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IN THE UNITED STATES COURT OF APPEALS

FOR THE ELEVENTH CIRCUIT

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U.S. COURT OF APPEALS
ELEVENTH CIRCUIT
March 2, 2005
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No. 03-12776

D. C. Docket No. 01-01801-CV-AR-S

JOHNNY C. MCCLAIN,
ANNIE MCCLAIN,

Plaintiffs-Appellees,

SHIRLEY FRANKS,
WILMER HUDSON, et al.,

Plaintiffs-Appellees,
Cross-Appellants,

versus

METABOLIFE INTERNATIONAL, INC.,
a corporation,

Defendant-Appellant,
Cross-Appellee.

Appeals from the United States District Court
for the Northern District of Alabama

(March 2, 2005)

Before ANDERSON and BIRCH, Circuit Judges, and ROYAL*, District Judge.

ROYAL, District Judge:

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*Honorable C. Ashley Royal, United States District Judge for the Middle District of Georgia, sitting by designation.

This is an appeal of a jury verdict in a products liability action against Metabolife International, Inc. At trial Plaintiffs claimed that they suffered serious medical problems after taking Metabolife 356, an herbal weight-loss supplement, manufactured, marketed, and sold by Metabolife. After hearing the evidence, a jury returned a verdict in Plaintiffs' favor. Metabolife now appeals that verdict on the ground that the trial court erred in admitting the testimony of Plaintiffs' experts on the issue of causation. For the reasons discussed below, we find that the trial court erroneously admitted Plaintiffs' experts' testimony. Accordingly, we **REVERSE and REMAND** for proceedings below consistent with these rulings.

I. Background Information

Annie McClain, Shirley Franks, Connie Thornburg and Wilmer Hudson contend that they suffered serious injuries after taking Metabolife 356, an herbal appetite suppressant containing ephedrine and caffeine. Ephedrine occurs naturally in a plant called ma huang and has been used for decades for treating adults and children, especially in over-the-counter medicines.

Plaintiffs brought this action against Defendant Metabolife International, Inc., charging that Metabolife manufactured, marketed, and sold an unreasonably dangerous diet drug. Plaintiffs further contend that Metabolife knew that its product could cause heart attacks and strokes, but nonetheless, continued to sell

the drug without adequate warning. All four Plaintiffs took the dietary aid. Plaintiffs Thornburg, Franks, and McCain suffered ischemic cerebral events (strokes), and Plaintiff Hudson suffered an acute myocardial infarction (heart attack).

Before trial Metabolife moved to exclude Plaintiffs' experts' testimony on medical causation asserting that Plaintiffs' experts' opinions lacked a reliable foundation for admission under the standards of *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 579 (1993). The trial court held a *Daubert* hearing, and Plaintiffs offered two expert witnesses to prove causation: James O'Donnell, Pharm. D., and Hashim Hakim, M.D., a neurologist. Dr. O'Donnell primarily offered opinions on general causation. Dr. Hakim offered testimony on both general and individual causation.

In its brief written order on the motion, the district court acknowledged its role as a gatekeeper under FED. R. EVID. 702, but concluded that it lacked sufficient knowledge on the scientific subject matter to exclude the testimony presented and that Defendant had not produced competing testimony for it to determine that, as a matter of law, testimony from Plaintiffs' experts was inadmissible. Metabolife later filed a motion for reconsideration on the issue, and it was denied. The two experts testified at trial on the issues covered by

Defendant's motion, and the jury returned a verdict for Plaintiffs. Defendant appealed contending that the district court abused it discretion in admitting Plaintiffs' experts' testimony on medical causation.

II. Legal Standard

This is a toxic tort case. Plaintiffs contend that the toxic combination of ephedrine and caffeine in the Metabolife 356 that they ingested harmed them. To prove their toxic tort claims, Plaintiffs must prove the toxicity of the ephedrine/ caffeine combination and that it had a toxic effect on them causing the injuries that they suffered — ischemic strokes in three Plaintiffs and a heart attack in the other.

This type of proof requires expert testimony, and when a party offers expert testimony and the opposing party raises a *Daubert* challenge, the trial court must "make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). This requirement for proof of the reliability of the expert's method comes from FED. R. EVID. 702, which authorizes the admission of expert opinion testimony "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." Rule 702 lays the foundation for the trial court's *Daubert* analysis. 509 U.S. at 590.

Daubert requires the trial court to act as a gatekeeper to insure that speculative and unreliable opinions do not reach the jury. *Id.* at 589 n. 7, 597. As a gatekeeper the court must do "a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue." *Id*. at 593-94. The proposed testimony must derive from the scientific method; good grounds and appropriate validation must support it.[1] *Id*. at 590. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Id*. The court must consider the testimony with the understanding that "[t]he burden of establishing qualification, reliability, and

[1]While this opinion focuses upon the scientific methodology of an expert, it should be remembered that "experience in a field may offer another path to expert status." *United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004). "In fact, the plain language of Rule 702 makes this clear: expert status may be based on 'knowledge, skill, experience, training, or education.'" *Id*. (emphasis omitted).

helpfulness rests on the proponent of the expert opinion. . . ." *United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004).[2]

The court of appeals reviews a trial court's *Daubert* rulings under an abuse of discretion standard. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 140 (1999). A "district court enjoys 'considerable leeway' in making [reliability] determinations" under *Daubert*. *Kumho*, 526 U.S. at 152. Thus, "[w]hen applying [the] abuse of discretion standard, we must affirm unless we at least determine that the district court has made a 'clear error of judgment,' or has applied an incorrect legal standard." *See Piamba Cortes v. Am. Airlines, Inc.,* 177 F.3d 1272, 1306 (11th Cir. 1999) (quoting *SunAmerica Corp. v. Sun Life Assurance Co. of Canada*, 77 F.3d 1325, 1333 (11th Cir. 1996)).

A trial court, however, abuses its discretion by failing to act as a gatekeeper. In this case the trial court essentially abdicated its gatekeeping role. Although the trial court conducted a *Daubert* hearing, and both witnesses were subject to a

[2]In its order following the *Daubert* hearing, the court below indicated that it was unclear who bore the burden of proof as to the reliability of a proffered expert's opinions. That burden clearly rests with the proponent of that expert, *see Frazier* at 1260, and thus in this case Plaintiffs bore the burden of establishing the reliability of their experts' opinions.

thorough and extensive examination, the court ultimately disavowed its ability to handle the *Daubert* issues.[3] This abdication was in itself an abuse of discretion.[4]

Yet, even had the trial court fully accepted its role, it would have abused its discretion by admitting the experts' testimony. The record of their testimony in the pretrial hearing demonstrates that their testimony failed to satisfy the standards of reliability required under *Daubert* and its progeny. The admission of their testimony on medical causation in this toxic tort case substantially prejudiced Metabolife and authorizes reversal of the judgment. *See Piamba Cortes,* 177 F.3d at 1305.

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[3]In ruling on the *Daubert* motion, the trial court stated:

> Trying to cope in this case without a pharmacological, or a medical, or a chemical, or a scientific background, the court cannot fully and fairly appreciate and evaluate the methodology employed by either of these witnesses as they reached the conclusions they reached, conclusions that a jury could not reach without some expert opinion testimony. Neither can the court fully appreciate or evaluate the criticisms made by defendant of the proposed testimony of these witnesses, especially when the criticisms do not come from competing proposed experts. This court does not pretend to know enough to formulate a logical basis for a preclusionary order that would necessarily find, as a matter of law, that these witnesses cannot express to a jury the opinions they articulated to the court.

[4]*See Kumho*, 526 U.S. at 158-59 (Scalia, J. concurring) ("[T]rial-court discretion in choosing the manner of testing expert reliability — is not discretion to abandon the gatekeeping function. I think it worth adding that it is not discretion to perform the function inadequately. Rather, it is discretion to choose among *reasonable* means of excluding expertise that is *fausse* and science that is junky."); *Joiner,* 522 U.S. at 148. (Breyer J. concurring) ("Of course, neither the difficulty of the task nor any comparative lack of expertise can excuse the judge from exercising the 'gatekeeper' duties that the Federal Rules of Evidence impose . . . .").

In analyzing the experts' testimony, we note that toxic tort cases usually come in two broad categories: first, those cases in which the medical community generally recognizes the toxicity of the drug or chemical at issue, and second, those cases in which the medical community does not generally recognize the agent as both toxic and causing the injury plaintiff alleges. Examples of the first type include toxins like asbestos, which causes asbestosis and mesothelioma; silica, which causes silicosis; and cigarette smoke, which causes cancer. This case, involving Metabolife's combination of ephedrine and caffeine, falls into the second category. The medical community does not generally recognize the toxicity of this drug combination or ephedrine alone as causing the injuries Plaintiffs allege.

The court need not undertake an extensive *Daubert* analysis on the general toxicity question when the medical community recognizes that the agent causes the type of harm a plaintiff alleges. The battleground in this first category of cases focuses on plaintiff-specific questions: was plaintiff exposed to the toxin, was plaintiff exposed to enough of the toxin to cause the alleged injury, and did the toxin in fact cause the injury? A *Daubert* analysis in the first type of case deals with questions of individual causation to plaintiff.

In the second category of toxic tort cases, the *Daubert* analysis covers not only the expert's methodology for the plaintiff-specific questions about individual

causation but also the general question of whether the drug or chemical can cause the harm plaintiff alleges.[5] This is called general causation. "General causation is concerned with whether an agent increases the incidence of disease in a group and not whether the agent caused any given individual's disease." Michael D. Green et al., *Reference Guide on Epidemiology, in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 392 (Federal Judicial Center, 2d ed. 2000). Thus, in this case, Plaintiffs' experts must offer reliable opinions about Metabolife's general toxicity for the harm Plaintiffs allege and that it in fact harmed them. The court will consider, therefore, the reliability of Plaintiffs' experts' opinions on the question of general causation and also the question of individual causation.

III. James O'Donnell, Pharm. D.

Dr. O'Donnell, Pharm. D., testified as an expert in pharmacy, pharmacology and nutrition; he is not a toxicologist or a medical doctor. He based his opinions

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[5]This is not an effort to resurrect the test first announced in *Frye v. United States*, 293 F. 1013, 1014 (D.C. Cir. 1923), and later applied by the Ninth Circuit Court of Appeals in its ruling on *Daubert* stating that "expert opinion based on a scientific technique is inadmissible unless the technique is 'generally accepted' as reliable in the relevant scientific community." *Daubert*, 951 F. 2d 1128, 1129-1130, *vacated*, 509 U.S. 579 (1993) (overruling *Frye)*. This two-part designation for toxic tort cases is devised to further the interests of judicial economy. There is rarely a reason for a court to consider opinions that medical doctors routinely and widely recognize as true, like cigarette smoking causes lung cancer and heart disease, too much alcohol causes cirrhosis of the liver, and that the ingestion of sufficient amounts of arsenic causes death. This two-part division follows a point made in *Kumho* that the trial court does not need to waste time with a *Daubert* hearing "where the reliability of an expert's methods is properly taken for granted, and to require appropriate proceedings in the less usual or more complex cases where cause for questioning the expert's reliability arises." *Kumho*, 526 U.S. at 152.

about Metabolife's toxicity and its ability to cause heart attacks and strokes in substantial part on ephedrine's classification as a sympathomimetic drug. He testified that drugs in the sympathomimetic family, including ephedrine, cause constriction of blood vessels that leads to increased pulse rate and increased blood pressure. The long-term use of ephedrine can cause narrowing of blood vessels, called vasospasm, a transitory constriction of a blood vessel, and also vasculitis, an inflamation or irritation of blood vessels. Vasospasm and vasculitis caused by extended use of ephedrine can lead to heart attacks and strokes. That Metabolife causes vasospasm and vasculitis, which in turn causes strokes and heart attacks, is O'Donnell's ultimate opinion that the court must analyze under *Daubert*.

O'Donnell also testified that adding caffeine to ephedrine in Metabolife 356 makes ephedrine more toxic, so any amount of caffeine added to ephedrine is too much. This combination of drugs poses an "imminent risk of death."

O'Donnell's opinions lack the indicia of reliability necessary to survive a *Daubert* inquiry and challenge under Rule 702. He draws speculative conclusions about Metabolife's toxicity from questionable principles of pharmacology, while at the same time, neglecting the hallmark of the science of toxic torts — the dose-response relationship. He also draws unsubstantiated analogies between ephedrine and phenylpropanolamine, infers conclusions from studies and reports that the

papers do not authorize, and unjustifiably relies on government public health reports and consumer complaints to establish medical causation. In short, O'Donnell does not support his opinions with sufficient data or reliable principles, as identified by the *Daubert* rubric, and fails to follow the basic methodology that experts should follow in toxic tort cases.

A. Application of Broad Scientific Principles

O'Donnell testified that ephedrine belongs to a family of drugs called the sympathomimetics. These drugs stimulate the cardiovascular system by raising heart rate and blood pressure. He drew key conclusions about ephedrine's toxicity from its classification as a sympathomimetic. A close examination of his testimony, however, shows that he dramatically dilutes the value of these conclusions, which in turn, impugns his methodology. About ephedrine's family or drug class connection and effects, he left a trail of equivocation by making the following statements at various points in his testimony: Sympathomimetics can constrict blood vessels. And when you constrict blood vessels, you may raise blood pressure. Sympathomimetics stimulate the heart and increase the pulse, increase the heart rate. If you stimulate the heart, you may cause an abnormal heart rate or an abnormal heart rhythm. If you constrict blood vessels, if it happens in a

cerebral vessel in the brain, it may cause vasospasm which may lead to a stroke. If you stimulate or cause a constriction in the coronary blood vessel that can cause vasospasm and it may lead to chest pain, angina, arrhythmia, or myocardial infarction. He also testified that "aggravation of blood pressure is something that the ephedrine and caffeine in Metabolife or any product containing those drugs can do." He further explained that the ephedrine/caffeine combination "can elevate blood pressure and stimulate the heart, and it has been reported to be associated with strokes and heart attacks." Or as O'Donnell stated: "this may be dangerous for some patients." O'Donnell's equivocation about the effects of sympathomimetics exposes a tenuous basis for his opinions about Metabolife's profound toxicity — that *any* level of caffeine combined with ephedrine poses "an unreasonable risk of harm."

O'Donnell likewise offered nothing specific about how Metabolife affects individuals. When asked how one tablet of Metabolife might increase heart rate, he could not give an answer and explained that it would vary from patient to patient. He also could not say how much it might elevate a patient's blood pressure. He agreed that effect would vary from patient to patient and admitted that it might not raise a person's blood pressure at all. He further said that aerobic exercise impacts

blood pressure and heart rate more than the maximum recommended dosage of Metabolife.

Although he agreed that a drug's effect is dose-driven, he offered no testimony about the dose of Metabolife required to injure Plaintiffs or anyone else. He could not say how much is too much. In explaining his opinion about the extreme danger of Metabolife, while at the same time offering no opinions about dose, he said: "[t]hat's why I always answer with potential, may, or could." On the other hand, he admitted that the amount of ephedrine in Metabolife 356 does not exceed the amount of ephedrine in the hundreds of over-the-counter products available to the public. Likewise, he conceded that many people take drugs containing ephedrine at the same time they ingest large amounts of caffeine from coffee, and that the recommended dose of Metabolife 356 contains 72 milligrams of ephedrine, roughly half the FDA allowable limits on ephedrine. His lack of testimony about the dose-response relationship combined with his vague testimony about significant individual variations leaves a muddle of ambiguity that undermines his opinions.

Because of this ambiguity, O'Donnell laid no reliable groundwork for determining the dose-response relationship for either ephedrine or ephedrine and caffeine. This signals a methodology problem. In toxic tort cases, "[s]cientific

knowledge of the harmful level of exposure to a chemical plus knowledge that plaintiff was exposed to such quantities are minimal facts necessary to sustain the plaintiff's burden . . . ." *Allen v. Pennsylvania Eng'g Corp.*, 102 F.3d 194, 199 (5th Cir. 1996). Or, as the Court of Appeals for the Tenth Circuit explained in *Mitchell v. Gencorp*, 165 F.3d 778, 781 (10th Cir. 1999), to carry the burden in a toxic tort case, "a plaintiff must demonstrate 'the levels of exposure that are hazardous to human beings generally as well as the plaintiff's actual level of exposure to the defendant's toxic substance before he or she may recover,'" (quoting *Wright v. Willamette Indus., Inc.*, 91 F.3d 1105, 1106 (8th Cir. 1996)); *see also Moore v. Ashland Chem. Inc.*, 151 F.3d 269, 278 (5th Cir. 1998) (excluding expert testimony which "offered no scientific support for his general theory that exposure to toluene solution at any level would cause RADS.").[6]

Although Plaintiffs can testify about how much Metabolife 356 they took, O'Donnell could not provide any opinions about the general dose-response levels for Metabolife's toxicity, i.e., the dose or level of exposure at which it causes harm. O'Donnell opined that any level is too much, but this statement conflicts with the importance of individual responses to toxins — "[b]ecause of individual variation,

[6]One should not conclude from this analysis that to pass *Daubert* muster an expert must give precise numbers about a dose-response relationship. Some ambiguity about individual responses is expected. However, the link between an expert's opinions and the dose-response relationship is a key element of reliability in toxic tort cases.

a toxic agent generally will not cause disease in every person exposed." Green, *supra,* at 392.

When analyzing an expert's methodology in toxic tort cases, the court should pay careful attention to the expert's testimony about the dose-response relationship. The dose-response relationship is "[a] relationship in which a change in amount, intensity, or duration of exposure to an agent is associated with a change — either an increase or decrease — in risk of disease." *Id.* at 390. The expert who avoids or neglects this principle of toxic torts without justification casts suspicion on the reliability of his methodology.

To help federal judges deal with *Daubert* issues in toxic tort cases, the Federal Judicial Center published several articles in the *Journal of Law and Policy* under the title "Science for Judges I: Papers on Toxicology and Epidemiology." 12 J.L. & POL'Y 1 (2003).[7] The article entitled "Scientific Judgment and Toxic Torts — A Primer in Toxicology for Judges and Lawyers" by Dr. David Eaton provides valuable insight for understanding how to assess *Daubert* issues in these cases. *Id.* at 5. Dr. Eaton, Ph.D., is a toxicologist and Professor of Environmental and Occupational Health Sciences at the University of Washington. *Id.* He also

[7]The FJC collaborated on this work with the Brooklyn Law School's Center for Health Law and Policy and the Panel on Science, Law and Technology of the National Academy of Sciences. 12 J.L. & POL'Y 1 (2003).

serves as Associate Dean for Research, School of Public Health and Community Medicine at the University. *Id.*

In his article Eaton describes some key principles of toxicology that a court should consider in "any attempt to establish whether a chemical exposure was causally related to a specific adverse effect or disease in an individual." *Id*. at 9. Foremost among these principles is the dose-response relationship.

Dr. Eaton explains that "the relationship between dose and effect (dose-response relationship) is the hallmark of basic toxicology." *Id*. at 15. "Dose is the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect." *Id*. at 11. Often "low dose exposures — even for many years — will have no consequence at all, since the body is often able to completely detoxify low doses before they do any damage." *Id*. at 13. Furthermore, "for most types of dose-response relationships following chronic (repeated) exposure, thresholds exist, such that there is some dose below which even repeated, long-term exposure would not cause an effect in any individual." *Id*. at 16.

These essential principles of toxicology directly contradict several of what O'Donnell calls "the broad principles of pharmacology" upon which he bases his opinions. But more importantly, it shows something about O'Donnell's

methodology: he does not follow the basic methodology that scientists use to determine causation — the dose-response relationship.

Beyond explaining the importance of the dose-response relationship, Dr. Eaton offers four scientific criteria for proving causation between a chemical exposure and a particular illness in an individual. First, "the toxic substance in question must have been demonstrated to cause the type of illness or disease in question." *Id*. at 38. This focuses on the issue of general causation. O'Donnell has failed to show that Metabolife 356 causes either strokes or heart attacks. Furthermore, the medical literature does not support this opinion. O'Donnell has simply substituted his own *ipse dixit* for scientific proof on this essential issue.

Second, "the individual must have been exposed to a sufficient amount of the substance in question to elicit the health effect in question." *Id*. at 39. This requires not simply proof of exposure to the substance, but proof of enough exposure to cause the plaintiff's specific illness. This focuses on the issue of individual causation.

As already shown, O'Donnell offers no opinion about the dose of Metabolife that caused ischemic strokes in three Plaintiffs and a heart attack in the other. He

only said that any amount of Metabolife is too much, which clearly contradicts the principles of reliable methodology delineated by Eaton.[8]

Third, "the chronological relationship between exposure and effect must be biologically plausible." *Id*. On this point Eaton explains that "if a disease or illness in an individual preceded the established period of exposure, then it cannot be concluded that the chemical caused the disease, although it may be possible to establish that the chemical aggravated a pre-existing condition or disease." *Id*. at 39-40. This also focuses on individual causation.

The issue of the chronological relationship leads to another important point — proving a temporal relationship between taking Metabolife and the onset of symptoms does not establish a causal relationship. In other words, simply because a person takes drugs and then suffers an injury does not show causation. Drawing such a conclusion from temporal relationships leads to the blunder of the *post hoc ergo propter hoc* fallacy.

The *post hoc ergo propter hoc* fallacy assumes causality from temporal sequence. It literally means "after this, because of this." BLACK'S LAW

[8]Although the court understands that *Daubert* focuses on the methodology used to derive opinions rather than on the accuracy of the opinion, when the opinions clearly demonstrate something about the expert's methodology, as in this case, the court can draw inferences about the methodology from the opinions. As the Supreme Court said in *Joiner*: "Conclusions and methodology are not entirely distinct from one another." 522 U.S. at 147.

DICTIONARY 1186 (7th ed. 1999). It is called a fallacy because it makes an assumption based on the false inference that a temporal relationship proves a causal relationship. As the Court of Appeals for the District of Columbia explained in a similar context: "[i]n essence, the requirement of 'adequate documentation in scientific literature' ensures that decision makers will not be misled by the *post hoc ergo propter hoc* fallacy — the fallacy of assuming that because a biological injury occurred after a spill, it must have been caused by the spill." *Ohio v. U.S. Dept. of the Interior,* 880 F.2d 432, 473 (D.C. Cir. 1989).

Fourth, and finally, "the likelihood that the chemical caused the disease or illness in an individual should be considered in the context of other known causes." Eaton, *supra,* at 40. This refers to the background risk of a specific disease — the risk that everyone faces of suffering the same malady that a plaintiff claims without having exposure to the same toxin.

A reliable methodology should take into account the background risk. The background risk is not the risk posed by the chemical or drug at issue in the case. It is the risk a plaintiff and other members of the general public have of suffering the disease or injury that plaintiff alleges without exposure to the drug or chemical in question. The background risks include all those causes of a disease, whether known or unknown, excluding the drug or chemical in question. So, the

background risk for heart attack is very high because heart disease is the leading cause of morbidity and mortality in America. *See Heart Attacks*, Nat'l Heart, Lung, & Blood Inst., *at* http://www.nhlbi.nih.gov (last visited Dec. 27, 2004). Likewise, stroke is the third leading cause of death in America and the leading cause of disability. *See* Jeffrey L. Arnold, *Ischemic Stroke*, emedicine, at http://www.emedicine.com (last visited Dec. 27, 2004). Ischemic strokes, like three Plaintiffs suffered in this case, account for 80% of all stroke cases. *Id.*

Thus, in evaluating the reliability of the experts' opinions on general causation, it would help to know how much additional risk for heart attack or ischemic stroke Metabolife consumers have over the risks the general population faces. If ephedrine or an ephedrine/caffeine combination do not increase the incidence of heart attack and ischemic stroke in persons who ingest it, as opposed to all those who do not and still have heart attacks and strokes, that fact would reduce the likelihood that Metabolife harmed Plaintiffs. Likewise, if Plaintiffs could show that taking Metabolife increases the risk of heart attack and ischemic stroke beyond the usual incidence of these common diseases, that would support their methodology in this case. O'Donnell offered no evidence of additional risk. The court must assume that it does not exist. (Indeed, O'Donnell testified that he did not know the background risk for stroke and heart attack.)

Toxicologists and medical doctors doing research commonly assess risks posed by drugs, chemicals and other agents. A quick internet search of TOXNET for "risk assessment" or "background risks" will show thousands of articles about risks for various drugs and chemicals — Plaintiffs' experts offered no such evidence. *See generally*, *Thomas v. Hoffman-LaRoche, Inc.*, 949 F.2d 806, 816 (5th Cir. 1992); *Norfolk v. W. Ry. Co. v. Ayers*, 538 U.S. 135, 156 (2003).

Now as to these four criteria for proving causation, O'Donnell failed to demonstrate a link between Metabolife and the types of injuries Plaintiffs suffered as required by the first criteria. He also failed to show that Plaintiffs had sufficient individual exposure to Metabolife to cause the medical problems as required by the second criteria, and he further failed to show evidence of an increased incidence of strokes and heart attacks from Metabolife 356 over the background risk as required by the fourth criteria. There is evidence in the case supporting the third criteria, the chronological relationship between exposure and effect, but this does not overcome the failure of proof on the other three propositions.

Finally, on the speculative nature of his testimony, O'Donnell attempts to anoint his opinions by claiming that he based them on the "broad principles of pharmacology." In the *Daubert* context, such phrases have little value. They are not shibboleths that distinguish those experts that offer reliable science from those

who foist junk science on the court. "The expert's assurances that he has utilized generally accepted scientific methodology [are] insufficient." See *Moore,* 151 F.3d at 276. Such statements can spring just as quickly from the *ipse dixit* of the expert as some ultimate opinion about causation or toxicity. As the Supreme Court explained in *Joiner*: "nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert." 522 U.S. at 147. Moreover, "[t]he trial court's gatekeeping function requires more than simply 'taking the expert's word for it.'" FED. R. EVID. 702 advisory committee's note (2000).

B. The PPA Analogy

In reaching his opinions about general causation, O'Donnell relies heavily on an analogy between ephedrine and phenylpropanolamine (PPA). PPA is a sympathomimetic drug that has been used widely in over-the-counter cough and cold medications and weight loss products. RALPH I. HOROWITZ ET AL., PHENYLPROPANOLAMINE & RISK OF HEMORRHAGIC STROKE: FINAL REPORT OF THE HEMORRHAGIC STROKE PROJECT (2000). The conclusions that O'Donnell draws about ephedrine by analogy from PPA are very important to his opinions, but he did not show the reliability of each of his steps in deducing Metabolife's toxicity from this analogy. This is a fatal defect under *Daubert*. "The *Daubert* 'requirement

that the expert testify to scientific knowledge — conclusions supported by good grounds for each step in the analysis — means that *any* step that renders the analysis unreliable under the *Daubert factors renders the expert's testimony inadmissible*.'" *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 267 (2002) (quoting *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 745 (3rd Cir. 1994)).

When O'Donnell described how ephedrine damages blood vessels based on the PPA analogy, he stated that the longer one has exposure to a chemical, the more rigid a blood vessel becomes, and it takes time for the body to release a chemical even after the person stops taking the medicine. Thus, the drug can cause vasospasm or vasculitis and continue to cause these problems even after someone stops taking the drug. These steps are essential to his analysis of Metabolife's toxicity in general and for Plaintiffs' specific injuries. But he admitted that this theory has only been proven with PPA, not ephedrine.

O'Donnell cannot show that Metabolife causes vasospasm and vasculitis, which in turn causes ischemic strokes and heart attacks, except by a leap of faith. He also cannot show that Metabolife stays in the body for prolonged periods after someone stops taking it or that its effects linger. The medical articles do not support these conclusions. Speculation replaces science in this unreliable analogy

between ephedrine and phenylpropanolamine. "Subjective speculation that masquerades as scientific knowledge" does not provide good grounds for the admissibility of expert opinions. *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 989 (8th Cir. 2001).

According to O'Donnell, studies have shown that PPA causes vasospasm and vasculitis that lead to stroke and heart attack, and the studies also show that long-term use of the drug can cause a continuation of symptoms even after a person stops taking it. For these conclusions he relied primarily on the Hemorrhagic Stroke Project (HSP) that showed a 15-fold increase in the risk of hemorrhagic strokes in patients who took PPA as a diet supplement rather than as a cough and cold remedy. Horowitz, *supra*, at 2. These results, he said, should be reasonably analogized to ephedrine and especially ephedrine with caffeine. This analogy authorizes him to conclude that not only will ephedrine cause the hemorrhagic strokes demonstrated in the HSP from taking PPA, but also ischemic strokes and heart attacks. (None of the Plaintiffs in this case had hemorrhagic strokes.) Yet, he admitted that while the FDA banned PPA because of the risk of strokes, it authorized ephedrine to replace PPA in over-the-counter medications. But more importantly, the plain reading of the HSP article does not authorize O'Donnell's conclusions.

In 2000, the New England Journal of Medicine published the report on the Hemorrhagic Stroke Project. The report shows that the investigators devised and implemented a scientific approach to evaluate the toxicity of PPA. *Id.* The authors concluded that "the results of the HSP suggest that PPA increases the risk for hemorrhagic strokes. For both individuals considering use of PPA and for policy-makers, the HSP provides important data for a contemporary assessment of risks associated with the use of PPA." *Id.* at 3. The authors draw no conclusions about ephedrine and nowhere say that ephedrine is analogous to PPA in any respect.

The authors likewise do not say that PPA is associated with ischemic stroke or heart attack or that one can analogize that because PPA may cause hemorrhagic strokes, it also causes ischemic strokes and heart attacks. Furthermore, the authors do not attempt to explain the physiological mechanism by which PPA causes strokes. Although O'Donnell contends that the PPA analogy supports his opinions that ephedrine causes vasospasm or vasculitis, nowhere in the HSP study do the authors assert this about PPA, much less about the ephedrine/caffeine combination. This study offers no support for O'Donnell's opinions.

But another methodological problem undermines O'Donnell's analogical approach. As Dr. Eaton explains: "even small differences in chemical structure can

sometimes make very large differences in the type of toxic response that is produced." See Eaton, *supra,* at 10-11. Likewise, as this court noted in *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194 (11th Cir. 2002), "[e]ven minor deviations in chemical structure can radically change a particular substance's properties and propensities." *Id*. at 1201 (citing *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001)). O'Donnell failed to show that the PPA analogy is valid or that the differences in chemical structure between PPA and ephedrine make no difference. He simply assumes its validity without offering any scientific evidence. As he said, one presumes the same effect by drugs in the same class until proven otherwise. Such presumptions do not make for reliable opinions in toxic tort cases. (As Dr. Hakim admitted, if one product had the same effect as another product, it would be the same product.)

The court addressed drug analogies in detail in *Rider* where plaintiffs sued Sandoz claiming that they suffered postpartum hemorrhagic strokes from ingesting Parlodel to suppress lactation after childbirth. *Id.* at 1196. Plaintiffs' experts in that case followed an analogical approach similar to O'Donnell's. They testified that Parlodel (bromocriptine) is a member of a class of drugs known as ergot alkaloids, and that ergot alkaloids can cause vasoconstriction, which suggests that Parlodel causes vasoconstriction. *Id.* at 1198. Animal studies also suggest that

Parlodel causes vasoconstriction. *Id.* Vasoconstriction can cause high blood pressure and ischemic stroke. *Id.* Because Parlodel can cause vasoconstriction, which causes high blood pressure resulting in ischemic stroke, it can also cause hemorrhagic stroke. *Id.* Thus, Parlodel caused plaintiffs' hemorrhagic strokes, according to Plaintiffs' experts. *Id.*

This drug analogy is stronger than O'Donnell's because in *Rider* the experts analogized from the same drug and also had some partial support for their theory from animal studies. 295 F.3d at 1200-02. O'Donnell, on the other hand, compares one drug, PPA, to a different drug, ephedrine, to reach his opinions that not only does ephedrine cause hemorrhagic stroke, as reported about PPA, it also causes ischemic stroke and heart attack. (Hemorrhagic stroke occurs when a blood vessel ruptures. Ischemic stroke occurs because of decreased blood flow to the brain.) The court in *Rider* properly rejected the testimony because of the unreliable analogy. *Id.* As the court stated, "[e]vidence suggest[ing] that [a chemical] may cause ischemic stroke does not apply to situations involving hemorrhagic stroke. This is 'a leap of faith' supported by little more than the fact that both conditions are commonly called strokes." *Id.* at 1202.

Finally, on O'Donnell's analogy methodology, he agreed that: "[t]here is a tendency in the literature, particularly in government monographs, to lump together

all ephedrine alkaloids. Doing so is both foolish and misleading as it implies that the toxicity of all enantiomers is equivalent, which is clearly not the case." After agreeing with this statement, he went on to say that "it's not predictable."

This lack of predictability, O'Donnell's use of an unreliable analogy and his inclination to draw overreaching conclusions from self-limiting medical articles, show the speculative nature of his opinions. As Judge Posner explained: "the courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996).

C. Reliance on Other Studies and Reports

O'Donnell also relied on several other studies to support his opinions about the toxicity of ephedrine and caffeine. A close analysis of the studies, however, shows that they do not authorize his opinions. The authors of the articles limit the application of their studies consistent with the principles of good science; O'Donnell expands the application beyond good science.

O'Donnell relied heavily on a report by Haller and Benowitz published in the New England Journal of Medicine that concluded that the ephedrine/caffeine combination "in some patients may cause toxicity." Christine A. Haller & Neal Benowitz, "*Adverse Cardiovascular and Central Nervous System Events*

Associated with Dietary Supplements Containing Ephedra Alkaloids," 343 NEW ENG. J. MED. 1933-38 (2000) (emphasis supplied). The authors studied 140 adverse incident reports from persons who took dietary supplements containing ephedra alkaloids. *Id.* The authors said that "these interactions between phenylpropanolamine and caffeine support the idea that the combination of ephedrine and caffeine could increase the risk of adverse effects." *Id.* (emphasis supplied). The authors, however, admit that their study does not offer a basis to determine the incidence of serious adverse effects of ephedrine alkaloids, and they recognize the necessity for study of "the determinants of individual susceptibility to serious adverse effects of dietary supplements containing ephedra alkaloids so that the appropriate guidelines and warnings can be devised." *Id.* Moreover, O'Donnell agreed that Haller and Benowitz concluded from this study that "the use of dietary supplements that contained ephedra alkaloids may pose health risks to some persons." *Id.* (emphasis supplied). He further conceded that the authors sent a letter to the editor explaining that the study did not prove causation.

In the same volume of the New England Journal of Medicine, Dr. G. Alexander Fleming published an editorial entitled "The FDA, Regulation, and the Risk of Stroke," in which he discusses the Haller and Benowitz study that O'Donnell considers so important. 343 NEW ENG. J. MED. 1886-87 (2000). About

that study Fleming stated: "the study by Haller and Benowitz represents only an early step in the process of pharmacologic vigilance. Data from spontaneous reports usually provide only preliminary evidence of risk and not proof of risk." *Id.* Fleming reviewed the eleven cases of sudden catastrophic cardiovascular and cerebrovascular events that Haller and Benowitz attributed as definitely or probably caused by ephedra alkaloids. *Id.* He concluded that only one of the cases should be attributed to supplements containing ephedra alkaloids. *Id.* He reached this conclusion in substantial part because of the background risk of subarachnoid hemorrhage and myocardial infarction. As he explained, "subarachnoid hemorrhage and myocardial infarction are too common, even among young and middle-aged people to be pathognomonic of complications of the use of products containing ephedra alkaloids." *Id.* He acknowledges the importance of background risks in reaching conclusions about toxicity and individual injury. *Id.*

Fleming went on to explain that

> it is much less clear whether the FDA should take steps to ban or even restrict the use of products containing ephedra alkaloids. The risks of such products, when they are used as directed, have not been adequately established. A large body of data suggests that products containing ephedra alkaloids and ephedrine as an over-the-counter drug have a low risk of adverse effects at the recommended levels of consumption. The report by Haller and Benowitz provides

> information that justifies the initiation of the same kind of study that was conducted by the Hemorrhagic Stroke Project.

Id.

Fleming neither exonerates nor indicts ephedra alkaloids, but he does explain the limitations of the Haller and Benowitz study which, in turn, shows that O'Donnell does not follow the conservative approach of scientists in this field. Dr. Fleming exemplifies this approach by limiting conclusions about causation from insufficient evidence. Indeed, Haller and Benowitz limit the conclusions authorized from their study by saying that it does not prove causation. The comments of Fleming and Haller and Benowitz demonstrate the intellectual rigor in this field of science, an intellectual rigor that is conservative and does not leap to specific conclusions about causation or toxicity from incomplete evidence or broad principles. But the record offers yet more evidence of O'Donnell's willingness to exceed the limits of the conservative scientific methodology.

He also relies on an article called "*Adverse Cardiovascular Events Temporally Associated with Ma Huang, an Herbal Source of Ephedrine*" published in the Mayo Clinic Proceedings. David Samenuk et al., 77 MAYO CLIN PROC. 12-16 (2002). The author studied adverse reaction reports filed with the FDA by consumers of ma huang, a natural source of ephedrine. The study focused on the safety of ma huang for adverse cardiovascular effects. *Id.* Of the 926

complaints studied, 37 involved serious cardiovascular events. *Id.* at 15. But the authors of the study explained that their report "must be interpreted as demonstrating only a temporal, *not a causal*, relationship between ma huang (ephedrine) and the adverse cardiovascular events." *Id.* at 13. The authors further explained that "[o]ur report has the limitation of being an observational study and as such does not definitively establish the relationship between ma huang use and the risk of adverse cardiovascular events." But this shows again O'Donnell's lack of scientific rigor in that he draws unauthorized conclusions from limited data — conclusions the authors of the study do not make.

D. Reliance on FDA Reports and Recommendations

O'Donnell also placed great weight on a Food & Drug Administration (FDA) proposal to severely restrict the sale and distribution of herbal supplements containing ephedrine. But the FDA did not publish those rules because the General Accounting Office (GAO) reviewed the FDA data and found a need for further study.

The GAO determined that the FDA's methodology relied heavily on adverse incident reports without sufficient scientific controls. In other words, the FDA employed a flawed methodology to reach its proposal to restrict ephedrine in herbal

supplements. In response to this criticism, the FDA withdrew the proposed rules.

But O'Donnell's use of FDA data and recommendations raises a more subtle methodological issue in a toxic tort case. The issue involves identifying and contrasting the type of risk assessment that a government agency follows for establishing public health guidelines versus an expert analysis of toxicity and causation in a toxic tort case.

> The *Reference Manual on Scientific Evidence* explains that
>
> > [p]roof of risk and proof of causation entail somewhat different questions because risk assessment frequently calls for a cost-benefit analysis. The agency assessing risk may decide to bar a substance or product if the potential benefits are outweighed by the possibility of risks that are largely unquantifiable because of presently unknown contingencies. Consequently, risk assessors may pay heed to any evidence that points to a need for caution, rather than assess the likelihood that a causal relationship in a specific case is more likely than not.

Margaret A. Berger*, The Supreme Court's Trilogy on the Admissibility of Expert Testimony*, *in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, 33 (Federal Judicial Center, 2d. ed. 2000). Obviously, in a toxic tort case the court must focus on assessing causation, not on a cost-benefit analysis for restricting the sale and use of a drug.

As Dr. Eaton explains:

> [i]t is important to recognize that the procedures commonly used in "risk assessment" for the purpose of establishing public health guidelines that represent "acceptable" exposure levels for large populations are often, in this author's opinion, of marginal relevance to estimating "causation" in an individual — e.g., whether a particular chemical caused or contributed to a particular disease or illness in a given person. Although toxicological data — and the basic principles of toxicology outlined above — are useful for both (establishing guidelines for protection of public health and establishing "causation"), there are substantial differences in approach.

Eaton, *supra*, at 34.

He then gives a helpful explanation of this difference. "Public health guidelines, however, should not be interpreted as predicting exact levels at which effects would occur in a given individual." *Id.*

> Because a number of protective, often "worst-case" assumptions . . . are made in estimating allowable exposures for large populations, these criteria and the resulting regulatory levels . . . generally overestimate potential toxicity levels for nearly all individuals. Furthermore, because these guidelines are intended to be protective of all individuals in a population, including the very young, the very old, and other potentially "sensitive" individuals, the theoretical risks from exposure at the guideline range level is likely to be substantially over-estimated for the large majority of individuals in the population.

Id. at 34-35.

Understanding how government agencies establish rules for public health is important in this case for two reasons. First, in trying to determine the reliability

of an expert's opinions based on agency rules, it is important to know both what the agency intended by setting the guidelines and how the expert uses the guidelines to support his opinions. The court is not rejecting public health rules from consideration in a *Daubert* analysis. Rather, in ruling on methodology issues, the trial court should understand what the rule really means about causation for the specific plaintiff, not simply about protecting the public-at-large from risk of harm based on a risk-utility analysis of the drug.

As this court explained in *Rider*:

> [the] risk-utility analysis involves a much lower standard than that which is demanded by a court of law. A 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.

295 F.3d at 1201.

The Court of Appeals for the Eighth Circuit further explained the difference between a public agency approach and a courtroom causation approach in a case involving Parlodel.

> The FDA's approach differs from ours in another critical aspect. The FDA will remove drugs from the marketplace upon a lesser showing of harm to the public than the preponderance-of-the-evidence or the more-like-than-not standard used to assess tort liability. "The methodology employed by a government agency 'results from the preventive perspective that the agencies adopt in order to reduce

> public exposure to harmful substances. . . .'" The FDA's 1994 decision that Parlodel can cause strokes is unreliable proof of medical causation in the present case because the FDA employs a reduced standard (vis-a-vis tort liability) for gauging causation when it decides to rescind drug approval.

Glastetter, 252 F.3d at 991 (internal cites omitted).

Consideration of the risk-utility or the cost-benefit approach versus the expert-causation approach is important in this case for a second reason. O'Donnell testified at the *Daubert* hearing in a way more adjusted to agency-risk analysis than courtroom-causation analysis. For example, he said: "[s]o the issue of risk benefit is, what is the benefit? If there is no proven benefit, it's all risk. So the risk benefit analysis is lopsided on the risk side." Also, when asked about how much Metabolife is too much, he said: "I don't have a number. I've said I think it's unreasonable to combine caffeine because it adds to the toxicity. I don't see a beneficial effect in using this in the population." This implies a risk-benefit analysis, which does not directly focus on the question of causation in these four Plaintiffs — the heart of this toxic tort case.

E. Reliance on Anecdotal Consumer Complaints

The FDA's adverse events reports (AERs) and other consumer complaints also provided another important source for O'Donnell's opinions. But these FDA reports reflect complaints called in by product consumers without any medical

controls or scientific assessment. Under the adverse events reporting system, consumers call in to describe medical problems that they think they are experiencing from taking a product. These complaints provide the basis for the AERs. O'Donnell also considered the same type of complaints called into the "Metabolife health-line." Yet, both O'Donnell and Hakim testified that such anecdotal reports do not prove causation.

Uncontrolled anecdotal information offers one of the least reliable sources to justify opinions about both general and individual causation. The GAO found that the FDA's heavy reliance on the AERs without sufficient scientific controls undermined the FDA's analysis, yet O'Donnell relies on them in a significant way. This again implies that O'Donnell follows more of a federal agency risk analysis approach, rather than a courtroom causation analysis. It also shows that he relied on data that lacks the indicia of scientific reliability.

F. O'Donnell's Methodology Ultimately Fails to Satisfy the Requirements of the *Daubert* Rubric or to Otherwise Comport with the Basic Methodology which should be Utilized by Experts in Toxic Tort Cases

While we have addressed certain types of unreliable evidence used by O'Donnell in reaching his opinions in this case, we find it necessary to also note that O'Donnell's methodology would have failed to survive the *Daubert* inquiry

using those guidelines set forth in *Daubert* itself. The Supreme Court in *Daubert* identified four nonexclusive factors for trial courts to use in determining the reliability of scientific opinions; i.e: (1) whether the theory can and has been tested; (2) whether it has been subjected to peer review; (3) the known or expected rate of error; and (4) whether the theory and methodology employed is generally accepted in the relevant scientific community. *Daubert*, 509 U.S. at 593-94.

There is no doubt that O'Donnell's theory of the toxicity of the ephedrine/ caffeine combination can be tested, as can most theories; but, he has offered no evidence of any testing of his theory, and therefore, he has shown no proof for support of his opinions by the scientific community. General acceptance of his theory would offer important support for the reliability of his opinion. As the United States Supreme Court has explained:

> Finally, "general acceptance" can yet have a bearing on the inquiry. A "reliability assessment does not require, although it does permit, explicit identification of a relevant scientific community and an express determination of a particular degree of acceptance within that community . . . ." Widespread acceptance can be an important factor in ruling particular evidence admissible, and "a known technique which has been able to attract only minimal support within the community" . . . may properly be viewed with skepticism.

Id. at 594 (internal citations omitted).

O'Donnell has also failed to present evidence of any peer review of his opinions about the extreme toxicity of ephedrine and caffeine or that their use can cause strokes and heart attacks. He submitted no publication linking ephedrine and caffeine to strokes and heart attacks beyond the general incident rate or background risk for these two very common ailments. He likewise failed to offer any testimony about the known or expected rate of error of his theories, and although he has provided unsupported testimony about the general acceptance within the relevant scientific community of his "broad principles of pharmacology," he has offered no testimony about the acceptance of his specific opinions. In fact, his own sources say that their studies cannot be used to show causation.

It is also important to consider what other evidence O'Donnell failed to present that might have supported the reliability of his opinions in this case. He offered no epidemiological data. He offered no clinical trials. He offered no animal studies to support his opinions. O'Donnell also offered no long-term studies about the toxicity of the ephedrine/caffeine combination on humans. As even O'Donnell explained: "[l]ong term studies are used for chronic use to determine safety;" still, he offered opinions about the safety of Metabolife in absence of such long-term studies.

Ultimately, O'Donnell failed to show the trial court either that his opinions were based upon reliable sources and data or that his methodology comported with that criteria listed in *Daubert* or with those standards otherwise utilized by experts in the field of toxicology. It was therefore error to admit his testimony to establish general causation at trial.

IV. Hashim Hakim, M.D.

Dr. Hakim is a medical doctor specializing in the practice of neurology; he is a clinician and not a medical researcher. He treated Plaintiff Thornburg and then saw the other three Plaintiffs on referral from Plaintiffs' counsel. He offered opinions at the *Daubert* hearing about the general toxicity of Metabolife and about its effects on the individual Plaintiffs, including that Metabolife caused ischemic strokes in three Plaintiffs and a heart attack in the other.

Hakim followed a methodology similar to O'Donnell's in determining the general toxicity of Metabolife. He relied in significant part on ephedrine's classification as a sympathomimetic, the PPA analogy, the Haller and Benowitz study, and the Hemorrhagic Stroke Project. To the degree to which Hakim and O'Donnell shared the same methodology about the general toxicity of Metabolife, their opinions share the same fate. Their opinions lack sufficient reliability to satisfy *Daubert*. Furthermore, like O'Donnell, Hakim failed to offer the type of

evidence that could support his methodology, so his opinions are subject to the same conclusions that the court made about O'Donnell's opinions. The only question then about Hakim's testimony is whether the additional bases for his opinions, which O'Donnell's did not have, can overcome the defects in the methods they shared. The answer is no.

A. The Differential Diagnosis Method

Hakim used the "differential diagnosis" approach to rule out all causes for Plaintiffs' injuries, except Metabolife 356. Under certain circumstances, circumstances that ensure reliability, this approach may offer an important component of a valid methodology. This approach, however, will not usually overcome the fundamental failure of laying a scientific groundwork for the general toxicity of the drug and that it can cause the harm a plaintiff suffered.

Differential diagnosis involves "the determination of which one of two or more diseases or conditions a patient is suffering from, by systematically comparing and contrasting their clinical findings." *DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 240,* (Douglas M. Anderson et al. ed., 29th ed. 2000). This leads to the diagnosis of the patient's condition, not necessarily the cause of that condition. The more precise but rarely used term is differential etiology, which is "a term used on occasion by expert witnesses or courts to describe the

investigation and reasoning that leads to the determination of external causation, sometimes more specifically described by the witness or court as a process of identifying external causes by a process of elimination." *See* Mary Sue Henifin et al., *Reference Guide on Medical Testimony, in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 439, 481 (Federal Judicial Center, 2d ed. 2000). The etiology of a disease is the cause or origin of the disease, and in this case Plaintiffs allege that Metabolife is the etiology of their medical problems.[9]

To support this theory, Hakim testified that he employed the differential diagnosis method. He took medical histories from Plaintiffs, examined them, and did some tests. After taking these steps, he concluded that he could rule out all the usual causes for Plaintiffs' injuries and therefore inferred that Metabolife caused the injuries. He assumed that Metabolife could cause these injuries using the same evidence offered by O'Donnell, the deficiencies of which the court has demonstrated at length.

A valid differential diagnosis, however, only satisfies a *Daubert* analysis if the

[9]Hakim's differential diagnosis primarily involved determining the etiology of Plaintiffs' diseases rather than the diagnoses of three ischemic strokes and a heart attack. Although defendants often dispute the injuries that plaintiffs allege in toxic tort cases, Defendant does not dispute the nature of Plaintiffs' injuries, only that Metabolife caused the injuries.

expert can show the general toxicity of the drug by reliable methods. As the Court of Appeals for the Ninth Circuit explained:

> The first step in the diagnostic process is to compile a comprehensive list of hypotheses that might explain the set of salient clinical findings under consideration . . . . The issue at this point in the process is which of the competing causes are *generally* capable of causing the patient's symptoms or mortality. Expert testimony that rules in a potential cause that is *not* so capable is unreliable . . . ." It is important to realize that a fundamental assumption underlying [differential diagnosis] is that the final, suspected 'cause' . . . must actually be capable of causing the injury.

Clausen v. M/V New Carissa, 339 F.3d 1049, 1057-58 (9th Cir. 2003) (internal citations omitted). Thus, an expert does not establish the reliability of his techniques or the validity of his conclusions simply by claiming that he performed a differential diagnosis on a patient. As the Court of Appeals for the Fifth Circuit has explained:

> No one doubts the utility of medical histories in general or the process by which doctors rule out some known causes of disease in order to finalize a diagnosis. But such general rules must . . . be applied fact-specifically in each case. <u>The underlying predicates of any cause-and-effect medical testimony are that medical science understands the physiological process by which a particular disease or syndrome develops and knows what factors cause the process to occur</u>. Based on such predicate knowledge, it may then be possible to fasten legal liability for a person's disease or injury.

Black v. Food Lion, Inc., 171 F.3d 308, 314 (5th Cir. 1999) (emphasis added).

Here, neither O'Donnell nor Hakim have offered a reliable explanation of the physiological process by which Metabolife causes heart attacks and ischemic strokes, i.e., establish general causation. Their PPA analogy does not show it. The medical articles do not explain it. In the absence of such a foundation for a differential diagnosis analysis, a differential diagnosis generally may not serve as a reliable basis for an expert opinion on causation in a toxic tort case.

B. Reliance on Anecdotal Case Reports

In defending his methodology, Hakim also testified about case reports that he found in the medical literature. The case studies involve reports by doctors about patients whom the doctor suspects suffered a serious adverse reaction to ephedrine. These reports are anecdotal, meaning that they are "based on descriptions of unmatched individual cases rather than on controlled studies." DORLAND'S, *supra*, at 76. Because they are anecdotal, "case studies lack controls and thus do not provide as much information as controlled epidemiological studies do . . . . Causal attribution based on case studies must be regarded with caution." Henifin*, supra,* at 475.

We in fact discussed the value of case reports in *Rider*, explaining that:

> Much of the plaintiffs' expert testimony relied on case reports in which patients suffered injuries subsequent to the ingestion of Parlodel. Although the court may rely on anecdotal evidence such as

> case reports, . . . courts must consider that case reports are merely accounts of medical events. They reflect only reported data, not scientific methodology. . . . Some case reports do contain details of the treatment and differential diagnosis. Even these more detailed case reports, however, are not reliable enough, by themselves, to demonstrate the causal link the plaintiffs assert that they do because they report symptoms observed in a single patient in an uncontrolled context. They may rule out other potential causes of the effect, but they do not rule out the possibility that the effect manifested in the reported patient's case is simply idiosyncratic or the result of unknown confounding factors. As such, while they may support other proof of causation, case reports alone ordinarily cannot prove causation.

295 F.3d at 1199 (internal citations omitted). Simply stated, case reports raise questions; they do not answer them.

This analysis of the value and limitations of case reports is important in this case for two reasons. First, it explains something about Hakim's differential diagnosis method. If he had taken his findings and opinions about these four Plaintiffs and submitted them to a medical journal for publication, they would simply be case reports — anecdotal information, nothing more. Second, in light of all the other failures of proof on the reliability of their methods, Plaintiffs' experts cannot now redeem their opinions with this type of anecdotal evidence. They do not offer the underlying toxicological data in a scientifically reliable form to satisfy *Daubert*. Anecdotal evidence will not cure that failure.

C. Challenge/De-challenge/Re-challenge Methodology

Finally, in reaching his opinions that Metabolife 356 in fact caused each of the Plaintiff's injuries, Hakim claims to have used a "challenge/de-challenge/re-challenge" methodology. To explain this methodology during the *Daubert* hearing, Hakim testified that while treating Plaintiff Thornburg he noticed a pattern. When she took Metabolife 356, she had strokes, but when she did not take it, she did not have strokes until she started it again. In essence, the stroke occurred during the challenge stage when she took the drug. The de-challenge occurred when she came off the drug and did not have a stroke, and the re-challenge occurred when she started taking the drug again and had another ischemic event. But this theory has a serious flaw.

In April of 2000, Hakim decided that Metabolife had caused Thornburg's strokes and told her to stop taking it. In June of 2000, after being off Metabolife for two months, she had another ischemic event. In other words, according to his challenge/de-challenge/re-challenge theory, she had another ischemic event during the de-challenge phase. During the hearing, Hakim attempted to explain away that inconsistency by saying that the ischemic event during the de-challenge phase occurred because of the lingering effects of ephedrine. To bolster this opinion he resorted to another medical analogy — the analogy of alcohol causing liver

damage. Nothing in the evidence, however, supports the dubious analogy that the ephedrine causes strokes and heart attacks like alcohol causes cirrhosis of the liver.

Furthermore, "[t]he temporal connection between exposure to chemicals and an onset of symptoms, standing alone, is entitled to little weight in determining causation." *Moore*, 151 F.3d at 278. It is also subject to the problem of assuming what the witness is trying to prove. This pitfall will most likely arise when, as here, there are not scientific controls in place.

As this court explained in *Rider*, "de-challenge/re-challenge tests are still case reports and do not purport to offer definitive conclusions as to causation." 295 F.3d at 1200. Their value is directly related to the degree of scientific control used in the testing. Because there were insufficient controls employed in Hakim's crude challenge/de-challenge/re-challenge methodology, and Hakim's own testimony established that Thornburg suffered ischemic events when she was not taking Metabolife 356, this methodology does not provide the necessary indicia of reliability to his final opinions on causation.

D. Hakim's Overall Methodology

Again, like O'Donnell, Hakim failed to offer the type of evidence that could support the methodology he employed in reaching his opinions. Even considering the three additional methodologies he used, we must conclude that Hakim failed to rely upon reliable sources and data and that his overall methodology falls short of those standards otherwise utilized by experts testifying as to causation in a toxic tort case. It was therefore error to admit his testimony to establish general or individual causation at trial.

V. Conclusion

At the outset, we noted that the primary purpose of any *Daubert* inquiry is for the district court to determine whether that expert, "whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho*, 526 U.S. at 152. As shown in this case, however, neither O'Donnell nor Hakim utilized a reliable methodology to prove that use of Metabolife 356 actually causes strokes or heart attacks, either generally or in these Plaintiffs. The medical literature does not support such opinions. Plaintiffs' experts took leaps of faith and substituted their own *ipse dixit* for scientific proof on essential points. Here, "there is simply too great an analytical gap between the data and the opinion proffered." *See Joiner*, 522 U.S. at 146.

Thus, in the end, we must find that there was no basis for the court below to conclude that Plaintiffs' experts employed the same level of intellectual rigor that characterizes the practice of an expert testifying about causation in a toxic tort case. Plaintiffs' expert testimony did not satisfy the foundational requirements of Rule 702, because their opinions were not based on sufficient data and were not the product of reliable methods. Because they did not establish the requisite scientific reliability *Daubert* demands, the trial court abused its discretion both by abdicating its gatekeeper responsibilities and by admitting the expert testimony at trial. We reverse.

REVERSED and REMANDED.