant mice were administered a dose equivalent to 18 times the recommended maximum dose, but no effect was seen at or below nine times the recommended maximum dose,

[49] *See* Def.'s Brief, Doc. No. 692 at 11 (quoting Dr. Sadlers's deposition testimony).

[50] Sadler N.T., 4/8/14 Tr. at 156:17-19. This testimony appears to be inconsistent with Dr. Sadler's report, in which he discusses the necessity for "an optimum concentration" of serotonin for normal embryonic development. Even if not inconsistent, his report provides no information about what an optimum concentration of serotonin is, what change in serotonin levels is necessary to disrupt embryonic development, and how Zoloft, at typical doses, impacts serotonin levels; thus his discussion of dose response is incomplete.

and there was no effect at any dose in rabbits.[51] The FDA-approved label for Zoloft states that: "reproduction studies have been performed in rats and rabbits at doses up to 80 mg/kg/day and 40 mg/kg/day respectively. These doses correspond to approximately 4 times the maximum recommended human dose. . . .There was no evidence of teratogenicity at any dose level."[52] Dr. Cabrera provided a thoughtful analysis of some of the weaknesses of the Pfizer studies summarized in the Zoloft label, yet his report did not address the high doses at which adverse outcomes were seen in those studies, doses equivalent to four times the maximum human doses. Although Dr. Cabrera acknowledged that many adverse effects of SSRIs are dose dependent, he failed to identify any studies demonstrating an increased risk of birth defects at doses equivalent to or below the maximum recommended clinical doses.[53]

In order to reliably opine as to human causation, the experts must address whether the children of pregnant women taking Zoloft in typical (or even maximum) clinical doses are at an increased risk of birth defects. The *in vitro* and *in vivo* animal studies have found associations between exposure and adverse outcomes only at concentrations well above the maximum recommended human dose. The experts have not reconciled the dose-response evidence with their opinions on human causation. Under both Wilson's criteria and the Bradford-Hill criteria, reaching conclusions about human causation without careful consideration of the dose response is a significant methodological flaw.

2. *No Supportive Data from Live Mammals*

One problem with generalizing from *in vitro* studies is that drugs are not metabolized by the mother in an *in vitro* system, as they are when a pregnant mammal is exposed. This is also a

[51] Cabrera N.T., 4/8/14 Tr. at 78:11-18; 80:5-6.

[52] The label appears to use the term teratogenicity narrowly, to mean capable of causing birth defects, not death or growth retardation, as the Pfizer studies did show an increase in pup deaths with high-dose Zoloft exposure.

[53] *See, e.g.*, Cabrera report at 26.

problem when generalizing from frogs, fish, or chick embryos, which develop in eggs without a maternal metabolism. Therefore, the impact of a medication on a developing embryo may vary significantly in a system which includes a maternal metabolism. The experts have not addressed this issue in their reports.

When one does look at live animal studies, and SSRIs have been studied in living mammals, including rats and rabbits, there is little evidence of an association between Zoloft and birth defects when administered at typically-used concentrations, or even at higher concentrations, as noted above. Although Dr. Cabrera provided a detailed critique of Pfizer's animal reproductive toxicity studies, and explained that the evidence could also support "a hypothesis that vascular damage or malformations were present in these organs,"[54] he points to no studies in which this alternative hypothesis was tested. Neither he nor Drs. Sadler or Levin cited any studies of live mammals in which investigators concluded that Zoloft (or any SSRI) caused the birth defects at issue in this litigation at typical doses, nor have they themselves conducted such studies in order to test their hypotheses.[55]

3. *Lack of Evidence that Proposed Pathways Are Conserved in Humans*

In vitro studies can best be used to explore mechanisms of toxicity. However, to then draw conclusions about toxicity in humans, the researcher must establish the link between the animal mechanism and human mechanism (i.e. similar developmental processes, pathways, etc.). This is the concept of biological conservation: certain genetic components and molecular pathways exist (are conserved) throughout the animal kingdom. "Extrapolating data from

[54] Cabrera Report at 30.

[55] *See, e.g.*, Sadler N.T., 4/8/14 Tr. at 200:1-201:23.

animals to humans is more accurate if the mechanism of action of the teratogen is well-defined and one that is fundamental to normal development for a wide range of species."[56]

Dr. Levin's opinion is based primarily upon studies conducted using non-mammals (such as frogs, chickens, and zebrafish)[57]—and in his published, peer-reviewed work he acknowledges that the serotonin pathways he has found in those life forms have not been well-established in humans, or even other mammals.[58] The Court notes that in his published work, Dr. Levin cautions against drawing any conclusions with regard to use of Zoloft by pregnant humans, stating that laterality (left/right) defects have not been described in mice or rabbits exposed to even very high doses of Zoloft, and so more evidence is needed to establish that serotonin plays a role in left/right patterning in mammals.[59] Without evidence that the effects on the serotonin transporter are conserved across species, it is speculative to draw conclusions about human development from *in vitro* or even animal studies.

4. *Lack of Information Regarding Optimal Serotonin Ranges in Humans*

Embryonic serotonin is naturally produced both by the maternal system and the embryo itself.[60] Even in the absence of medication, "embryos appear to begin life with very variable levels of maternal serotonin . . . [which makes] the individual embryos differentially susceptible to the effects of serotonin modulators such as SSRIs like Zoloft."[61]

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[56] Sadler Report at 7.

[57] In support of his opinion on a third mechanism, calcium signaling, he relies on *in vitro* studies performed on human cancer cells and canine kidney cells exposed to very high doses of Zoloft, without establishing a basis for concluding that either type of cell is similar to human embryonic cells.

[58] Dr. Levin testified that research indicates that the calcium and ion channels he discusses in his report are conserved across species, including humans, but it is not well-established that serotonin impacts these channels.

[59] *See* Levin N.T., 4/10/14 Tr. at 81:4-13, 82:4-14.

[60] Levin Report at 4.

[61] Levin Report at 27.

Because there are individual differences in natural serotonin levels, in making causal conclusions about the impact of Zoloft on the developing embryo, it would be useful to know the optimal range of serotonin in pregnant mothers, the impact of depression on serotonin levels, and the impact of Zoloft on those levels. Yet, none of the experts testified as to the optimal range of serotonin in pregnant women, or the impact of depression or Zoloft on that range. Dr. Cabrera testified that scientists do not know the optimal level of serotonin in human embyros.[62] Dr. Levin agreed, testifying that there is no data available to answer such questions.[63] Therefore, although the experts have hypothesized that Zoloft alters the concentration of serotonin in a developing human embryo, and that the altered concentration *could* disrupt signaling channels and left-right patterning, causing the birth defects at issue in this litigation, the research does not indicate the typical or ideal range of serotonin in the developing organism (of any species) or the range of serotonin present in the developing embryo when a pregnant woman with depression is exposed (or unexposed) to Zoloft in pregnancy.

C. The Opinions Expressed As to Human Causation Must be Excluded

Plaintiffs concede the Bradford-Hill criteria "have been recognized for decades as a generally accepted methodological approach for determining causation in tort cases involving toxic exposure."[64] Yet, the experts here rely heavily on one factor—biological plausibility—and give little consideration to the other criteria, even where the *in vitro* and *in vivo* animal studies upon which they rely are useful in addressing those criteria (such as the dose response criteria). While an expert need not consider or satisfy every criteria in order to reach a reliable causation opinion, here, the Court finds that the experts failed to adequately address important factors such

[62] Cabrera N.T., 4/8/14 Tr. at 57:24-58:3; 59:2-10.

[63] Levin N.T., 4/14/14 Tr. at 94:19-21.

[64] PSC Brief, Doc. No. 712 at 10.

as: 1) the strength of the association between maternal Zoloft exposure and birth defects in human infants; 2) the lack of replicated, statistically significant findings in the epidemiological literature; 3) the dose-response relationship, with attention to evidence regarding SSRI exposure at typical and maximum recommended clinical doses; and 4) alternative explanations for any associations between Zoloft exposure and birth defects in human babies (e.g. confounding factors). Because the experts have not adequately considered the Bradford-Hill criteria as a whole, the Court finds that their causal conclusions were not formed using reliable scientific methodology.[65]

The Court cannot allow unscientific speculation to be offered, even by genuinely talented scientists. The Court holds that the evidence upon which the experts rely in their reports is not sufficient to support a non-speculative opinion that Zoloft can cause birth defects in humans when used at conventionally prescribed doses. The Court notes that *in vitro* and *in vivo* animal research is useful for generating hypotheses about human causation, but each hypothesis must be tested and scientifically verified before it can form the basis for a conclusion about causation. These experts have not demonstrated that such testing and verification has been accomplished to date. In addition, the Court notes that these scientists have never published their litigation opinions about human causation for their peers, and neither their opinions about human causation nor their methods for reaching those opinions, which bypass crucial hypothesis testing and analysis, are generally accepted by scientists in their fields. Finally, many essential questions which would connect the animal data to human embryonic development are unanswered at this time.

[65] Looking at Wilson's principles, the experts have failed to adequately address three of the six principles: the impact of genotype, the route of exposure, and the dosage effect. Thus, any analysis using Wilson's principles is also incomplete.

Therefore, the Court holds that it is premature to draw conclusions about human causation from the evidence relied upon by these experts. Because of the current state of the science, Drs. Sadler, Cabrera, and Levin's opinions about human causation require speculative leaps which are unacceptable in science and in the courthouse; their opinions about human causation are therefore inadmissible under *Daubert*.

IV. CONCLUSION

The Court must act as a gatekeeper, to ensure that expert opinions are based upon reliable scientific methods. The Court holds that the methodology Drs. Sadler, Cabrera and Levin used to reach their opinions that Zoloft, when used by pregnant women at conventional doses, causes an increased risk of congenital malformations in human babies does not meet the *Daubert* standard, and their opinions on human causation must be excluded.

Pfizer argues that the testimony of Drs. Sadler, Cabrera and Levin should be excluded in its entirety because the experts' opinions on human causation do not meet the *Daubert* standard. However, this argument conflates the sufficiency of the evidence with the admissibility of the testimony. The experts at issue here have conducted and reviewed *in vitro* and *in vivo* research which they believe demonstrates the existence of one or more plausible biological mechanisms by which altered concentrations of serotonin in a developing embryo may cause birth defects. The Court finds that the methodology these experts used to reach their conclusions about biological plausibility is generally reliable, and will not exclude their opinions regarding biological mechanisms, if they are otherwise admissible, except that Dr. Levin may not testify regarding ion and calcium channels.

An appropriate Order follows.