WO

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF ARIZONA

IN RE: Zicam Cold Remedy Marketing, Sales Practices, and Products Liability Litigation. THIS DOCUMENT RELATES TO: All Personal Injury Actions.	No. 09-md-2096-PHX-FJM **ORDER**

We have before us defendants' "Motion for a Ruling to Exclude The Expert Reports and Testimony of Plaintiffs' General Causation Experts Ashim Mitra, Ph.D., Greg Davis, M.D. and Steven Pike, M.D." (doc. 1061), plaintiffs' response (doc. 1230), and defendants' reply (doc. 1274). Plaintiffs have proffered the opinions of Dr. Greg Davis, Dr. Ashim Mitra, and Dr. Steven Pike as general causation experts. Defendants move to exclude the opinions and testimony of all three causation experts.

We also have defendants' "Motion to Exclude Expert Report and Testimony of Plaintiffs' Expert Jay Sirois" (doc. 1063), plaintiffs' response (doc. 1227), and defendants' reply (doc. 1275).

I. MDL Background

A. Zicam intranasal products

Zicam Cold Remedy Nasal Gel (Zicam) is a homeopathic (treatment with small

amounts of a drug that is believed to produce symptoms similar to those of the disease being treated) cold product marketed by defendants Matrixx Initiatives, Inc. (Matrixx) and Zicam LLC. It is a viscous gel that is applied to the nose with either a spray pump or a swab resembling a q-tip. This litigation concerns three "intranasal" products: Zicam Cold Remedy Nasal Gel, Zicam Cold Remedy Nasal Swabs, and Zicam Cold Remedy Swabs, Kids Size. The active ingredient in the products is zinc gluconate, at a level of 1.58% concentration. Each dose or swab contains 130-140 microliters of gel, or about .0274 teaspoons. The amount of zinc in each dose is .231% of the gel, or 260-280 micrograms of zinc. See Motion to Exclude Causation Experts at 6.[1] The package instructions on the pump products direct the user to place the applicator tip one-eighth of an inch past the nasal opening, angle the nozzle slightly outward, pump the applicator once in each nostril, and not to "sniff up" the gel, in order to avoid irritation. The swab directions instruct the user to dab the gel from the swab just inside the nasal opening.

The anatomy of the nasal cavity is complex. See Dalby Report at 7 (doc. 1066-1); Mitra Report at 6 (doc. 1067-7). The cavity is divided into right and left halves by the nasal septum, and is lined by tissue called mucosa. Cilia line the mucosa and carry the mucous through the cavity. The parts of the mucosal lining that contain sensory cells that detect smell are called olfactory epithelium ("OE"). The bones that curve into the nasal passageway on each side of the cavity are called turbinates. They are identified as inferior (lower), middle, and superior (upper) turbinates. Above the superior turbinate is the olfactory region, or olfactory cleft, a portion of the ceiling of the nasal cavity densely covered by olfactory receptors.

B. Earlier Zicam litigation

Before the creation of this MDL, earlier actions against Matrixx alleged anosmia (loss of sense of smell) as a result of Zicam usage. All the courts that evaluated plaintiffs' causation experts' opinions excluded them. In most of these cases, the plaintiffs sought to

[1] All page numbers refer to the CM/ECF page numbers.

rely on the opinions of Dr. Jafek and/or Dr. Davidson. See Rose v. Matrixx, 2009 WL 902311 (W.D. Tenn. 2008) (excluding causation opinions of Dr. Davidson because they do not meet standards of admissibility); Wyatt v. Matrixx Initiatives, Inc., 2007 U.S. Dist. LEXIS 67986, *17 (N.D. Ala. 2007) (excluding testimony of Dr. Jafek); Lusch v. Matrixx Initiatives, Inc., 2007 U.S. Dist. LEXIS 72068 (D. Ore. 2007) (excluding Dr. Jafek and other causation experts' opinions as insufficiently relevant or reliable); O'Hanlon v. Matrixx Initiatives, 2007 WL 2446496 (C.D. Cal. 2007) (excluding causation opinions of Drs. Jafek and Davidson); Hilton v. Matrixx Initiatives, Inc., 2007 U.S. Dist. LEXIS 73264, *6–7 (N.D. Tex. 2007) (finding Dr. Jafek's general causation testimony unreliable); Hans v. Matrixx Initiatives, Inc., 2006 U.S. Dist. LEXIS 96779, *22 (W.D. Ky. 2006) (excluding Dr. Jafek's testimony as unreliable); Benkwith v. Matrixx Initiatives, Inc., 467 F. Supp. 2d 1316 (M.D. Ala. 2006) (Dr. Jafek's general causation opinion relies on reasoning, authorities, and experiments which do not demonstrate requisite level of scientific rigor); Sutherland v. Matrixx Initiatives, Inc., 2006 U.S. Dist. LEXIS 96652, *41 (N.D. Ala. 2006) (excluding Dr. Jafek because his testimony is methodologically unsound); see also Evans v. Matrixx Initiatives, Inc., 2009 WL 2914252 (M.D. Fla. 2009) (excluding causation opinions of Drs. Loper and Carreno); Salden v. Matrixx Initiatives, Inc., 2007 U.S. Dist. LEXIS 18552, 12 (E.D. Mich. 2007) (excluding Dr. Hirsh's conclusion that Zicam can cause anosmia).

C. FDA action

On June 16, 2009, after receiving 131 adverse event reports since the introduction of Zicam in 1999, the Food and Drug Administration ("FDA") issued a Public Health Advisory and a Warning Letter to Matrixx. See FDA, Public Health Advisory: Loss of Sense of Smell with Intranasal Cold Remedies Containing Zinc (June 16, 2009) ("FDA Health Advisory") (doc. 1231-2); FDA, Warning Letter to Matrixx Initiatives, Inc. (June 16, 2009) ("FDA Warning Letter") (doc.1231-2). The FDA recommended that consumers stop using the products, and alerted "consumers that Zicam Cold Remedy Nasal Gel, Zicam Cold Remedy Nasal Swabs, and Zicam Cold Remedy Swabs, Kids Size, a discontinued product that consumers may still have in their homes, have all been associate [sic] with long lasting or

permanent loss of smell (referred to as anosmia)." FDA Health Advisory at 21. The FDA Warning Letter further noted that "the agency is aware that Matrixx appears to have more than 800 reports related to loss of sense of smell associated with Zicam Cold Remedy intranasal products." FDA Warning Letter at 26.

Following receipt of the FDA Warning Letter, defendants voluntarily withdrew the intranasal products from the market. On March 1, 2010, Dr. Charles Lee, who led the FDA's investigation of Zicam, issued a memorandum concluding that there was a strong safety signal associated with the use of the Zicam intranasal products, and noting concern that anosmia associated with the products may be permanent. See FDA, Dep't Health of Health and Human Services, Memorandum Re: Safety Review, Zicam Cold Remedy Nasal Gel, Zicam Cold Remedy Gel Swabs (March 1, 2010) ("Lee Memorandum") (doc. 1070-7).

II. Rule 702 and Daubert

Rule 702, Fed. R. Evid., provides that "[i]f scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case." Fed. R. Evid. 702.

We perform a gatekeeping function to ensure "that any and all scientific testimony or evidence admitted is not only relevant, but reliable." Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 589, 113 S.Ct. 2786, 2795 (1993). This requires that we assess whether "the reasoning or methodology underlying the testimony is scientifically valid," and "whether that reasoning or methodology properly can be applied to the facts in issue." Id. 509 U.S. at 592–93, 113 S.Ct. at 2796. Plaintiffs bear the burden of proving the admissibility of their experts' testimony. See Lust By and Through Lust v. Merrell Dow Pharmaceuticals, Inc., 89 F.3d 594, 598 (9th Cir. 1996).

In Daubert, the Court outlined five flexible, non-exhaustive factors in assessing reliability: (1) whether the theory can be or has been tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) the known or potential rate of error; (4) standards; and (5) general acceptance in the scientific community. Daubert, 509 U.S. at 593, 113 S.Ct. at 2786. However, the Daubert "test of reliability is flexible, and Daubert's list of specific factors neither necessarily nor exclusively applies to all experts or in every case." Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 141, 119 S.Ct. 1167, 1171 (1999).

The test of reliability "is not the correctness of the expert's conclusions but the soundness of his methodology." Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1318 (9th Cir. 1995) ("Daubert II"). However, conclusions and methodologies are not unrelated. "A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." General Elec. Co. v. Joiner, 522 U.S. 136, 146, 118 S.Ct. 512, 519 (1997). We also determine whether the experts propose to testify about matters growing out of their own research, independent of the litigation, and if not, whether there "exists any other objective, verifiable evidence that the testimony is based on scientifically valid principles." Metabolife Intern., Inc. v. Wornick, 264 F.3d 832, 841 (9th Cir. 2001). Where peer-reviewed articles are not written by the experts who wish to interpret them, the methodology of the experts' interpretation is open to scrutiny. Id. at 844.

The Advisory Committee Note for Rule 702, Fed. R. Evid., suggests that we also consider whether: (1) an expert's testimony grows naturally and directly out of research he has conducted independent of the litigation; (2) " the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion"; (3) "the expert has adequately accounted for obvious alternative explanations"; (4) the expert "is being as careful as he would be in his regular professional work outside his paid litigation consulting"; and (5) whether the field of expertise claimed by the expert is known to reach reliable results. Fed. R. Evid. 702 Advisory Committee Note (2000 amendments).

III. Causation experts

A. Dr. Greg Davis

1. Qualifications

Dr. Greg Davis is an Assistant Professor of Otolaryngology – head and neck surgery (ear, nose and throat surgery) at the University of Washington. Davis Report at 2 (doc. 1067-3). He has a Masters in Public Health in epidemiology. He has been a board certified otolaryngologist since 2009, with a speciality in anterior base skull surgery (the area containing the olfactory cleft), and a sub-speciality in rhinology (the study of the nose and nose diseases). Dr. Davis was a principal investigator in a study conducted by Dr. Charles Lim, a research resident at the University of Washington.[2] Dr. Davis commented on a portion of the study in which Dr. Lim applied Zicam to explanted nasal tissue. The study was published before plaintiffs retained Dr. Davis. Dr. Davis had not consulted or testified in any litigation until after the study was published. Dr. Davis has not published any other research on smell dysfunction, zinc compounds, nasal drug deposition and distribution (i.e., where drug particles land), or cold drug efficacy.

Dr. Davis offers opinions on four issues: (1) the location of olfactory tissue in the nose; (2) the distribution of Zicam within the nose; (3) the toxicity of Zicam; and (4) the effectiveness of Zicam.

2. Opinions

a. Location of olfactory tissue

Dr. Davis believes olfactory tissue, also called olfactory epithelium ("OE"), is spread throughout the nasal cavity. "Olfactory sensorineuron distribution appears to be diffuse in nature," and exists "beyond the confines of the olfactory cleft." Davis Report at 6. Dr. Davis

---

[2] The National Institute of Health defines a principle investigator as an "individual designated by the grantee to direct the project or activity being supported by the grant. He or she is responsible and accountable to the grantee and [] for the proper conduct of the project or activity." See Dep't of Health and Human Services, Glossary & Acronym List, http://grants.nih.gov/grants/glossary.htm (last visited Feb. 14, 2011).

acknowledges that this is contrary to the historical teaching that the OE is located exclusively in the olfactory cleft. Davis Deposition at 45 (doc.1067-4). Dr. Davis relies on three peer-reviewed, publications, the Feron, Leopold, and Nibu papers, and states he knows of no other scientific investigations of the location of the OE.[3] Davis Deposition at 60. He further reports that there is much variety in the location of the OE, and that there is no way to determine exactly how much of the OE is located outside the olfactory cleft. Davis Deposition at 51.

Dr. Davis states that in the Feron study, researchers showed that "50% of the specimens biopsied from the front of the middle turbinate and 58% of specimens from the back of the middle turbinate were positive for containing olfactory sensorineurons. Specimens from the superior turbinate and superior nasal septum (which are included in the area known as the olfactory cleft) were even more likely to contain olfactory sensorineurons (73% and 76% respectively)." Davis Report at 5 (citing Francois Feron et al., New Techniques for Biopsy and Culture of Human Olfactory Epithelial Neurons, 124 Arch Otolaryngol Head Neck Surg. 8, 861–66 (1998) ("Feron study")). In the Leopold study, researchers reviewed biopsied nasal tissue from twelve volunteers and used an electro-olfactogram ("EOG") (a recording of electrical changes of the OE that occur in response to olfactory stimulation) to investigate the location of the OE. See Donald Leopold et al., Anterior Distribution of Human Olfactory Epithelium, 110 The Laryngoscope 417 (2000) ("Leopold study") (doc. 1069-4). The researchers found that nine of nineteen biopsied specimens from the septum and ten of twenty-four specimens from the lateral wall had olfactory sensoneurons present, and concluded that "olfactory epithelium appear to be distributed more anteriorly than previously assumed." Id. at 2, 5. According to Dr. Davis, the Nibu study reported similar results using surgical biopsies and specimens from autopsies.

---

[3] Dr. Davis is also currently studying human nasal tissue to determine the location of olfactory sensorineurons, but because the research is not yet complete, the parties have stipulated that Dr. Davis will not reference his own research. Motion to Exclude Causation Experts at 17.

Davis Report at 6 (citing Ken-ichi Nibu et al., Olfactory Neuron-Specific Expression of NeuroD in Mouse and Human Nasal Mucosa, 298 Cell Tissue Res. 3, 405–14 (1999) ("Nibu study")).

Defendants concede that Dr. Davis is qualified to testify about the location of olfactory tissue, and clearly his academic and clinical background in otolaryngology qualifies him to testify on the issue. However, defendants contend that his diffuse OE theory is a speculative, untested hypothesis and therefore unreliable. Motion to Exclude Causation Experts at 22.

We disagree. While Dr. Davis's opinion about the location of the OE may not be the majority view, it is based on valid scientific methodology, and therefore is admissible under Rule 702, Fed. R. Evid. and Daubert. The first Daubert reliability factor, whether the theory can be or has been tested, weighs in favor of admissibility. Dr. Davis relies on three studies that tested his conclusion, and is currently conducting his own research about the location of OE. While the findings based on his own research are not yet admissible, the fact that he is conducting the research suggests that his opinion can be tested. The second factor also supports admissibility – the three studies were all peer-reviewed and published. Third, there is no suggestion that the researchers' techniques are susceptible to a particularly high rate of error. Four, standards do not yet exist. Five, Dr. Davis concedes that his opinion is not yet generally accepted. It is too new. Of course, under "the Daubert interpretation of F.R.E. 702, general acceptance is not a necessary condition to admissibility; expert scientific opinion is admissible if it qualifies as scientific knowledge and is therefore sufficiently reliable." Lust By and Through Lust, 89 F.3d at 597. Dr. Davis did not conduct the underlying research himself, but his credentials qualify him to interpret the studies of others reliably.

Defendants contend that because there is no scientific basis to quantify how much OE is located in a particular part of the nose, and how much OE must be compromised to produce smell loss, there is no basis to infer that Zicam could cause smell loss. Motion to Exclude Causation Experts at 22. However, that level of precision is not necessary to establish the relevance of Dr. Davis's opinions. According to Dr. Davis, more precise information regarding the location of the OE and the amount that would have to be destroyed to cause

anosmia is not yet available. Even without more data, Dr. Davis's theory about the diffuse location of OE may still be helpful to a jury in deciding whether Zicam caused a particular plaintiff's anosmia. See Clausen v. M/V NEW CARISSA, 339 F.3d 1049, 1059–60 (9th Cir. 2003) ("While precise information concerning the exposure necessary to cause specific harm is beneficial, such evidence is not always available, or necessary, to demonstrate that a substance is toxic ... and need not invariably provide the basis for an expert's opinion on causation.") (internal citations omitted).

Because we find that Dr. Davis's methodology is sound and his opinion relevant, we deny defendants' motion to exclude Dr. Davis's conclusion that OE is located diffusely in the nasal cavity.

b. Distribution of Zicam within the nose

Dr. Davis opines that "a Zicam-like product can reach the olfactory cleft" and sinuses. Davis Report at 6. Defendants argue that Dr. Davis's opinions about drug deposition do not meet the threshold requirement of Rule 702, Fed. R. Evid., because Dr. Davis is not "qualified as an expert by knowledge, skill, experience, training, or education." Motion to Exclude Causation Experts at 17. Defendants note that Dr. Davis has never performed research on drug deposition and distribution. Davis Deposition at 32. He has neither used the Zicam sprayer, nor seen it operated. Davis Deposition at 11.

While Dr. Davis's work has not focused on drug delivery, we nevertheless conclude that he is competent to opine about the distribution of Zicam. "Rule 702 contemplates a broad conception of expert qualifications." Hangarter v. Provident Life and Acc. Ins. Co., 373 F.3d 998, 1015 (9th Cir. 2004). Dr. Davis's board certification in otolaryngology, sub-speciality in rhinology, and ear, nose, and throat clinical practice qualify him as an expert in nasal anatomy. While he lacks similar knowledge and experience with nasal drug delivery systems, the structure and operation of the Zicam sprayer and swabs are less complicated than the human anatomy and physiology with which they interact. Dr. Davis's professional background qualifies him to interpret nasal deposition studies.

In reaching his conclusion about the distribution of Zicam, Dr. Davis relies on three

studies: (1) the Berridge study; (2) the Scheibe study, and (3) the University of Pittsburgh study (referred to as the "Ferguson study" by Dr. Davis). We consider each in turn.

In the Berridge study, researchers directed four volunteers to use the nasal spray medicine Nasocort, a thixatropic formulation (a fluid that becomes thinner when shaken or agitated), which is released in an atomized state (reduced to tiny particles or a fine spray) and thickens upon deposition. See Marc S. Berridge et al., Biodistribution and Kinetics of Nasal Carbon-11-Triamcinolone Acetonide, 39 J. Nuclear Med. 1972 (1998) ("Berridge study") (doc. 1068-4). The researchers found that the drug reached the subjects' superior turbinates. Berridge Study at 7.

Defendants argue that the Berridge study is not evidence that Zicam reaches the olfactory cleft. Motion to Exclude Causation Experts at 21. Defendants contend that the study is inapposite because: (1) Zicam is a gel, which is more viscous than a thixatropic formulation; (2) Zicam is delivered through a swab or sprayer, rather than an atomizer; and (3) research nurses administered the solution and sprayed it towards the olfactory cleft, while the individuals inhaled, which is significantly different than ordinary Zicam use. Motion to Exclude Causation Experts at 27. Defendants contend that Dr. Davis's failure to take these differences into account renders his extrapolated conclusion invalid.

We agree with defendants that Dr. Davis's conclusion that Zicam can reach the olfactory cleft based on the Berridge study is inadmissible.[4] The study analyzed only four participants, who used a different product with a different formulation and different delivery system, and not under conditions of ordinary use. Moreover, the authors expressly noted

[4] Defendants also argue that Dr. Davis did not sufficiently address the ambiguity of the study. It is unclear whether the solution in the study reached the superior turbinate, or only the inferior and middle turbinates. Motion to Exclude Causation Experts at 26. Plaintiffs note there is no evidence of any flaw in the study, or that the authors mistakenly reported that the solution reached the superior turbinate. See Response to Motion to Exclude Causation Experts at 22; Berridge Study at 7 ("superior turbinates received about half the total dose of the inferior turbinates") (doc. 1068-4). We need not reach this issue because the study is not a reliable basis for Dr. Davis's opinion.

"[t]he purpose of this study was limited to demonstration of the ability of PET [a type of medical imaging] to provide this unique type of information . . . It was not intended to address clinical use and effectiveness or to assess the delivery system." Berridge Study at 7. There is too great an analytic gap between the Berridge study and Dr. Davis's conclusion that Zicam reaches the OE. See Joiner, 522 U.S. at 146, 118 S.Ct. at 519.

Defendants similarly challenge Dr. Davis's reliance on the Scheibe study. See Mandy Scheibe et al., Intranasal Administration of Drugs, 134 Arch.Otolaryngol. Head Neck Surg. 643 (2008) (doc. 1069-8) ("Scheibe study"). Researchers there compared the distribution of drugs delivered to fifteen users through (1) nasal drops applied with a pipette; (2) nasal spray; and (3) a system producing squirts of the drug solution. The researchers artificially decongested the participants (relieved excessive mucous), and used blue food dye to visualize the intranasal distribution of the liquid. Researchers applied three pumps of an aerosol device directed toward the olfactory cleft. They found that the solution reached the olfactory cleft in only one participant when using the nasal spray. Scheibe study at 4. Defendants note that researchers artificially widened the nasal passageways and intentionally directed the spray toward the olfactory cleft. Defendants also argue Dr. Davis failed to account for differences in the device, formulation, and use. Motion to Exclude Causation Experts at 28.

Again, the analytic gap between the Scheibe study and Dr. Davis's conclusion is too great. The researchers' finding that dye from an aerosol pump that was directed into artificially decongested individuals reached the olfactory cleft in one of fifteen participants does not support Dr. Davis's conclusion about Zicam's reach with sufficient reliability. "We may weigh this disconnect - whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion - against admissibility." Cooper v. Brown, 510 F.3d 870, 946 (9th Cir. 2007). Dr. Davis's conclusion is inadmissible.

Defendants also argue that Dr. Davis's interpretation of the University of Pittsburgh study data is unreliable. See Joseph E. Dohar, University of Pittsburgh Study (2005) (unpublished) ("Pittsburgh study") (doc. 1068-8). Matrixx commissioned the study to test whether ordinary or extraordinary use of Zicam could result in the gel reaching the OE.

Researchers injected dyed zinc gluconate free Zicam into study participants. Dye reached the olfactory cleft in two of the thirteen decongested subjects who were incorrectly administered Zicam, and two of the ten not decongested subjects who were incorrectly administered Zicam. See Pittsburgh Study at 2.

Defendants note that the study participants were anesthetized, allowing for deeper insertion of the sprayer, and instructed to direct the sprayer towards the olfactory cleft and to sniff deeply, contradicting the package instructions. See Pittsburgh Study. Defendants argue these differences between the application in the study and ordinary use make the research an insufficient basis for the conclusion that normal use of Zicam delivers any significant amount of gel to the olfactory cleft.

This study cannot reliably support Dr. Davis's conclusion about Zicam's distribution.[5] The study was unpublished, and therefore not subject to peer review. It also involved a limited number of participants, many of whom did not use the product in its ordinary manner.[6] The gap is too great to justify Dr. Davis's conclusion.

None of the three studies that Dr. Davis cites is a reliable basis for concluding that Zicam can reach the olfactory cleft. Dr. Davis's opinion about Zicam distribution is not based on sufficient facts or data and is therefore inadmissible.[7]

---

[5] We also do not reach Dr. Davis's statements about the email correspondence between the Pittsburgh researchers regarding conversations with Matrixx executives. Davis Report at 7 ("No one wants us to alter our interpretations as a result of litigious pressure. At the same time, however, this issue can put this small company into bankruptcy."). These communications are irrelevant to the scientific foundations of Dr. Davis's opinions.

[6] If anything, this study hints at the kind of research that would be useful to a jury, but which is absent from this litigation. A published study with a significant number of participants applying a formulation similar to that used in the Pittsburgh study (i.e. dyed Zicam without the zinc gluconate), under circumstances of both ordinary and extraordinary use, would be helpful and relevant in showing whether Zicam can reach the olfactory cleft.

[7] We therefore need not reach defendants' argument that Dr. Davis's opinion is inadmissible because he did not mention the Herranz studies. See Motion to Exclude Causation Experts at 31; Jesus Herranz Gonzalez-Botas et al., Anatomical Distribution and Transport of a Topical Liquid Nasal Gel, 57 Acta Otorringolaringol Esp. 130 (2006) (doc.

c. Toxicity of Zicam

Dr. Davis opines that it is "more likely than not that intranasal Zicam gel causes necrosis (destruction) of human olfactory tissue including the superior nasal septum (olfactory cleft region), middle turbinate and inferior turbinate." Davis Report at 9.

In arriving at this conclusion, Dr. Davis relies on both an animal study and *in vitro* studies. Defendants argue that Dr. Davis lacks the threshold qualifications to testify about the toxicity of Zicam. Motion to Exclude Causation Experts at 17. Although Dr. Davis is not a toxicologist or an expert on zinc, his background in otolaryngology, rhinology, and epidemiology, as well as his participation in the Lim study, demonstrate that he has the knowledge, experience, and education necessary to testify about the effect of Zicam on nasal tissue.

i. Animal study

Dr. Davis relies on the Lim study, a published, peer-reviewed paper for which he was principal investigator. See Jae H. Lim et al., Zicam-Induced Damage to Mouse and Human Nasal Tissue, 4 Plos ONE. 10, e7647 (2009) ("Lim study") (doc. 1231-2). Researchers examined the effects of several intranasal agents, including Zicam, using both mice and cultures from human nasal tissue. Lim study at 10. For the mouse component, researchers performed EOG analysis on mouse main olfactory epithelium ("MOE") three and nine days after intranasal administration of Zicam. They found that the Zicam-treated MOE did not react to odorant stimulants, and they "consistently observed atrophic [i.e. deteriorated] MOE in Zicam-treated animals as compared to the animals treated with other intranasal agents." Id. Impairment continued at least sixty-five days after the Zicam treatment. The researchers concluded, "The data collectively indicate a remarkable damage to the olfactory epithelium and a significant loss of regenerative capacity in Zicam-treated mice." Lim study at 14. Dr.

1068-10); Jesus Herranz Gonzalez-Botas et al., Study to Determine the Distribution Pattern of a Nasal Gel Using a Radial Design Nasal Actuator (2010) (unpublished) (sealed) (doc. 1068-9). We also do not reach Dr. Davis's opinions about the role of nostril flair on nasal airflow. See Davis Report at 7.

Davis noted that, "[w]hether or not this finding can extrapolate to permanence of olfactory loss in humans related to Zicam toxicity was not studied in this series of experiments." Davis Report at 10.

"The extent to which animal and cell experiments accurately predict human responses to chemical exposures is subject to debate." Fed. Judicial Ctr., Reference Manual on Scientific Evidence 405 (2000). Nonetheless, animal studies can be a necessary second-best way to show causation. Because it "is often unethical to experiment on humans by exposing them to known doses of chemical agents, animal toxicological evidence often provides the best scientific information about the risk of disease from a chemical exposure." Id. "In qualitative extrapolation, one can usually rely on the fact that a compound causing an effect in one mammalian species will cause it in another species." Id. at 410. An expert should review similarities and differences between the animal species and humans. Id. at 419.

The Lim study is a reliable basis for Dr. Davis's conclusion that Zicam is toxic to OE. The study is a peer-reviewed and published test of Dr. Davis's theory. There is no contention that the methods or results contradict generally accepted principles. It is also significant that the study grew out of independent research conducted before Dr. Davis's involvement in this litigation. See Fed. R. Evid. 702; Daubert II, 43 F.3d at 1317. While a mouse study does not provide the most direct evidence of the effect of Zicam on human nasal tissue, given the ethical challenge of performing research on human subjects, it is methodologically sound to consider this kind of data. Defendants may challenge the strength of the study at trial. "In most cases, objections to the inadequacies of a study are more appropriately considered an objection going to the weight of the evidence rather than its admissibility." Hemmings v. Tidyman's Inc., 285 F.3d 1174, 1188 (9th Cir. 2002).

ii. *In vitro* studies

Dr. Davis also relies on the *in vitro* portion of the Lim study in concluding that Zicam is toxic to olfactory tissue. See Davis Report at 8. The Lim study researchers applied Zicam to eight samples of explanted human nasal tissue. The results "suggested cell death mediated by necrosis," contrasted with the nasal explants treated with other intranasal products, which

showed no cytotoxicity (toxic effects on cells) on the nasal tissue. Lim study at 14. The researchers found that overall, "cellular damage to human nasal tissue induced by Zicam was severe and was observed in every tissue that we examined for this study." Id at 14.

Defendants argue that the extrapolation limitations are too great for the study to serve as a reliable basis for Dr. Davis's conclusion. They contend that because *in vitro* studies involve the interaction of a chemical with isolated cells, they "shed no light whatsoever on causation of any specific medical conditions in living humans with intact physiology and operative metabolic and immune function." Motion to Exclude Causation Experts at 34. To be sure, *in vitro* studies present unique problems in interpretation. "The problem with this approach is also extrapolation—whether one can generalize the findings from the artificial setting of tissues in laboratories to whole human beings." Reference Manual on Scientific Evidence. at 346. However, "often toxicologic studies are the only or best available evidence of toxicity." Id at 422. A particularly significant challenge is inferring the human-dose response to the tested compound. The problem is "the inability to relate doses that cause cellular toxicity to doses that cause whole-animal toxicity. . . . Nevertheless, the ability to quickly test new products through *in vitro* tests, using human cells, provides invaluable 'early warning systems' for toxicity." Id.

The *in vitro* portion of the Lim study is reliable for the same reasons that the animal portion is: it is a scientifically-reliable alternative to potentially unethical zinc gluconate toxicity studies on human beings. Defendants' expert concedes that Zicam could be toxic to olfactory cells at sufficient concentrations, and that it would be unethical to attempt to deliberately bring Zicam into contact with olfactory mucosa. See Schwob Deposition at 65 (doc. 1231-2). Although evidence of the exact amount of Zicam necessary to cause anosmia would be useful, its absence does not render *in vitro* toxicity research inadmissible. "[W]hile precise information concerning the exposure necessary to cause specific harm to humans and exact details pertaining to the plaintiff's exposure are beneficial, such evidence is not always available, or necessary, to demonstrate that a substance is toxic to humans given substantial exposure and need not invariably provide the basis for an expert's opinion on causation."

Westberry v. Gislaved Gummi AB, 178 F.3d 257, 264 (4th Cir. 1999).

Defendants do not challenge the underlying methodology of the *in vitro* portion of the Lim study, or the reliability of its results. The study was peer-reviewed and published. The inherent difficulties in translating scientifically-valid *in vitro* results into conclusions about the human response to Zicam is the proper subject of cross-examination, not the basis for excluding Dr. Davis's opinions.

Dr. Davis also cites the Pavlica study. That study compared the toxicity of several zinc salts. See Sanja Pavlica et al., Comparative *in vitro* of seven zinc-salts towards neuronal PC12 cells, 23 Toxicology In Vitro 4, 653–59 (2009) (doc. 1231-2) ("Pavlica study"). The study's authors classified zinc gluconate as having moderate cytotoxicity, and capable of killing 100% of mammalian cells *in vitro* at a dose of .3 millimolars. Pavlica study at 5. Dr. Davis believes that the Pavlica results support the Lim study's findings about the cytotoxic effects of zinc gluconate. Davis report at 9.

As discussed above, the results of this *in vitro* study are not direct evidence of Zicam's toxicity to humans. Rather, an expert must explain his extrapolation theory. But the report's findings are nevertheless admissible for Dr. Davis's purposes, i.e. supporting the Lim study results. Defendants do not challenge the scientific reliability of the Pavlica study itself, and it is methodologically sound to use its results to suggest that Zicam could be toxic to OE.

iii. FDA human adverse events report

Dr. Davis also relies on the FDA's report and analysis of information from its adverse events report ("AERs") database. He notes that of the 131 reports, 127 people reported permanent anosmia (though in two of the reports, the anosmia resolved in two weeks, and in three of the reports, the condition improved). See Davis Report at 9; FDA Warning Letter at 24. Dr. Davis also relies on the FDA's finding that there is a significantly higher adverse event rate associated with Zicam than with three other cold treatments. He concludes that "data reported as adverse events to the FDA describe[] that the anosmia associated with Zicam use in humans is permanent out to at least a mean duration of 7 months and out to at least 4 years in one case." Davis Report at 10.

Defendants argue that the FDA's determination that a greater than expected rate of reports of smell dysfunction constituted a safety signal is not a reliable basis for expert causation opinion. Motion to Exclude Causation Experts at 36. Defendants contend that the prevention-oriented standards the FDA uses are materially different than the rigorous standards that toxicologists and epidemiologists apply to their work, and the differences create a substantial danger of misleading the jury. They further argue that the reporting rate to the FDA never exceeded twenty per 100,000 units sold, and there is no evidence this exceeds the background rate of smell loss from colds and associated sino-nasal disease. Moreover, signal analysis based on spontaneous adverse reports is a method for generating hypotheses, not for proving causation.[8]

The FDA AERs data and the agency's reports are not admissible bases for concluding that Zicam can cause anosmia. First, the data is a collection of spontaneous event reports. The reports "reflect complaints called in by product consumers without any medical controls or scientific assessment." McClain v. Metabolife Int'l., Inc., 401 F.3d 1233, 1250 (11th Cir. 2005). In particular, the reporting rate may be subject to publicity bias. They are not the kind of "facts or data" that can underlie reliable scientific testimony on causation. See Fed. R. Evid. 702. Uncontrolled anecdotal information is not the foundation of a reliable causation methodology.

Second, agency actions are not the result of a Daubert level of scrutiny, but rather reflect the agency's purpose to protect the "public-at-large from risk of harm based on a risk-utility analysis of the drug." McClain, 401 F.3d at 1249. This risk-utility approach employs a lower standard than a scientific causation approach requires. The FDA "may remove drugs from the marketplace upon a lesser showing of harm to the public than the preponderance-of-the-evidence or more-likely-than-not standards used to assess tort liability." Glastetter v. Novartis Pharmaceuticals Corp., 252 F.3d 986, 991 (8th Cir. 2001). "A

[8] Defendants also argue that Dr. Lee's hearsay report is not admissible, or reasonably relied upon by plaintiffs' experts under Rule 703(b). We do not reach this argument.

regulatory agency such as the FDA may choose to err on the side of caution. Courts, however, are required under the Daubert trilogy to engage in objective review of evidence to determine whether it has sufficient scientific basis to be considered reliable." Rider v. Sandoz Pharmaceuticals Corp., 295 F.3d 1194, 1201 (11th Cir. 2002).

The data from the AERs database, the FDA's actions, and related letters and reports are not reliable evidence of causation of anosmia. We therefore exclude the portion of Dr. Davis's opinions that relies on this information.

iv. Defendants' other challenges to Dr. Davis's toxicity opinion

Defendants also argue that Dr. Davis's toxicity opinion is inadmissible because he does not know exactly how much of the OE must be compromised to produce smell dysfunction or loss. Motion to Exclude Causation Experts at 32. Defendants claim that because the vast majority of OE must be destroyed to cause dysfunction, evidence that Zicam can destroy only some OE is irrelevant to the issue of causation. See Schwob Deposition at 159. Plaintiffs counter that it is not established that most OE must be destroyed to cause anosmia.

We agree with plaintiffs that it is not established that all OE must be destroyed to cause anosmia. Dr. Davis's lack of knowledge of the exact amount of OE damage necessary to cause smell dysfunction does not undermine the reliability of his testimony. Every step of a theory of causation need not be supported by research on the identical point. Domingo ex rel. Domingo v. T.K., 289 F.3d 600, 607 (9th Cir. 2002). Dr. Davis's conclusion that based on demonstrations of toxicity in animals and *in vitro*, Zicam can be toxic to human OE is methodologically sound.

Defendants also fault Dr. Davis's report for its omission of any reference to a clinical study of Cold-Eeze, another intranasal zinc gluconate product. Motion to Exclude Causation Experts at 38; Clinical Research Laboratories, Inc., Final Report – A Double-Blind Placebo Controlled Study to Evaluate the Safety of Three New Formulations of a Zinc Nasal Spray (2003) (unpublished) ("Quigley Study") (1069-6). The study tested smell function before and after application of the drug, and found no adverse effect.

Failure to consider all relevant research may weaken the strength of Dr. Davis's

opinions, but does not make them inadmissable. Experts must explain how they have taken into account results from different research studies that reach different conclusions. See Reference Manual on Scientific Evidence 431. But the absence of reference to an unpublished study of a different product does not in and of itself undermine the soundness of Dr. Davis's methodology. The significance of the Quigley study and other contradictory research may be explored through defendants' cross-examination of Dr. Davis.

d. Effectiveness of Zicam

Dr. Davis proposes to testify that "there does not appear to be any benefit from using intranasal zinc gluconate or Zicam." Davis Report at 10. However, Dr. Davis is not qualified to provide opinions about the efficacy of Zicam. He has no background in pharmacology, and no experience regarding zinc compounds or zinc gluconate.[9] Although Rule 702, Fed. R. Evid., classifies experts broadly, at least some relevant background is required. Dr. Davis has no academic training or clinical experience in pharmaceutical efficacy. Because he lacks the knowledge, skill, experience, training, or education to determine whether the available clinical evidence supports a finding of efficacy, we exclude Dr. Davis' opinion about the efficacy of Zicam.

In sum, Dr. Davis may testify about (1) his theory of the diffuse location of OE ,and (2) the toxicity of Zicam, but without reference to FDA reports. Dr. Davis may not testify about (1) the distribution of Zicam within the nose and (2) the efficacy of Zicam.

B. Dr. Ashim Mitra

1. Qualifications

Dr. Ashim Mitra is the Curators Chair Professor of Pharmacy at the University of Missouri, Kansas City. He has a Bachelor of Science in Pharmacy, a Master of Science in Pharmaceutics (the science of preparing and dispensing drugs), a Master of Science in Pharmaceutical Chemistry, and a Ph.D. in Pharmaceutical Chemistry from the University of

---

[9] Pharmacology is the study of the effects of therapeutic drugs on living organisms. See Reference Manual on Scientific Evidence 447.

Kansas. Mitra Report at 3 (doc. 1067-7). The focus of Dr. Mitra's work is drug-delivery systems. His research is funded by the National Institute of Health. Dr. Mitra co-edited a volume called Nasal Drug Delivery, 29 Advanced Drug Delivery Reviews 1 (1998), and has published over 240 articles and book chapters on prodrugs (inactive drugs that are converted into active form in the body by metabolic processes), nasal formulations, and drug delivery. Dr. Mitra does not have a background in toxicology or epidemiology.

Dr. Mitra proposes to opine that with reasonable scientific probability: (1) Zicam is toxic to the OE; (2) zinc ions reach the human OE in toxic concentrations following nasal administration of Zicam; (3) Zicam can cause anosmia as a result of normal use; (4) the preservative benzalkonium chloride ("BAC"), present in Zicam, enhances absorption of zinc ions; and (5) the risk of nerve damage and irreversible anosmia overweighs Zicam's therapeutic benefits.

2. Opinions

a. Zicam is toxic to olfactory epithelium

Dr. Mitra does not meet the threshold requirement of qualification to offer opinions about the cause-and-effect relationship between exposure to zinc gluconate and human anosmia. Dr. Mitra does not have an academic or professional background in toxicology, or in a related field (e.g., pharmacology,[10] biochemistry, environmental health, or industrial hygiene), and he has not published any research on the toxicity of any chemical. See Reference Manual on Scientific Evidence 415. We therefore exclude his opinions about the

[10] Dr. Mitra's background is in pharmaceutical chemistry, a field that is not sufficiently similar to pharmacology. At the University of Missouri, Dr. Mitra is the chair of Pharmaceutical Sciences at the School of Pharmacy, which is separate from the Division of Pharmacology & Toxicology, and Dr. Mitra is not on faculty of that division. See Faculty & Staff Directory, School of Pharmacy, University of Missouri- Kansas City, http://pharmacy.umkc.edu/faculty-staff/directory/ (last visited Feb. 18, 2011). In contrast to pharmacology's focus on how drugs interact with living organisms, Dr. Mitra's research interests are the "development of drug delivery systems." Mitra Report at 4.

toxicity of Zicam.[11]

b. Zicam use administers zinc ions to olfactory epithelium in toxic concentrations

Dr. Mitra opines that "Zinc ions reach the human olfactory epithelium in toxic concentrations following nasal administration of Zicam in therapeutic amounts." Mitra Report at 16. As explained above, Dr. Mitra is not qualified to testify about what amount of Zicam or zinc could be toxic. But as a separate matter, he is qualified to testify about the distribution and deposition of the Zicam gel and zinc ions within the nasal cavity. His degrees in pharmaceutics and pharmaceutical chemistry and his extensive research into drug delivery systems provide him the necessary knowledge and experience to competently testify about how Zicam and zinc ions might move within the nose. Dr. Mitra may opine about Zicam distribution and deposition, but not about any possible resulting toxicity or smell dysfunction.

It is Dr. Mitra's opinion that zinc ions can reach the OE. Dr. Mitra asserts that positively charged zinc ions disassociate from zinc gluconate once the gel enters the body. Mitra Report at 16. This explanation of a basic scientific principle and how it could affect the absorption of Zicam is reliable. Dr. Mitra's testimony about the chemistry of Zicam, and how human physiology may affect the breakdown and movement of gel molecules is admissible.

c. Zicam can cause anosmia as a result of normal use and diffusion

Dr. Mitra proposes to testify that Zicam can cause anosmia as a result of normal use of the product. Mitra Report at 20. As explained in relation to his opinion that Zicam is toxic to OE, Dr. Mitra is not qualified to opine about the toxicity of the drug, and therefore cannot testify about the drug's potential to cause anosmia. We exclude his opinions about anosmia.

However, Dr. Mitra also offers his opinions about the movement of zinc ions within the nasal cavity after having been introduced by sprays, drops, and gels. See Mitra Report at 22. After reviewing several studies about the movement of zinc ions, Dr. Mitra concludes, "following application of Zicam™ inside the nostril it is likely that zinc ions reach the

[11] This exclusion also applies to a later section of Dr. Mitra's report, somewhat confusingly entitled "Viscosity issues with Zicam." Mitra Report at 25–28

olfactory mucosa present in the posterior area of medial turbinate due to capillary action, postural effects and sniffing." Mitra Report at 24.

Defendants argue that this theory is unsupported because there is no evidence that a significant amount of the gel (or zinc ions) could overcome gravity, mucociliary clearance, absorption into the nasal mucosa and bloodstream, and then reach the OE. Motion to Exclude Causation Experts at 19. They argue that plaintiffs' experts have not established an electrical gradient from the lower nasal cavity to the OE that would "traverse" the countervailing forces. Reply to Motion to Exclude Causation Experts at 6.

Dr. Mitra's opinions about diffusion are admissible. First, the principles of diffusion and the release of ionic zinc are generally accepted. See Schwob Deposition at 61 (doc. 1231-2). Indeed, defendants' experts agree that some diffusion of zinc ions in the nasal cavity is likely and it is plausible that zinc could reach the OE. See Dalby Deposition at 88 (doc. 1278-1) (expert recognizes that "clearly molecules of zinc can diffuse," but he does not know that a significant amount of zinc could reach olfactory region); Schwob Deposition at 61 ("The extent of that diffusion, I think, is going to be very limited and not very significant."). The theory that zinc ions diffuse to the OE has not been directly tested, although Dr. Mitra does cite several relevant published studies on which he relies. See Mitra Report at 22. Nonetheless, Dr. Mitra's extrapolation based on the principle of diffusion and Zicam's propensity to release zinc ions that zinc could reach the OE is not a significant analytic gap, and is methodologically reliable.[12] Defendants' questions about the rate of substance dispersion, clearance and absorption, how much of the OE would interact with the zinc, and about the relevance of the Matrixx dye studies go to the weight, not the admissibility of Dr. Mitra's opinion. See Reply to Motion to Exclude Causation Experts at 7.

d. The preservative benzalkonium chloride in Zicam enhances absorption of zinc ions

[12] Plaintiffs also cite the Zicam patent's explanation that the product "permits ionic zinc to diffuse through the composition to the nasal epithelial membrane or mucous on the epithelial membrane." Response to Motion to Exclude Causation Experts at 10 (citing U.S. Patent No. 6,080,783 (filed 06/26/2000)). However, Dr. Mitra does not rely on the patent.

Dr. Mitra concludes that based on a number of published studies, "it is quite obvious that BAC [benzalkonium chloride] which has penetration enhancing properties further increase[s] the zinc ion concentration leading to destruction of olfactory epithelium and anosmia." Report at 25. As explained above, Dr. Mitra has no background in toxicology, and therefore is not qualified to opine about anosmia. However, to the extent that Dr. Mitra's conclusions about BAC relate to the movement and deposition of Zicam within the nose, they are admissible.

Dr. Mitra also opines that "sniffing" helps increase drug concentration inside the nasal cavity, and that patients tend to sniff after nasal administration of Zicam. Mitra Report at 29. However, Dr. Mitra cites no data or research that support his conclusions about how sniffing affects absorption of Zicam. This conclusion fails at the first prong of the Rule 702, Fed. R. Evid., because it is not "based upon sufficient facts or data." We therefore exclude Dr. Mitra's opinions about sniffing.

e. Risk of harm from Zicam use outweighs its therapeutic benefits

Dr. Mitra opines, "intranasal delivery of Zicam™ through either nasal swab or spray can result in olfactory epithelial toxicity and anosmia. Moreover the risk of nerve damage and irreversible anosmia overweighs the therapeutic benefits such as treatment of cold and allergic rhinitis." Mitra Report at 29. This conclusion is inadmissible. As explained, Dr. Mitra is not a toxicologist, and cannot testify about the possibility that Zicam can cause anosmia. Similarly, Dr. Mitra has no background in cold drugs, and is not qualified to testify about Zicam's efficacy. His opinions about anosmia and Zicam's efficacy are excluded.[13]

In sum, Dr Mitra may testify about (1) the distribution and deposition of Zicam within the nasal cavity; (2) diffusion; and (3) the effect of BAC on absorption of Zicam. Dr. Mitra may not testify about (1) Zicam's toxicity to the OE; (2) anosmia; or (3) the efficacy of Zicam. **C. Dr. Steven Pike**

---

[13] This exclusion based on Dr. Mitra's qualifications extends to his opinions about the FDA reports. See Mitra Report at 29. Of course, Dr. Mitra may not rely on the FDA analysis for the same reasons that Dr. Davis may not. See Section III(A)(2)(c)(iii), supra.

1. Qualifications

Dr. Steven Pike is a physician. He has a Master of Science in Toxicology from the University of Arizona and is a board certified medical toxicologist,[14] occupational and environmental physician, emergency physician, and industrial hygienist. He has been an associate at the Center of Toxicology at the University of Arizona, and a consultant to the Arizona Poison Control Center. Dr. Pike does not have a background in anosmia, zinc toxicity, or nasal drug distribution or deposition.

Although Dr. Pike divides his opinions into six sub-opinions, in effect he proposes to testify about two basic conclusions: Zicam is toxic to OE and Zicam can cause anosmia.[15] The majority of Dr. Pike's report reviews the scientific principles and research he considers relevant to his conclusions. Defendants challenge the admissibility of some, but not all of this underlying evidence. We therefore consider the admissibility of the challenged research.

2. Kinds of evidence

a. Applicability of research on different zinc compounds

Dr. Pike explains that the toxic effect of zinc compounds is caused by the released positively charged ions, or "cations," which can be distinguished from non-toxic negatively charged ions of the zinc compounds, or "anions." Pike Report at 10. As evidence of this, Dr. Pike points to the safe, therapeutic uses of gluconate and sulfate in certain medical procedures.

---

[14] While most physicians have little training in chemical toxicology, an "exception is a physician who is certified in medical toxicology by the American Board of Medical Toxicology, based on substantial training in toxicology and successful completion of rigorous examinations." Reference Manual on Scientific Evidence 416.

[15] The six sub-opinions are: (1) human and animal studies have demonstrated an increased risk of anosmia and olfactory nerve toxicity after application of zinc gluconate and zinc salts; (2) zinc gluconate present in a concentration of 31 mM in Zicam has been recognized as causing anosmia after nasal application; (3) many Zicam consumers developed nasal burning and headache followed by anosmia; (4) adults and children are at risk for anosmia; (5) the relative risk of anosmia following use of Zicam was higher than after use of similar products; and (6) to reasonable degree of medical probability the zinc gluconate in Zicam was the cause of the high incidence of anosmia.

Because the zinc cations are toxic, the compound in which it is found does not matter. Therefore, Dr. Pike argues, any published toxicology research "that involves zinc sulfate, zinc chloride, zinc gluconate or other zinc salts is directly applicable and fungible with regard to dose response, mechanism of toxicity, target biomolecules, target cells, and target organs, and physiological and physical effects of zinc cation toxicity." Pike Report at 12. Dr. Pike opines that dose-response data from zinc-sulfate experiments is directly applicable to understanding the dose-response of zinc gluconate, because toxicity is just the result of the concentration of zinc ions in the substance (or the "molar concentration").

In arriving at this conclusion, Dr. Pike also relies on the Pavlica study. Pike Report at 14. As explained above, the Pavlica researchers compared the toxicity of different zinc compounds. See Section III(A)(2)(c)(ii), supra. Dr. Pike notes that the researchers found that all zinc salts were toxic at .3 molar concentration, and concludes that the dose-response data from other zinc salts is directly applicable to the zinc gluconate dose response. Pike Report at 16. Defendants argue that *in vitro* studies cannot form the basis of general causation conclusions, because they do not account for human physiology and the zinc-tissue cell relationship. Motion to Exclude Causation Experts at 29. However, as discussed supra, defendants do not challenge the underlying Pavlica results. Therefore, they are a reliable basis for Dr. Pike's opinion about the interchangeability of zinc sulfate and zinc gluconate toxicity results.

b. Distribution of Zicam and zinc in the nasal cavity

Dr. Pike further opines that the form in which the zinc salt is delivered into the nasal cavity influences its distribution, clearance and retention time. Pike Report at 12. Dr. Pike believes that a viscous solution like Zicam lasts longer in the olfactory mucosa. Pike Report at 12, 21, 25 (citing S.T. Charlton et al., Distribution and Clearance of Bioadhesive Formulations From the Olfactory Region in Man: Effect of Polymer Type and Nasal Delivery Device, 30 European J. Pharmaceutical Sciences 295–302 (2007) (doc. 1068-6)). Defendants argue that Dr. Pike's reliance on the Charlton study is misplaced. Motion to Exclude Causation Experts at 27. In that study, researchers used a Beconase brand spray device to

deliver a thixatropic solution into the noses of three volunteers. "The results of the present study show that delivery to the olfactory region can be achieved using a spray device, however, only a small amount of the dose reached the target site and the reproducibility was poor." Charlton Study at 8. Defendants argue that in concluding that Zicam reaches the OE, Dr. Pike has not accounted for differences in formulation, delivery, and administration. Plaintiffs counter that the study's demonstration that the bioadhesive formulations could reach the olfactory region supports the biological plausibility of Zicam's ability to reach the OE. Response to Motion to Exclude Causation Experts at 26.

The Charlton study is not a reliable basis for Dr. Pike's theory that Zicam can reach the OE. The study was published, and involves a testable theory. However, the conditions of the study are not sufficiently similar to the normal use of Zicam to justify Dr. Pike's extrapolation. Researchers used a different device with a different solution, administered by professionals. The study also involved only twelve participants. Moreover, the researchers found low reproducibility of the ability of the solution to reach the olfactory region. We therefore exclude any reliance on the Charlton study.

Dr. Pike also believes that disassociated zinc ions can reach the OE because of differences in the electronegativity of the nose and mouth. He explains that pH differences between Zicam and the nasal cavity create an electrical gradient that allows the zinc ions to overcome the counteractive effects of gravity and nasal-clearance mechanisms and reach the olfactory cleft. Pike Report at 13. Dr. Pike relies on studies determining the pH level of the mouth, nose, and Zicam. Defendants contend this is an untested, unproven theory, and cannot support a reliable and admissible expert opinion. Motion to Exclude Causation Experts at 19. But as we concluded with respect to Dr. Mitra's opinions about diffusion, an extrapolation from the principle of diffusion and Zicam's propensity to release zinc ions to the conclusion that zinc could reach the OE does not present a large analytic gap, and is based on reliable scientific principles. Therefore, testimony about zinc ion diffusion within the nasal cavity is admissible.

c. Polio experiments

Dr. Pike cites experiments done in the 1930s in which researchers applied a one percent zinc sulfate solution to children's noses (out of the erroneous belief that the solution might prevent polio). Pike Report at 22, 34. Every court to consider the admissibility of the polio literature has rejected it. As one court put it, "there are too many dissimilarities between the experimental application of zinc sulfate to prevent the spread of polio in the 1930s and the use of an over-the-counter cold treatment today." Sutherland, 2006 U.S. Dist. LEXIS 96652, at *26–27. In addition, the Pavlica study's results comparing the toxicity of zinc sulfate and zinc gluconate do not make extrapolations from the polio study justified. The differences between the compound's formulation and application in the polio study as compared to the normal use of Zicam create too great an analytic gap between data and opinion, and leave any resulting conclusions about Zicam's toxicity inadmissible.

d. Case studies

Dr. Pike also considers a case study by Dr. Davidson. Pike Report at 24 (citing Thomas Alexander & Terrence Davidson, Intranasal Zinc and Anosmia: the Zinc- Induced Anosmia Syndrome, 116 Laryngoscope 2, 217–20 (2006)). Dr. Davidson reported on seventeen patients who complained of anosmia after Zicam use. Other courts have rejected Dr. Davidson's case study as unreliable evidence of causation. "Although the studies may raise questions regarding the possible relationship between anosmia and Zicam, they do not provide an adequate scientific basis for general causation." Rose 2009 WL 902311, at *15 (citing Sutherland, 2006 U.S. Dist. LEXIS 96652, at *31 & McClain, 401 F.3d at 1254 ("case reports raise questions, they do not answer them")). We agree that the Davidson case study is not admissible evidence of causation. We thus exclude Dr. Pike's causation opinions to the extent that they are based on the Davidson study.

e. Lim study

Dr. Pike also considers the Lim study. Pike Report at 24. As we stated in connection with Dr. Davis's proposed testimony, both the animal and *in vitro* portions of the Lim study are admissible bases for expert opinion on causation. See Section III(A)(2)(c), supra. Accordingly, Dr. Pike may use the Lim study in concluding that Zicam causes anosmia.

f. FDA reports

Dr. Pike also cites the FDA's analysis of reports of Zicam-related anosmia. Pike Report at 27, 32, 34, 35, 36. We have previously concluded that this information is not a reliable foundation for scientific causation opinions. See Section III(A)(2)(c)(iii), supra. We therefore exclude Dr. Pike's references to the FDA reports.

3. Opinion admissibility

Defendants also make more general challenges to the admissibility of Dr. Pike's opinions. Defendants argue that Dr. Pike's opinion that Zicam is toxic to the OE is inadmissible because Dr. Pike does not know how much of the OE must be compromised to produce smell dysfunction or loss. Motion to Exclude Causation Experts at 27. However, as stated in relation to Dr. Davis's testimony, a lack of knowledge as to the exact amount of OE damage necessary to cause smell dysfunction does not necessarily render Dr. Pike's opinions about Zicam's toxicity unreliable. See Section III(A)(2)(a), supra. The same is true of Dr. Pike's decision not to reference the clinical trials of Quigley Co.'s Cold-Eeze. These concerns about the expert's opinions go to their weight, not their admissibility.

In sum, Dr. Pike may testify about the toxicity of Zicam to OE and the drug's potential to cause anosmia. However, he may not cite the Charlton study, the polio experiments, Dr. Davidson's case studies, or the FDA's AERs data and its analysis.

IV. Labels and Warnings

Plaintiffs proffer the opinion of Dr. Jay Sirois as an expert on the regulation and labeling of Zicam. See Sirois Report (doc. 1068-2). Dr. Sirois offers the following conclusions: (1) Matrixx failed to fully document, evaluate, and report a number of adverse events regarding anosmia associated with Zicam; (2) in response to internally-accumulated anosmia reports, Matrixx failed to comply with industry standards relating to product labeling; (3) the need for Zicam label information about the risk of anosmia was apparent beginning as early as 2001-2002; (4) Matrixx failed to adequately evaluate and report the risks of anosmia; and (5) risk evaluation and reporting were especially critical in light of the relatively

modest potential benefit associated with Zicam (shortened duration or severity of the common cold) compared to the potential risk of permanent anosmia. Sirois Report at 19.

Dr. Sirois is the Director of Scientific Research and Clinical Studies at Pharmaceutical Development Group, Inc., a consulting firm specializing in pharmaceutical development and registration activities, located in Tampa, Florida. Sirois Report at 3. Dr. Sirois has a Ph.D. in Pharmacology and Toxicology-Environmental Toxicology from Michigan State University and a B.A. in Toxicology from Northeastern University. He is a member of the Regulatory Affairs Professionals Society. Dr. Sirois develops regulatory strategies for safety and efficacy evaluations of new and existing drugs, and participates in the monitoring of pharmacovigilance profiles (data relating to detection, assessment, understanding and prevention of adverse effects of drugs regulated by the FDA). He reviews and helps prepare a variety of drug applications to the FDA. He has published several articles and is a peer reviewer for the journal Neurotoxicology.

Defendants contend that Dr. Sirois's opinions about labeling and FDA requirements are not admissible. They also argue that his opinion about the biologic plausibility of Zicam-induced anosmia is inadmissible.

A. Labeling and FDA requirements

1. Threshold requirements for testimony about labeling and FDA requirements

Defendants argue Dr. Sirois does not possess the threshold qualifications to testify about appropriate labels, violations of FDA regulations, or pharmacovigilance monitoring for homeopathic products. Motion to Exclude Sirois at 9, 11.

Defendants note that Dr. Sirois has never advised a company about a homeopathic product. See Sirois Deposition at 3 (doc. 1068-3). Dr. Sirois also has not previously worked with zinc or zinc gluconate products. He has never drafted a drug label, but he has evaluated evidence and prepared summaries that were the basis of his company's advice to clients about labeling. Id. at 10. Similarly, he has not directly advised clients on "good manufacturing process" ("GMP") issues, but has prepared sections of GMP reports for clients. He has not submitted materials to the FDA under his name, but has contributed to clients' submissions.

Id. at 17. Dr. Sirois has not conducted any research on Zicam or zinc gluconate. Id. at 13, 19.

Despite these limitations, Dr. Sirois is qualified to testify about product labeling and FDA and industry requirements. Dr. Sirois's Ph.D. in Pharmacology and Toxicology, his membership in the Regulatory Affairs Professionals Society, his professional experience providing regulatory advice to drug companies, and his research on the effect of mercury on neuron (nerve cell) health and function enable him to testify reliably. His inexperience in drafting labels and his failure to identify the language he thinks the Zicam label should contain are not critical to the reliability of his opinion that Zicam should have provided some kind of warning about the risk of anosmia. Additionally, although he does not have experience with homeopathic labeling or reporting requirements in particular, specific experience is not necessary to qualify Dr. Sirois to opine about how defendants should have reacted to the safety signals he identifies. Defendants do not contend that the recognition of safety signals or the related obligation to warn of possible health risks is significantly different for homeopathic remedies than allopathic drugs (conventional or Western drugs). Dr. Sirois's experience with the regulation of allopathic drugs is sufficient. Dr. Sirois meets the threshold requirement to testify as a regulatory expert under Rule 702, Fed. R. Evid.

2. Reliability

Defendants contend that Dr. Sirois's opinions about labeling, regulatory, and industry requirements are not based on reliable evidence. Dr. Sirois states in his report, "[t]he need for labeling information concerning the risk of anosmia associated with the use of intranasal Zicam products was apparent beginning as early as 2001-2002." Sirois Report at 19.[16] Defendants claim that the polio studies and isolated event reports made to Matrixx and the FDA cannot be the basis for reliable expert opinion about defendants' obligation to warn of

[16] In his deposition, Dr. Sirois notes that defendants had reports of anosmia as early as 1999. However, he does not go so far as to say that defendants should have warned of anosmia by then, but rather, "no later than 2002." Sirois Deposition at 51. Because this does not conflict with the dates he gave in his report, we consider Dr. Sirois's opinion to be that defendants should have warned consumers of anosmia risks by 2001 or 2002, not 1999 as defendants assert.

a risk of anosmia. They also argue that Dr. Sirois may not rely on FDA analysis and internal Matrixx reports. Finally, they contend that Dr. Sirois's failure to address the background rate of anosmia undermines his opinion.

a. Polio studies, animal studies, and event reports

Defendants contend that the 1930s polio studies, animal studies , and event reports are not reliable evidence that Matrixx should have warned of anosmia in 2001-2002.

Defendants contend there is no scientific basis to conclude from the polio studies, which involved zinc sulfate administered at different doses, that Zicam can be toxic. Motion to Exclude Sirois at 13. Defendants argue that because the conditions of the polio studies have no resemblance to the proper use of Zicam, they are not reliable evidence of a safety signal. They further contend that the animal studies present the additional challenge of having to extrapolate between species. Motion to Exclude Sirois at 14.

As explained in relation to defendants' Motion to Exclude Causation Experts, we agree with the courts that have excluded the polio literature as evidence of causation of anosmia. See Section III(C)(2)(c) , supra. But causation and a duty to warn are very different issues. Dr. Sirois will testify that "the appearance of a safety signal would prompt a reasonable pharmaceutical company to warn of the possible risk of anosmia even though causation might not be fully proven as a scientific fact." Response to Motion to Exclude Sirois at 8. Although the polio studies involved a different compound applied very differently than Zicam, the research still could have alerted defendants to the toxicity of zinc. Reliable testimony "need not establish every element that the plaintiff must prove, in order to be admissible." Primiano v. Cook, __ F.3d___, ___, 2010 WL 1660303, *5 (9th Cir. 2010). The studies are not admissible evidence of causation, but they may be a reliable foundation for Dr. Sirois's opinion that defendants were aware of safety signals, and those triggered an obligation to alter the Zicam labeling. The same is true of research using animals to test zinc toxicity. See Sirois Report at 8, n.23.

Defendants also challenge Dr. Sirois's reliance on several adverse event reports. Motion to Exclude Sirois at 14. Dr. Sirois states that based on four or five complaints of

anosmia, defendants at least had a duty to start to study the issue and an obligation to change the label. Sirois Deposition at 40. We agree with defendants that uncontrolled anecdotal reports are not a reliable foundation for causation opinions. See Section III(A)(2)(c)(iii), supra; Motion to Exclude Sirois at 16. But Dr. Sirois is not a causation expert. The standard that defendants should have applied in determining whether to warn consumers of a risk of anosmia, and the standard applied in admitting expert causation testimony under Rule 702, Fed. R. Evid., are not the same. We conclude there is no methodological problem in Dr. Sirois's conclusion that consumer reports of anosmia were safety signals about Zicam.

b. Reliance on FDA documents

Defendants argue that Dr. Sirois may not rely on the FDA Warning Letter or FDA internal memoranda that were not shared with Matrixx. Motion to Exclude Sirois at 17. Defendants contend that the FDA reports are not relevant to Dr. Sirois's labeling opinions.

Clearly, any documents that were not shared with Matrixx cannot be the basis for imputing knowledge to defendants. But Dr. Sirois does not rely on the FDA reports as direct evidence of what Matrixx knew and when. Instead, he considers the event data underlying the reports as an indication of the kind of information that Matrixx would have had at different points in time. See Sirois Deposition at 48 ("I couldn't find any evidence that FDA communicated their analysis to Matrixx, but Matrixx certainly had similar information available to them."). Because the FDA AERs data is publicly accessible, it is reasonable to believe that defendants did know or should have had known about the events underlying the FDA documents even if defendants never saw the FDA's analysis. Therefore, the underlying data support Dr. Sirois's opinions about what defendants' knew or should have known about reports of anosmia.

Defendants also fault Dr. Sirois for not reviewing individually the adverse event reports submitted to the FDA and Matrixx. See Motion to Exclude Sirois at 5, 15. Dr. Sirois's dependence on the secondary reports might be problematic if he were relying on the them as evidence of causation of anosmia. But instead, he considers the underlying event reports to be an indication of what defendants could have known about adverse events.

Defendants do not challenge the accuracy of the Matrixx documents or of the FDA's tallies of the number and dates of adverse events. The data underlying the analysis by the FDA and Matrixx are an admissible basis for Dr. Sirois's opinions, and he may rely on the summaries of that data contained in the FDA documents. Dr. Sirois may not testify about the FDA's conclusions regarding the data.

c. Background rate of anosmia

Defendants also fault Dr. Sirois for not giving any consideration to the background rate of anosmia. Motion to Exclude Sirois at 15. Defendants argue that this is particularly problematic given Dr. Sirois's heavy reliance on anecdotal adverse event reports. Dr. Sirois concedes that he "probably should have" mentioned the background rate of anosmia in his report. Sirois Deposition at 32. However, he believes that the descriptions of a burning sensation in the reports of smell loss suggest that the reported anosmia was not a reflection of the background rate. Id. at 31.

Defendants' contention that the number of event reports is within the background rate, and therefore was not a reason for defendants to warn of the risk of anosmia, goes to the weight of Dr. Sirois's opinions, not their admissibility. "Normally, failure to include variables will affect the analysis's probativeness, not its admissibility." Hemmings, 285 F.3d at 1188 (citing Bazemore v. Friday, 478 U.S. 385, 400, 106 S.Ct. 3000, 3009 (1986)). Because Dr. Sirois's omission of any discussion of the background rate of anosmia in his report is not fatal to its reliability, his opinion is admissible.

3. Helpfulness of Dr. Sirois's testimony on labeling and FDA requirements

Defendants argue that Dr. Sirois's testimony amounts to little more than reading exhibits, and therefore his testimony would not be helpful to a jury. Motion to Exclude Sirois at 18. They contend that because Dr. Sirois is not qualified to testify about drug regulation and labeling, his testimony is based solely on reading internal FDA memoranda, a task the jury is qualified to do.

The requirement that expert testimony assist the trier of fact goes primarily to relevance. Daubert, 509 U.S. at 591, 113 S.Ct. at 2795. "Expert opinion testimony is relevant

if the knowledge underlying it has a valid connection to the pertinent inquiry." Primiano, 2010 WL 1660303, *5. In this case, the pertinent inquiries are whether (and if so, when) industry and regulatory standards required defendants to warn Zicam consumers about possible health risks, what defendants should have known about a possible risk of anosmia, and when they should have known it. Dr. Sirois is qualified to testify about these issues. His testimony has a valid connection to the issue of defendants' obligation to warn consumers.

Industry practices and the regulatory framework governing both prescription and over-the-counter drugs, as well as homeopathic and allopathic drugs, are complex. As illustrated by the FDA's 2009 actions in relation to Zicam, the agency's proactive approach to drug safety requires that manufacturers take specific steps in response to the detection of certain safety signals. Expert testimony could help a jury understand agency rules and procedures. The same is true of industry standards regarding a company's responsibilities when it learns of consumer health complaints. Because the concept and practices of pharmacovigilance are intricate and technical, expert testimony may assist a jury in understanding the process of detecting and responding to safety signals. See In re: Gadolinium-Based Contrast Agents Product Liability Litigation, 2010 WL 1796334, *16 (N.D. Ohio 2010) (permitting colleague of Dr. Sirois's to testify about pharmacovigilance and the interpretation of safety signals in medical product liability litigation).

Because expert testimony could be helpful to a jury in understanding the extent of defendants' compliance with industry and regulatory standards, Dr. Sirois's assessment of defendants' response to reports of anosmia is relevant and admissible.

B. Biologic plausibility of Zicam-induced anosmia

1. Threshold requirements for biologic plausibility testimony

Defendants contend that Dr. Sirois may not opine about the biologic plausibility of Zicam causing anosmia because he fails to meet the threshold requirement that he possess the necessary specialized, skill, training, or knowledge. Sirois Report at 8, 15; Motion to Exclude Sirois at 18–19. Biologic plausibility refers to a theory's "coherence with existing knowledge" and is one factor that guides causation judgments of epidemiologists. See

Reference Manual on Scientific Evidence at 375. Defendants argue that Dr. Sirois is not an expert on the toxicity of zinc gluconate or on whether Zicam can reach the OE. They note that he has never done any research on zinc toxicity, or worked with any homeopathic drugs outside this litigation.

Whether Dr. Sirois is qualified to testify as an expert about zinc toxicity or Zicam-induced anosmia is not at issue because he has not been proffered as a causation expert. Plaintiffs agree that Dr. Sirois will not testify on causation or whether Zicam is defective. See Response to Motion to Exclude Sirois at 9. However, Dr. Sirois may offer his opinions about the kinds of reports he believes should have alerted defendants to the possibility that Zicam could cause smell dysfunction. He may testify about what information he considers to be safety signals about Zicam (and what responsibilities defendants' awareness of these signals imposed upon them). These signals may include studies suggesting the biologic plausibility of Zicam-related anosmia. Such an opinion is distinguishable from a causation expert's opinion that the use of Zicam can cause anosmia. Because of his academic background in toxicology and professional experience with drug regulation, Dr. Sirois is qualified to testify about what kinds of information should have alerted defendants to the biologic plausibility of Zicam-induced anosmia.

2. Reliability of biologic plausibility testimony

Defendants further argue that Dr. Sirois's opinions about biologic plausibility are not reliable. Motion to Exclude Sirois at 19. Dr. Sirois bases his opinion about the biologic plausibility of Zicam-induced anosmia on the polio studies, case reports, incident reports made to Matrixx and the FDA, and his knowledge of the toxicity of other metals. Sirois Deposition at 34. As we have explained, these studies and reports are not reliable scientific evidence of causation. However, they are a reliable basis for Dr. Sirois's opinion that it is biologically plausible for intranasally-applied zinc gluconate to produce anosmia. Biologic plausibility is just one factor in causation analysis. To say that a cause and effect relationship is plausible is not to offer an opinion about the likelihood that such a relationship actually exists. Biologic plausibility opinions reflect only the expert's belief that a theory is coherent

with existing knowledge, not that the theory is correct. See Reference Manual on Scientific Evidence 378 (the salience of biologic plausibility in evaluating causation depends "on the extent of scientific knowledge about the cellular and subcellular mechanisms through which the disease process works."). Therefore, evidence underlying an expert opinion about biologic plausibility need not meet the standards applicable to causation opinions.

Dr. Sirois reviews what he believes is the existing knowledge of the toxicity of zinc, and opines that it is biologically plausible that Zicam could cause anosmia. There is no analytic gap between this conclusion and the cited research. Because Dr. Sirois's methodology is sound, his biologic plausibility opinion is admissible. Fears that a jury may use his opinions or their bases as evidence of causation can be addressed in limited admissibility instructions.

C. Zicam Gel Swabs testimony

Defendants also argue that Dr. Sirois may not opine about safety and labeling issues related to the Zicam Cold Remedy Nasal Gel Swabs and Swabs (kid size). They note that Dr. Sirois has offered no testimony about the swabs, which were first sold in 2002. Motion to Exclude Sirois at 7. They argue that because plaintiffs have not disclosed any opinions about the swabs, Dr. Sirois may not testify about the swabs. See Fed. R. Civ. P. 26(a)(2)(C) (requiring disclosures within time set by court); Fed. R. Civ. P. 37(c)(1) (party cannot use information it failed to disclose unless the failure was substantially justified or harmless).

Because plaintiffs do not address the omission of opinions about the Zicam swab products in Dr. Sirois's report, see Response to Motion to Exclude Sirois, we assume no such opinions will be offered.

V. Conclusion

IT IS ORDERED GRANTING IN PART AND DENYING IN PART defendants' "Motion for a Ruling to Exclude The Expert Reports and Testimony of Plaintiffs' General Causation Experts" (doc. 1061).

Dr. Davis may testify about (1) his theory of the diffuse location of OE and (2) the

toxicity of Zicam, but without reference to FDA reports. Dr. Davis may not testify about (1) the distribution of Zicam within the nose and (2) the efficacy of Zicam.

Dr Mitra may testify about (1) the distribution and deposition of Zicam within the nasal cavity, (2) diffusion, and (3) the effect of BAC on absorption of Zicam. Dr. Mitra may not testify about (1) Zicam's toxicity to the OE, (2) anosmia, or (3) the efficacy of Zicam.

Dr. Pike may testify about the toxicity of Zicam to OE and the drug's potential to cause anosmia. However, he may not testify about the Charlton study, the polio experiments, Dr. Davidson's case studies, or the FDA's AERs data and its analysis.

IT IS FURTHER ORDERED DENYING defendants' "Motion to Exclude Expert Report and Testimony of Plaintiffs' Expert Jay Sirois" (doc. 1063), except with respect to reliance on the FDA's analysis and conclusions.

DATED this 23rd day of February, 2011.

Frederick J. Martone

Frederick J. Martone
United States District Judge