

**UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA**

In re: LEVAQUIN PRODUCTS
LIABILITY LITIGATION

MDL No. 08-1943 (JRT)

**ORDER DENYING DEFENDANTS'
MOTIONS TO EXCLUDE
EXPERT WITNESSES**

This Document Relates to All Actions

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This multidistrict litigation (“MDL”) is before the Court on defendants’ motions to exclude the expert testimony of Drs. Thomas M. Zizic and Martyn T. Smith, under Federal Rule of Evidence 702. For the reasons set forth below, the Court denies the motions.

BACKGROUND

This multidistrict litigation consists of a significant number of cases involving the drug Levaquin. Levaquin is an antibiotic developed, manufactured, and marketed by

defendants Johnson & Johnson, Ortho-McNeil Pharmaceutical, Inc., and Johnson & Johnson Pharmaceutical Research and Development, LLC. The plaintiffs were all prescribed Levaquin, and alleged that it causes tendons to rupture.

ANALYSIS

I. STANDARD OF REVIEW

Rule 702 of the Federal Rules of Evidence governs the admissibility of expert testimony. Under Rule 702, proposed expert testimony is admissible if three prerequisites are met. *Lauzon v. Senco Prod., Inc.*, 270 F.3d 681, 686 (8th Cir. 2001). First, evidence based on scientific, technical, or specialized knowledge must be useful to the finder of fact in deciding the ultimate issue of fact. *Id.* Second, the proposed witness must be qualified. *Id.* Third the proposed evidence must be reliable in an evidentiary sense, so that if the finder of fact accepts it as true, it provides the assistance the finder of fact requires. *Id.*

With regard to the third prong, Rule 702 prescribes that evidence is reliable or trustworthy 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. The district court has a “gatekeeping” obligation to make certain all testimony admitted under Rule 702 satisfies these prerequisites. *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 597-98 (1993). The proponent of expert testimony has the burden to show by a preponderance of the evidence that expert testimony is admissible under Rule 702.

Lauzon, 270 F.3d at 686; *see also Daubert*, 509 U.S. at 592. However, “[t]he rule clearly is one of admissibility rather than exclusion.” *Lauzon*, 270 F.3d at 686 (internal quotation marks omitted). Expert testimony is admissible if it “rests on a reliable foundation and is relevant to the task at hand.” *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 141 (1999).

II. DEFENDANTS’ MOTIONS TO EXCLUDE THE EXPERT TESTIMONY

A. Experts

1. Dr. Thomas M. Zizic

Dr. Zizic (“Zizic”) is an Associate Professor of Medicine at Johns Hopkins University. He received his medical degree from the Johns Hopkins University School of Medicine in 1965. For the past twenty years, he has served on the Johns Hopkins Medical School faculty-part time and has maintained a private practice in rheumatology. He has published numerous articles and abstracts in peer-reviewed journals as well as several dozen chapters in textbooks of medicine.

Zizic’s opinions in this case are based on a review of peer-reviewed scientific and medical literature, clinical records, and documents specific to this litigation. His testimony is offered to support plaintiffs’ theory that Levaquin causes tendon disorders in human adults and poses a higher risk for tendon disorders compared to other fluoroquinolones, due to its higher tendo-toxic properties.

Defendants made no objections to Zizic’s qualifications as an expert. Defendants moved to exclude any testimony extrapolating an opinion as to the relative tendon

toxicity of levofloxacin and other fluoroquinolones in adult human tendons from animal studies, on the basis that Zizic's methodology is unreliable.

2. Dr. Martyn T. Smith

Dr. Smith ("Smith") is a Professor of Toxicology in the Division of Environmental Health Sciences, School of Public Health, University of California at Berkeley, a position he has held since 1992. Smith received his Bachelor of Science Degree in Biology from Queen Elizabeth College, University of London in 1977, and his Ph.D. in Biochemistry from the Medical College of St. Bartholomew's Hospital, London, England in 1980. Since 1979, he has authored or co-authored over 220 articles in peer-reviewed journals in the field of toxicology, thirty-seven book chapters, and over 200 abstracts, as well as technical reports for the United States Environmental Protection Agency and the California Environmental Protection Agency. Smith's opinions in this case are based on a review of peer-reviewed literature, materials publicly available and provided by the Food and Drug Administration, and confidential materials made available to him through counsel.

Smith's report and testimony are offered to compare and contrast the toxic effects of levofloxacin and ofloxacin. Specifically, Smith was asked to examine "what is known about the toxicity of the antibiotic fluoroquinolone drugs Levaquin and Floxin and to contrast and compare their toxic effects." (Expert Report of Martyn T. Smith ("Smith Rep.") ¶ 7, Aff. of Tracy J. Van Steenburgh in Supp. of Defs.' Mot. to Ex. the Expert Test. of Martyn T. Smith ("Steenburgh Smith Aff.") Ex. B, Docket No. 1669.)

Defendants made no objections to Smith's qualifications as an expert. Defendants moved to exclude Smith's testimony on the same grounds as Zizic's testimony.

B. Reliability of Animal Studies to Determine Causation in Humans

Defendants challenge the reliability of animal studies to determine effects in humans. In evaluating the issue of extrapolation by experts, the Supreme Court has said:

Trained experts commonly extrapolate from existing data. But 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. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.

Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997) (finding that the district court did not abuse its discretion when it determined that animal studies involving infant mice injected with massive doses of PCB were so dissimilar to the plaintiff's situation they were unreliable as a basis for expert's opinion as to causation).

In evaluating extrapolation from animal studies to humans, courts have said:

[I]n order for animal studies to be admissible to prove causation in humans, there must be good grounds to extrapolate from animals to humans, just as the methodology of the studies must constitute good grounds to reach conclusions about the animals themselves. Thus, the requirement of reliability, or 'good grounds,' extends to each step in an expert's analysis all the way through the step that connects the work of the expert of the particular case.

In re Paoli R.R. Yard PCB Litig., 35 F.3d 717, 743 (3d Cir. 1994) (finding that the district court abused its discretion when it excluded animal studies which were not contradicted by relevant epidemiological evidence, and opining that courts exclude animal studies when they are contradicted by conclusive epidemiological data); *see also Cavallo v. Star*

Enter., 892 F. Supp. 756, 762 (E.D. Va. 1995) *aff'd in part, rev'd in part on other grounds*, 100 F.3d 1150 (4th Cir. 1996) (holding that to ensure that the expert's conclusion based on animal studies is reliable, there must be a "scientifically valid link" – such as supporting human data – "between the sources or studies consulted and the conclusion reached.").

Defendants argue that "[a]nimal studies do not provide a sufficient foundation for opinions regarding causation in humans except where there is evidence providing a reliable scientific foundation supporting extrapolation of the results of such animal studies to humans." (Def's. Mot. to Ex. Smith at 2, Docket No. 1668.)

There is no single rule on the inherent reliability of animal studies in expert testimony for litigation. When courts exclude such opinions, it is often because the comparison between the animals and humans is too attenuated, or because of methodological problems with the studies themselves, such as a failure to compare with epidemiological data. *See Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 547 (W.D. Pa. 2003) (finding that plaintiff's experts failed to take into account critical differences between animal data and human experience – including but not limited to extrapolations in dosing, thus rendering their methodology scientifically invalid and unreliable); *Wade-Greaux v. Whitehall Lab., Inc.*, 874 F. Supp. 1441, 1477 (D. V.I. 1994) (rejecting plaintiff's expert's methodologies which relied on extrapolation from animal studies without also offering conclusive epidemiological data); *Allen v. Penn. Eng'g Corp.*, 102 F.3d 194, 195 (5th Cir. 1996) ("Where . . . no epidemiological study has found a statistically-significant link [in human studies]; the results of animal studies are

inconclusive at best.”); *Renaud v. Martin Marietta Corp., Inc.*, 972 F.2d 304, 307 (10th Cir. 1992) (“The etiological evidence proffered by the plaintiff was not sufficiently reliable, being drawn from tests on non-human subjects without confirmatory epidemiological data.” (footnotes omitted)).

When courts allow expert testimony premised on animal studies, it is because human studies cannot be done for ethical reasons, or there is a reasonable basis to believe that the results from the animal studies can be reliably extrapolated to humans. *See e.g., In re Paoli R.R. Yard PCB Litig.*, 35 F.3d at 743. Though courts should be cautious in presuming that findings derived from animal studies are applicable to humans, the applicability of animal studies is often appropriately explored during cross-examination. *See Gen. Elec. Co.*, 522 U.S. at 144-45; *In re Viagra Prods. Liab. Litig.*, 572 F. Supp. 2d 1071, 1089 (D. Minn. 2008) (refusing to exclude an expert’s testimony on the grounds that he refuted a causal connection based on visual symptoms in human clinical trials with animal studies, and reasoning that gaps in an expert’s knowledge generally go to the weight, not the admissibility of the witness’ testimony.).

Here, defendants have not argued that any study relied on by Zizic or Smith is flawed. Further, both Zizic and Smith have used the animal study data only **in conjunction** with epidemiological data. Therefore, as noted more fully in this Order, the Court finds that the conclusions Zizic and Smith draw from the use of animal studies are reliable data on which to base an opinion in this case.

C. Opinions Regarding Levofloxacin's Comparative Tendon Toxicity

Defendants argue that Zizic's testimony should be excluded because his opinions are not supported by any **human clinical** studies specifically involving levofloxacin. Defendants point to a number of studies Zizic relied on to form his opinion, arguing that some studies were only conducted on animals, thus it was improper to draw conclusions from them. Defendants' also state "**Zizic never supplements his reliance on animal studies with any 'human studies all pointing in the same direction' regarding levofloxacin.**" (Defs.' Mot. to Ex. Zizic at 7, Docket No. 1672 (emphasis added).) Defendants also criticize Zizic's reference in his rebuttal report to the "guiding principles" of the Committee on the Framework for Evaluating the Safety of Dietary Supplements.

Plaintiffs' respond that Zizic only used a small number of animal studies to arrive at his conclusions, and directs the Court's attention to the multiple human-based studies Zizic relied on. For example:

- In one series of 100 [human] cases . . . of fluoroquinolone disorders, the Achilles tendon was involved in 96 cases with almost half of these cases having bilateral involvement. (Expert Report of Thomas M. Zizic, M.D. ("Zizic Rep.") § E ¶ 5, Aff. of Tracy J. Van Steenburgh in Supp. of Defs.' Mot. to Ex. the Expert Test. of Zizic ("Steenburgh Zizic Aff.") Ex. A, Docket No. 1673.)
- Another study by Meissner et al (Concentrations of ofloxacin in human bone and cartilage, *Journal of Antimicrobial Chemotherapy*, 26:69-74, 1990) reported that the half-life of ofloxacin was longer in synovial tissues than in serum. Meissner also shows that ofloxacin . . . and levofloxacin diffuse more easily in tissues than does ciprofloxacin, a fact that contributes to the differences in tendon toxicity seen in clinical practice. (*Id.* § H ¶ 5.)

- In a retrospective study by Wilton *et al.* (Wilton *et al.*, British Journal of Clinical Pharmacology, 41:277-284, 1996), they compared over **11,000 patients in each group, treated with ciprofloxacin . . . [and] ofloxacin** during the early post-marketing period. (*Id.* § K ¶ 7 (emphasis added).)
- According to the British Medicines Control Agency assessment report of levofloxacin, in April, 2002, the key issue [was whether] there is a greater toxic effect on tendons with levofloxacin than with other fluoroquinolones. **This assessment critically analyzed two retrospective, cohort studies using CPRD data from the UK and the German Mediplus Data . . .** The British assessor wrote that “the studies have been well designed, and whilst they have limitations . . . they undoubtedly represent the best evidence available at the present time.” **The two studies have similar findings and taken together, suggest that levofloxacin produces tendinopathy about twice as frequently as ciprofloxacin . . . Thus there are two epidemiological studies with similar findings supporting a signal generated by spontaneous reporting with respect to an increased risk of tendinopathy with levofloxacin compared to other fluoroquinolones.** (*Id.* § K ¶ 15 (emphasis added).)
- The British Medical Control Agency [“MCA”] issued the following regulatory options and recommendations: “The current evidence . . . suggests a possible **doubling of relative risk for levofloxacin, relative to ciprofloxacin.**” (*Id.* (emphasis added).)
- **Levofloxacin was associated with the highest rate ratio [of tendinopathy] a finding which was statistically significant . . .** The study findings indicate almost two-fold greater risk of tendinopathy with levofloxacin than for ciprofloxacin (*Id.* § K ¶ 16 (emphasis added).)

Defendants suggest that the Court ignore the above citations and exclude Zizic’s testimony because he has not cited to (nor is there any) **human clinical** study indicating the comparative tendon toxicity of levofloxacin with other fluoroquinolones. Aside from the fact that numerous studies Zizic cites expressly evaluated the toxicity of various

fluoroquinolones in humans, Zizic also noted that conducting a direct, head-to-head survey would be unethical. The Court finds that Zizic's methods for reaching his conclusions were valid even though they involved some inferences drawn from animal studies.

Defendants also argue that Smith's opinion is not supported by any human clinical studies regarding levofloxacin's comparative tendon toxicity in human adults, but is dependent on animal studies. Specifically, defendants object that Smith's opinions "regarding the purported higher comparative tendon toxicity [between levofloxacin and other fluoroquinolones] is not supported by any human clinical studies specifically involving levofloxacin." (Defs.' Mot. to Ex. Smith at 1.) Defendants cite several articles used by Smith in his opinion, each of which used animals for toxicity experimentation.

Plaintiffs overall response is that defendants have addressed the wrong issue: "Dr. Smith's role in this litigation is to compare and contrast the toxicological profiles of Levaquin (levofloxacin) . . . to that of Floxin (ofloxacin) . . . Defendants' argument is addressed to proof of causation, testimony about which Dr. Smith has neither offered nor intends to offer." (Pls.' Resp. to Smith at 2, Docket No. 1945.) Specifically, plaintiffs argue that Smith's conclusions are admissible because they are based on sufficient and reliable data, are the product of reliable principles and methods which have been reliably applied to the facts of the case, and Smith is not opining on causation.

Smith's report discusses how levofloxacin and ofloxacin are essentially identical for toxicological purposes. (Smith Rep. § II ¶ 11) ("The similar pharmacokinetics, toxicology profile, and mechanism of action of levofloxacin and ofloxacin indicate that

they can be considered one and the same for toxicological purposes and that the epidemiological observations for ofloxacin are pertinent to levofloxacin as well.”). His comparison relies on “the available human, animal, and cell culture toxicology studies.” (Smith Rep. § XI ¶ 45.)

Next, Smith notes that “the most common side effects associated with fluoroquinolone antibacterial agents include . . . problems affecting connective tissue structure such as the tendons and cartilage.” (Smith Rep. § VI ¶ 18.) Addressing the issues in the case more directly, Smith then opines that “the available case reports, animal, and cell culture toxicology studies . . . show that levofloxacin and ofloxacin are among the most toxic fluoroquinolones to tendons, with levofloxacin being the same or slightly more toxic than ofloxacin.” (*Id.* § VII ¶ 30.) To reach this conclusion Smith relied on studies involving tendinopathy rates in young-adult rats, juvenile rats, rabbit tendon cells, and human case reports. (*Id.* at § VII ¶ 25-29.) The case reports were for humans who had taken levofloxacin. (*Id.*)

Defendants challenge Smith’s methods as far as he used animal studies to draw conclusions, noting that some of his testimony premised on animal studies was excluded in *In re Baycol Prods. Litig.*, 532 F. Supp. 2d 1029, 1065 (D. Minn. 2007). In *Baycol*, however, defendants sought to exclude Smith’s testimony because they believed the **study Smith relied on to be flawed**. *Id.* The issue here is different: in this case defendants challenge the reliability of using animal studies to predict biochemical processes in humans. In *Baycol*, Smith’s testimony was excluded because the underlying

data he relied on “did not provide a scientifically reliable basis for his opinion.” *Id.* A more telling quotation from *Baycol* is the court’s determination that:

[As] an experienced toxicologist . . . [,] Dr. Smith provides a thorough explanation for his opinion[s] . . . and Defendants simply argue that Dr. Smith could point to no peer-reviewed articles that support his theory. Having failed to demonstrate that Dr. Smith’s opinion . . . is so fundamentally unsupported that it can offer no assistance to the jury [the motion to exclude is denied].

Id. at 1066. Similarly, defendants here argue that Smith can point to no studies that directly support his theory as it applies to humans. Smith has extensively documented comparative tendon toxicities between levofloxacin and other fluoroquinolones. Though some of the evidence he relies on came from animal studies, there is no challenge to the studies themselves.

Smith’s testimony is being offered to discuss the comparative toxicity between levofloxacin and other fluoroquinolones on tendons. Though the most relevant research would directly compare levofloxacin to ofloxacin and other fluoroquinolones in humans, it would be unethical to conduct such a study, as noted above. Moreover, defendants’ claim that Smith’s opinion regarding the higher comparative tendon toxicity of levofloxacin has not been supported in human clinical studies misses the point: comparing the relative tendon toxicities does not **need** to be done in humans to demonstrate that one is more toxic than the other. Comparing the various fluoroquinolones is itself a separate step from extrapolating their toxicity to humans. Defendants argue that the comparison is “inextricably intertwined” with the extrapolation to humans. In this, defendants raise a valid point: Smith cites numerous studies suggesting that fluoroquinolones, specifically levo- and ofloxacin, **cause** tendinopathies.

To the extent Smith offers an opinion on this topic, the Court will limit his testimony. However, Smith's opinion is based upon more than sufficient facts and data, and he has applied reliable principles and methodologies logically to the facts of the case to reach conclusions on the relative tendon toxicity of levofloxacin and ofloxacin. *See Fed. R. Evid.* 702.

D. Reliable Scientific Foundation Supporting the Extrapolation of Results from Animal Studies to the Experts' Opinions

Defendants argue that Drs. Smith and Zizic have failed to use reliable methods of extrapolation to reach their conclusions. Specifically, defendants challenge the conclusion of both experts that the data about ofloxacin and levofloxacin is, for toxicological purposes, interchangeable. Defendants point to *In re Prempro Prod. Liab. Litig.*, 2010 WL 3447293, *5 (E.D. Ark. Aug. 30, 2010), for the proposition that “[e]ven minor deviations in molecular structure can radically change a particular substance’s properties and propensities.” From this statement, defendants argue that both Smith and Zizic impermissibly attributed the effects of ofloxacin to levofloxacin.

The *Prempro* court evaluated the chemical composition of substances that were part of a class of hormones, and found that the fact that the expert did not acknowledge the differences between two substances was a defect in her methodology. *In re Prempro*, 2010 WL 3447293 at *5. An Eighth Circuit case found expert testimony inadmissible when the expert sought to demonstrate that “medicinal substances” that were part of a class behaved the same as others in its class. *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001). The *Glastetter* court said that the **assumption** that one

substance in a class behaves like others “carries little scientific value.” *Id.* Though courts must be sensitive to comparisons of drugs that appear similar but are molecularly different, here, unlike in *Glastetter*, Smith and Zizic rely on a substantial body of evidence demonstrating that ofloxacin and levofloxacin are part of the same class of drugs, have similarly toxic effects, and are themselves more toxic than other fluoroquinolones. (Zizic Rep. § D; Smith Rep. § XI.) They both explicitly state that for toxicological purposes, ofloxacin and levofloxacin can be considered identical, and support their statements with extensive discussions of the chemical composition and properties of the two drugs.

Further, Smith describes the approach he took to compare levofloxacin and ofloxacin as the “weight of the evidence” (“WOE”) methodology. (Rebuttal Report of Martyn T. Smith (“Smith Rebuttal”) § III(a) ¶ 1, Steenburgh Smith Aff. Ex. D, Docket No. 1669.) Smith says “[i]n the absence of human studies a scientist . . . has to make conclusions about relative toxicities and hazards based on the WOE from experimental models . . . In assessing this WOE it is standard practice at FDA and regulatory agencies to use data from experimental animals.” (*Id.* § III(a)(2).) Smith also notes “[t]here are no human studies that directly compare the tendon toxicities of levofloxacin and ofloxacin. It would be . . . perhaps unethical to expose humans to these drugs with the sole purpose of comparing their toxicities.” (*Id.* § III(a) ¶ 11.) Finally, in relation to extrapolating from animal data to humans, Smith notes “[a]s a rule, humans are more susceptible than animals . . . Thus in doing a WOE assessment of the relative toxicities of levofloxacin and ofloxacin I have used data from juvenile animal studies because they are the most

sensitive experimental animal studies that are relevant to human health.” (*Id.* § III(b) ¶ 17.)

Defendants argue that both Smith and Zizic have premised support for their extrapolations on an irrelevant set of guidelines (“guiding principles”) propounded by the “Committee on the Framework for Evaluating the Safety of Dietary Supplements.” A review of the document itself is instructive. Inst. of Med. and Nat’l Research Council of the Nat’l Acads., *Dietary Supplements: A Framework for Evaluating Safety* (2005), http://www.nap.edu/openbook.php?record_id=10882&page=R1. The report states “Frameworks developed for reviewing the safety of other substances (i.e., in foods, in pharmaceuticals . . .) were also considered [in designing the guiding principles].” *Id.* at 43. Further, Appendix A to the guiding principles describes the evaluation process for new pharmaceuticals, and enumerates the principles the committee evaluated relating to new drug safety to inform their analysis for dietary supplements. *Id.* at 312. Though the guiding principles cannot be read as strict rules for appropriate extrapolation of animal studies to effects in humans, the committee’s consideration of the standards used for evaluating new drugs, coupled with the general nature of the provisions cited by Smith and Zizic, do not render their use of the guiding principles inappropriate or unreliable.

This case presents none of the methodological flaws that existed in other drug litigation cited by defendants. The experts here have not “summarily attributed” the effects of one substance to another; they have done so after careful exploration and analysis.

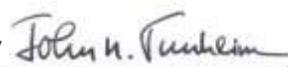
Defendants also argue that Zizic and Smith impermissibly extrapolate conclusions about tendinopathy, from comparisons of damage to cartilage in animals, to damage to tendons in humans. However, the cartilage-based studies comprise only a small portion of the support Zizic and Smith rely on for their opinions. Most of the studies involving humans evaluated tendon injuries. Extrapolation of cartilage injuries in animals, to tendon injuries in humans, would not by itself provide a sufficiently reliable scientific basis on which to base an opinion, nor would be it a sound methodology. However, Zizic and Smith have used many other studies specifically related to tendons, and the Court finds that the combination of all these methods constitutes a reliable methodology sufficient to satisfy the requirements of *Daubert*.

ORDER

Based on the foregoing, and the records, files, and proceedings herein, **IT IS HEREBY ORDERED** that:

1. Defendants' Motion to Exclude the Expert Testimony of Dr. Thomas M. Zizic [Docket No. 1671] is **DENIED**.
2. Defendants' Motion to Exclude the Expert Testimony of Dr. Martyn T. Smith [Docket No. 1667] is **DENIED**.

DATED: November 8, 2010
at Minneapolis, Minnesota.

s/ 

JOHN R. TUNHEIM
United States District Judge