UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF PENNSYLVANIA

IN RE: TYLENOL (ACETAMINOPHEN) MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION	§ § § § § §	**MDL NO. 2436** **2:13-md-02436** **HON. LAWRENCE F. STENGEL**
This Document Relates to: Rana Terry, as Personal Representative and Administrator of the Estate of Denice Hayes, Deceased, Plaintiff, vs. McNEIL-PPC, Inc., McNeil Consumer Healthcare, and Johnson & Johnson, Inc., Defendants.	§ § § § § § § § § § § § § § §	Civil Action No. 2:12-cv-07263

M E M O R A N D U M

Stengel, J. **July 26, 2016**

This case is part of a Multidistrict Litigation (MDL) involving claims of liver damage from the use of Tylenol at or just above the recommended dosage.[1] The first

[1] See Master Compl., 13-md-2436, Doc. No. 32. There are over two hundred other cases included in this MDL, along with several similar cases in New Jersey state court.

"bellwether" case is scheduled for trial.[2] The plaintiff plans to offer Dr. Neil Kaplowitz, M.D. as a general and specific causation expert. Dr. Kaplowitz opines that recommended doses of acetaminophen, the main ingredient in Tylenol, can cause acute liver failure (ALF). He is of the opinion that the decedent, Denice Hayes, died of acetaminophen-induced ALF after taking recommended doses. The defendants move to exclude his testimony under Daubert. For the reasons stated below, I will deny their motion.[3]

I. LEGAL STANDARD

The admissibility of expert testimony is governed by Federal Rules of Evidence 702 and 703 as well as by Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579 (1993), and its progeny.[4] See In re Paoli RR Yard PCB Litigation (Paoli II), 35 F.3d 717, 735 (3d Cir. 1994). "Under the Federal Rules of Evidence, a trial judge acts as a 'gatekeeper' to ensure that 'any and all expert testimony or evidence is not only relevant, but also reliable.'" Pineda v. Ford Motor Co., 520 F.3d 237, 243 (3d Cir. 2008)(quoting Kannankeril v. Terminix Int'l, Inc., 128 F.3d 802, 806 (3d Cir. 1997)). The Third Circuit recognizes a "liberal policy of admissibility" regarding Rule 702. Pineda, 520 F.3d at 243

[2] A "bellwether" case is a test case. "Bellwether" trials should produce representative verdicts and settlements. The parties can use these verdicts and settlements to gauge the strength of the common MDL claims to determine if a global resolution of the MDL is possible. See FEDERAL JUDICIAL CENTER, MANUAL FOR COMPLEX LITIGATION, FOURTH EDITION 360 (2004); DUKE LAW CENTER FOR JUDICIAL STUDIES, MDL STANDARDS AND BEST PRACTICES 16-21 (2014).

[3] In making my decision, I have reviewed all of the materials submitted as attachments to the parties' briefs, including those submitted during oral argument.

[4] Daubert held that the Federal Rules of Evidence, specifically Rule 702, controlled the issue of when experts were qualified. Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 587-88 (1993). It found that Rule 702 superseded the Court's prior precedent on the subject found in Frye v. United States, 54 App.D.C. 46, 47, 293 F. 1013, 1014 (1923). Daubert, 509 U.S. at 587. Daubert went on to clarify what was required under Rule 702, as compared to Frye. See id. at 589-598.

(quoting Kannankeril, 128 F.3d at 806); United States v. Schiff, 602 F.3d 152, 173 (3d Cir. 2010).[5]

"[B]ecause expert evidence is often more misleading than other evidence, Rule 403 gives a judge more power over experts than over lay witnesses." In re Paoli RR Yard PCB Litigation (Paoli II), 35 F.3d 717, 747 (3d Cir. 1994). However, "in order for a district court to exclude scientific evidence, there must be something particularly confusing about the scientific evidence at issue—something other than the general complexity of scientific evidence." Id.

a. Rule 702

Federal Rule of Evidence 702 has three major requirements: 1) the expert must be qualified; 2) the expert must testify about matters requiring scientific, technical, or specialized knowledge; and 3) the testimony must assist the trier of fact.[6] Pineda, 520 F.3d at 243 (citing Kannankeril, 128 F.3d at 806). 702's inquiry should be a "flexible one." Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 594 (1993).

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[5] See also Holbrook v. Lykes Brothers Steamship Company, Inc., 80 F.3d 777, 780 (3d Cir. 1996); Zaprala v. USI Servs. Gp., Inc., No. 09–1238, 2013 WL 1148335, at *6 (E.D. Pa. Mar. 20, 2013)(quoting Pineda, 520 F.3d at 243).

[6] Federal Rule of Evidence 702 states:

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

FED. R. EVID. 702.

i. Expert Must Be Qualified

An expert's qualifications may include education, provided it is in a field related to the one in which the expert intends to testify. Fedor v. Freightliner, Inc., 193 F. Supp. 2d 820, 827 (E.D. Pa. 2002). Overall, the court will consider both academic training and practical experience to determine if the expert has "more knowledge than the average lay person" on the subject. Id. at 827-28 (citing Waldorf v. Shuta, 142 F.3d 601, 627 (3d Cir. 1998)). "An expert may be generally qualified but may lack qualifications to testify outside his area of expertise." Calhoun v. Yamaha Motor Corp., U.S.A., 350 F.3d 316, 322 (3d Cir. 2003).

However, this does not mean that the "best qualified" expert must testify. "[W]itnesses may be competent to testify as experts even though they may not, in the court's eyes, be the 'best' qualified." Holbrook v. Lykes Bros. S.S. Co., Inc., 80 F.3d 777, 782 (3d Cir. 1995).[7] "Rule 702 and Daubert put their faith in an adversary system designed to expose flawed expertise." U.S. v. Mitchell, 365 F.3d 215, 244-45 (3d Cir. 2004)(citations omitted). "As long as an expert's scientific testimony rests upon 'good grounds, based on what is known,' it should be tested by the adversary process—competing expert testimony and active cross–examination—rather than excluded from jurors' scrutiny for fear that they will not grasp its complexities or satisfactorily weigh its inadequacies." Id. at 244 (citations omitted).

[7] See also Keller v. Feasterville Family Health Care, 557 F. Supp. 2d 671, 675 (E.D. Pa. 2008)(Rice, J.).

ii. Expert's Methods Must be Reliable

This Circuit interprets the second factor as one of "reliability," i.e., the testimony is admissible so long as the process or technique the expert used in formulating the opinion is reliable. Pineda, 520 F.3d at 244. An expert's opinion need not be correct, only reliable. See In re Paoli RR Yard PCB Litigation (Paoli II), 35 F.3d 717, 744 (3d Cir. 1994)("This does not mean that plaintiffs have to prove their case twice—they do not have to demonstrate to the judge by a preponderance of the evidence that the assessments of their experts are *correct*, they only have to demonstrate by a preponderance of evidence that their opinions are reliable." (emphasis in original)). "[A]n expert is permitted wide latitude to offer opinions, including those that are not based on firsthand knowledge or observation." Daubert, 509 U.S. at 592. "[I]t is the burden of the party offering the expert scientific testimony to demonstrate reliability by a preponderance of the evidence." In re TMI Litig., 193 F.3d 613, 705 (3d Cir. 1999)(citing Paoli II, 35 F.3d at 744).[8]

"Rule 702 grants the district judge the discretionary authority, reviewable for its abuse, to determine reliability in light of the particular facts and circumstances of the particular case." Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 158 (1999). Judges considering this factor should look to whether a theory, technique, or opinion can be tested or has been subject to peer review or publication. Daubert, 509 U.S. at 593. "The fact of publication (or lack thereof) in a peer reviewed journal thus will be a relevant,

[8] See also FED. R. EVID. 702, Advisory Committee Note (2000 Amendments)("Under that Rule, the proponent has the burden of establishing that the pertinent admissibility requirements are met by a preponderance of the evidence." (citing Bourjaily v. United States, 483 U.S. 171 (1987)).

though not dispositive, consideration in assessing the scientific validity of a particular technique or methodology on which an opinion is premised." Id. at 594. A court should also consider the known or potential rate of error involved in a scientific method. Id. "Reliability" does not require that a technique or methodology be generally accepted by a scientific community. Id. See also id. at 597-98. However, "[w]idespread acceptance can be an important factor in ruling particular evidence admissible" while a minimally supported technique "may properly be viewed with skepticism." Id.

iii. Expert Must be Helpful

The third factor "is typically understood in terms of whether there is a sufficient 'fit' between the expert's testimony and the facts that the jury is being asked to consider." United States v. Schiff, 602 F.3d 152, 172-73 (3d Cir. 2010)(citing Daubert, 509 U.S. at 591). See also In re: TMI Litigation, 193 F.3d 613, 670 (3d Cir. 1999). This factor is about relevance. "Expert testimony which does not relate to any issue in the case is not relevant and, ergo, non-helpful." Daubert, 509 U.S. at 591 (quoting 3 Weinstein & Berger ¶ 702[02], p. 702–18). "Rule 702's 'helpfulness' standard requires a valid scientific connection to the pertinent inquiry as a precondition to admissibility." Id. at 591-92.

b. Rule 703

Under Federal Rule of Evidence 703, the data underlying the expert's opinion is the central focus. Rule 703 states:

> An expert may base an opinion on facts or data in the case that the expert has been made aware of or personally observed. If experts in the particular field would reasonably rely on those kinds of facts or data in forming an opinion on the subject, they need not be admissible for the opinion to be admitted. But if the facts or data would otherwise be inadmissible, the

> proponent of the opinion may disclose them to the jury only if their probative value in helping the jury evaluate the opinion substantially outweighs their prejudicial effect.

FED. R. EVID. 703. The trial court must evaluate whether the data used by an expert is reasonably relied upon by experts in the field. See In re Paoli RR Yard PCB Litigation (Paoli II), 35 F.3d 717, 747-49 (3d Cir. 1994).

II. Dr. Kaplowitz is a Leading Expert in Drug-Induced Liver Injury (DILI)[9]

Neil Kaplowitz, M.D. is a gastroenterologist and hepatologist, specializing in drug-induced liver diseases. He is a Professor of Medicine at the Keck University of Southern California (USC) School of Medicine and Chief of the USC School of Medicine Division of Gastrointestinal and Liver Diseases, positions that he has held since 1990. Since 1993, he has also been a Professor of Physiology. He is Director of USC Medical School's Liver Diseases Research Center, which is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Since 2006, he has been a Professor of Pharmacology and Pharmaceutical Sciences in USC's School of Pharmacy.

Dr. Kaplowitz is a former president for the American Association for the Study of Liver Diseases (AASLD), the leading organization of scientists and healthcare professionals committed to studying, preventing, and curing liver diseases in the United

[9] Though the defendants do not challenge Dr. Kaplowitz's qualifications, an overview of his credentials is helpful to understanding their challenge to his methodology. Information about Dr. Kaplowitz's credentials can be found in his Curriculum Vitae (Doc. No. 154, Ex. 2) and his expert report (Doc. No. 154, Ex. 15) unless noted otherwise.

States.[10] He has received several federal grants from the National Institutes of Health (NIH) and NIDDK for the study of liver disease.

Dr. Kaplowitz is a nationally-recognized expert in drug-induced liver disease and acetaminophen-induced liver injury.[11] He has authored over three hundred peer-reviewed research papers, book chapters, editorials, and symposia on the subject of liver disease. His research is specifically focused on drug-induced liver disease, including articles on acetaminophen toxicity in both humans and animals.[12] He is the editor of several textbooks on Liver Diseases, including the leading textbook in the field, called Drug-Induced Liver Disease, currently in its Third Edition.[13]

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[10] See AASLD website, http://www.aasld.org/about-aasld/our-story. Defendants' experts agree that this is an accurate description of the organization and its purpose. See R. Brown Dep., Apr. 30, 2015 at 85-88 (Doc. No. 154, Ex. 3); S. Flamm Dep., May 5, 2015 at 43-45 (Doc. No. 154, Ex. 4).

[11] The defense experts agree with this point. See R. Brown Dep., Apr. 30, 2015 at 39, 43 (Doc. No. 154, Ex. 3); S. Flamm Dep., May 5, 2015 at 26 (Doc. No. 154, Ex. 4).

[12] See, e.g., Kaplowitz, N., Direct protection Against Acetaminophen hepatotoxicity by Prropythiorracil: In Vitro Studies in Rats and Mice, J. Clin. Invest., 67: 688-696, 1980; Kaplowitz, N., Innate Immune System Plays a Critical Role for Determining The Progression and Severity of Acetaminophen Toxicity, Gastroenterology, 127:1760-1774, 2004; Kaplowitz, N., "Neutrophil Depletion Protects Against Murine Acetaminophen Toxicity," Hepatology, 43:1220-1230, 2006; Kaplowitz, N., JNK dependent acute Liver Injury for Acetaminophen of TNF Requires Mitochondrial Sab Expression, J. Biol. Chem., 286:35071-8, 2011; Kaplowitz, N., Protein Kinase C (PKC) Participates in Mediates Acetaminophen hepatotoxicity Through JNK Dependent and Independent Signaling pathways, Hepatology, 59: 1543-1554, 2014; Kaplowitz, N., Acetaminophen Hepatotoxicity, In Gastrointestinal Emergencies (Williams & Witkins, Ed.), 279-289, 1991; Kaplowitz, N., Drug Metabolism and hepatoxicity, in Liver and Billiary Diseases (Ed. N. Kaplowitz), Williams & Witkins, 82-97; Kaplowitz N., New Developments in Drug Hepatoxicity, Curr. Opinion Gastroent., 10:313-18, 1994; Kaplowitz, N., Mechanisms of Drug-Induced Liver Disease, Gastroent. Clin. NA, 24:787-810, 1995; Kaplowitz, N., Fulminate Liver Injury from Drugs and Toxins, In Fulminenet Hepatic Failure (R.W. Williams, W Lee) 19-31, 1977; Kaplowitz N., Causality Assessment verses Guilt by Association in Drug Hepatoxicity, Editorial, Hepatology, 33:308-310, 2001; Kaplowitz, N., Drug-Induced Liver Disorders: Implications for Drug Development and Regulation, Drug Safety, 24:483-390, 2001; Kaplowitz N., Drug-Induced Liver Disorders: Introduction and Overview, in Drug-Induced Liver Disease, First ed. (Ends Kaplowitz, N and DeLeve L), M. Decker, 1-13, 2002; Kaplowitz, N., Acetaminophen Hepatotoxicity: What Do We Know, What Don't We Know, and What Do We Do Next?, Hepatology, 2004: 40(1): 23-26 (Doc. No. 154, Ex. 27); Kaplowitz, N., Drug Hepatoxicity, Clinics Liver Disease, 10:207-217, 2006; Kaplowitz, N., How to Protect against Acetaminophen: Don't Ask for Junk, Editorial, Gastroent., 135: 1407-1051, 2008.

[13] Kaplowitz, N., DeLeve, L., Drug-induced Liver Disease, 3rd Ed. (May 14, 2013).

Dr. Kaplowitz has also been hired as a consultant by numerous pharmaceutical companies, including McNeil, to perform drug-induced liver injury (DILI) "causation assessments" for marketed drugs.[14] This causation methodology is explained more below.

III. Dr. Kaplowitz's General Causation Methodology is Reliable

The defendants challenge the reliability of Dr. Kaplowitz's general causation opinion methodology, claiming it is based on improper scientific methods and subjective experience (not reliable scientific data).

Dr. Kaplowitz opines that: 1) acetaminophen-induced liver failure ALF is a serious public health issue and can be life-threatening; 2) acetaminophen has a narrow therapeutic margin of safety; and 3) acetaminophen can cause liver damage at or near 4 grams (the recommended daily dose of acetaminophen at the time of the decedent's death).[15] In rendering his general causation opinions, Dr. Kaplowitz considered the totality of the evidence and weighed the available information about acetaminophen-induced ALF.[16] He relied on his own clinical experience, case reports, FDA documents including an analysis of the FDA's adverse event reports (AERs) database, published clinical studies and case series involving acetaminophen (including a study he co-authored in 2006), and animal studies.[17] His opinion that there is a risk of liver injury at 4

[14] N. Kaplowitz Dep., Apr. 21, 2015 at 310-312 (Doc. No. 154, Ex. 5)(Hayes Deposition); Doc. No. 154, Ex. 1 (under seal)(McNeil CAM assessment with emails between Kaplowitz and Temple).

[15] N. Kaplowitz Expert Report, May 5, 2014 at 9-10 (Doc. No. 154, Ex. 15).

[16] See N. Kaplowitz Expert Report, May 5, 2014 at 9 (Doc. No. 154, Ex. 15); N. Kaplowitz Dep., June 3, 2014 at 135-36 (Doc. No. 154, Ex. 9)(Lyles Deposition); Kaplowitz Dep., Apr. 21, 2015 at 329-32 (Doc. No. 154, Ex. 5)(Hayes Deposition).

[17] See, e.g., N. Kaplowitz Expert Report, May 5, 2014 at 9, 11-14 (Doc. No. 154, Ex. 15); N. Kaplowitz Dep., June 3, 2014 at 135-36 (Doc. No. 154, Ex. 9)(Lyles Deposition); Kaplowitz Dep., Apr. 21, 2015 at 329-32 (Doc. No. 154,

grams is one he has held since 2004, based on his experience and research in this field.[18] For this reason, he instructs his patients in clinical practice to take no more than 2 grams of acetaminophen a day.[19]

a. Lack of Epidemiological and Case-controlled Studies Does Not Render Opinion Unreliable

The defendants argue that Dr. Kaplowitz's general causation opinion is unreliable because he "cannot identify any controlled study showing a statistically-significant increased risk of ALF from recommended doses of acetaminophen reported at the 95% confidence interval" nor any case-control study of this nature.[20] Essentially, the defendants claim his opinion is invalid because it has not been statistically proven.[21]

Ex. 5)(Hayes Deposition); Watkins, P., et al., "Aminotransferase Elevations in Healthy Adults Receiving 4 grams of Acetaminophen Daily: A Randomized Controlled Trial," JAMA, 296:87-93, 2006 (Doc. No. 154, Ex. 17).

[18] See Kaplowitz, N., Acetaminophen Hepatotoxicity: What Do We Know, What Don't We Know, and What Do We Do Next?, Hepatology, 2004: 40(1): 23-26 (Doc. No. 154, Ex. 27).

[19] See N. Kaplowitz Dep., June 3, 2014 at 42-45 (Doc. No. 154, Ex. 9)(Lyles Deposition).

Defendants' experts Drs. Brown and Flamm also limit their patients to 2-4 grams a day. See R. Brown Dep., Apr. 30, 2015 at 72-73 (Doc. No. 154, Ex. 3)("I tell them to take no more than six or eight regular-strength tablets in a day, knowing that they'll take more….It's neigh on 2 grams [daily]."); S. Flamm Dep., May 5, 2015 at 168-73 (Doc. No. 95, Ex. 33)(explaining why he only recommends that patients take a maximum of 3 or 4 grams of Tylenol a day but advises them that this is the upper limit on what should be taken because he recognizes the likely risk of patients taking too much).

[20] The defendants argue that Dr. Kaplowitz's methodology is flawed because he did not look for statistically-significant associations between substance exposure and injury and then apply the Bradford-Hill method—a set of nine guidelines to evaluate scientific data to determine causation. The Bradford-Hill methods, enunciated by Sir Austin Bradford Hill in a 1965 speech before the Royal Society of Medicine, includes a collection of "nine different viewpoints" from which to "study association before we cry causation." Hill, A.B., The Environment and Disease: Association or Causation?, PROC. R. SOC. MED., 58(5):295–99 (May, 1965). These nine guidelines are: 1) the strength of the association; 2) consistency of the association; 3) specificity or whether there are multiple causes of a condition; 4) the temporal relationship between a condition followed the exposure to the agent; 5) biological gradient or the existence of a dose-response relationship; 6) how plausible the association is biologically; 7) whether the association is "coherent" with (i.e., does not seriously conflict with) generally known facts of the natural history and biology of the disease; 8) does experimentation—removing the causative agent—improve the condition; and 9) analogy. Id. See also In re Seroquel Products Liability Litigation, No. 6:06–md–1769–Orl–22DAB, 2009 WL 3806435, at *5, n. 5 (M.D. Fla. Jun. 23, 2009).

The Fourth Circuit addressed this exact same argument by the defendants in a similar case decided over twenty years ago. In Benedi v. McNeil, a jury found that the defendants failed to warn consumers about the risk of liver damage when acetaminophen was taken with alcohol. Benedi v. McNeil-P.P.C., Inc., 66 F.3d 1378, 1381 (4th Cir. 1995). On appeal, McNeil argued that Benedi's experts should have been excluded because they "did not rely upon epidemiological data in formulating their opinions." Id. at 1384. The Fourth Circuit rejected this argument:

> [W]e do not read Daubert as restricting expert testimony to opinions that are based solely upon epidemiological data. Daubert merely requires that

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The defendants seem to indicate that this is the only method by which a scientist could find a causal connection. From the evidence presented by both parties, this appears not to be true. The defendants' interpretation of the type of association needed before using Bradford-Hill appears to be overstated. There is nothing to say that a statistically-significant association must be found before applying the methodology. See In re: Lipitor (Atorvastatin Calcium) Marketing, Sales Practices and Products Liability Litigation, --- F.Supp.3d ----, MDL No. 2:14–mn–02502–RMG, 2016 WL 1251828, at *2 (D.S.C. Mar. 30, 2016)("Randomized, double-blind, clinical trials are the 'gold standard' for determining whether an association exists. However, the Reference Manual on Scientific Evidence recognizes that observational studies can be sufficient to establish an association.")(citation omitted); Federal Judicial Center, Reference Manual on Scientific Evidence, at 598-99 (3d ed. 2011)(recognizing that an association is needed first to apply Bradford-Hill but not a statistically significant one); id. at 217-18 (recognizing the role of observational studies in establishing causation).

Furthermore, the cases the defendants cite for this argument are unpersuasive and/or distinguishable from this case. See In re Zoloft (Sertraline Hydrocholoride) Products Liability Litig., 26 F. Supp. 3d 449, 456 (E.D. Pa. 2014)(excluding expert opinion on teratogenicity, not drug-induced liver injury, because expert failed to follow generally accepted method in that field); Wade-Greaux v. Whitehall Labs., Inc., 874 F. Supp. 1441, 1451, 1483 (D.V.I. 1994)(excluding expert opinion regarding teratogenicity because "positive human epidemiologic studies are always required to reach a conclusion as to whether a specific agent is teratogenic in humans" and such data was not relied upon by experts); Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 514-15 (W.D. Pa. 2003)(excluding expert opinion because facts established by an evidentiary hearing regarding summary judgment showed Bradford-Hill criteria could not be met); Magistrini v. One Hour Martinizing Dry Cleaning, 180 F.Supp.2d 584, 608 (D. N.J. 2002)(excluding opinion because expert did not use a particular methodology beyond expert's own "judgment"). I find nothing that requires the plaintiff's expert to use the methodology as prescribed by the defendants.

[21] I note that the way acetaminophen has been regulated—having been on the market, grandfathered in under the monograph system, and never issued a final monograph—may also explain why this type of research has never been conducted. See In re Tylenol (Acetaminophen) Marketing, Sales Practice, and Products Liability Litigation, MDL NO. 2436, 2015 WL 7075949, at *7-9 (E.D. Pa. Nov. 13, 2015)(decision on motion for summary judgment explaining regulatory framework). Unlike other drugs, pre-marketing research was not conducted on acetaminophen. While acetaminophen manufacturers are encouraged to perform research to determine acetaminophen's potential adverse events, they are not necessarily required to perform post-marketing research by regulation. See 21 C.F.R. § 330.12(c)(explaining how manufacturers of drugs with a Tentative Final Monograph are "encouraged to perform studies to obtain adequate evidence of effectiveness" and make appropriate changes in labels and formulations "to bring the products into conformity with current medical knowledge and experience").

> the expert testimony be both relevant and reliable; and Daubert clearly vests the district courts with discretion to determine the admissibility of expert testimony. Under the Daubert standard, epidemiological studies are not necessarily required to prove causation, as long as the methodology employed by the expert in reaching his or her conclusion is sound.

Id. See also id. at 1384-85. While epidemiological studies can be valuable evidence of causation, they are not a pre-requisite for products liability causation expert testimony in this Circuit.[22] The defense experts admit that having case-controlled epidemiological data is not a requirement in finding causation for drug-induced liver injuries.[23]

In this case especially, epidemiological studies and/or statistically-significant clinical evidence would be difficult to obtain.[24] Drug-induced ALF or

[22] See Wolfe v. McNeil-PPC, Inc., No. 07–348, 2011 WL 1673805, at *15 (E.D. Pa. May 4, 2011)(rejecting similar argument from McNeil in Motrin products liability action); Lanzilotti by Lanzilotti v. Merrell Dow Pharmaceuticals Inc., No. 82–0183, 1986 WL 7832, at *2 (E.D. Pa. Jul 10, 1986)("We note also that it has not been declared in this circuit that epidemiological studies are an indispensable element in the presentation of a prima facie drug product liability case, or that such studies must be the sole basis for expert opinion."); Mazur v. Merck & Co., Inc., 742 F.Supp. 239, 264 (E.D. Pa. 1990)(same). See also Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 449 (W.D. Pa. 2003)(discussing the value of epidemiological studies).

[23] See R. Brown Dep., Apr. 30, 2015 at 106-07 (Doc. No. 154, Ex. 3)("Q. My question is very specific, sir. My question is, is there a requirement in any of the peer-reviewed medical literature that before a drug can be ruled in as a potential hepatotoxic drug that there must be a case-controlled epidemiologic study?…A. The answer is, you have to have some data. What form that data takes varies, based upon the drug you're studying and what you're trying to assess. You have to have reliable data. And that reliable data can come from a number of sources. If you have randomized controlled clinical trial data, you don't have need much else. If you're requiring lower -- the way we grade data is you have a quality of the data and a confidence in the data, and then you come up with a strength of the recommendation. And that's a -- that was not a standard process in 1990 and 2000 when many of these articles were done, but it is the standard now. And so the higher the quality of the evidence, the fewer studies you need. The lower the quality of the evidence, the -- either you need stronger data or more research.") and at 107-109; S. Flamm Dep., May 5, 2015 at 97 (Doc. No. 154, Ex. 4)("Q. Okay. And there is no requirement in the causation algorithm that there be an epidemiologic study that would demonstrate a statistically significant 2.0 relative risk to a P-value of .05 standard epidemiologic association in order to rule in a drug as a potential cause for acute liver failure or DILI. True? A. Yes. Again, it's not a requirement, but for you to make a very good clinical decision and really understand an interaction with a particular patient and a product, you have to have some level of comfort in the data that are behind it.") and at 98.

[24] During oral argument, the defendants pointed to other epidemiological studies on other rare diseases which were conducted by Dr. Kaplowitz to show that such data could be produced. Simply because an epidemiological study could be produced for one rare disease does not necessarily indicate it could be designed for another rare disease. Factual differences between rare diseases may account for the availability of data for one disease and not another (i.e., one disease like ALF may lead to death so testing for it is riskier and unethical while another may not result in such dire consequences). Especially given Dr. Temple's own admission that this type of study is not possible for

severe liver damage is rare. Case-controlled epidemiologic studies of rare diseases, such as ALF, with control groups are difficult to perform. Drug-induced ALF is unlikely to ever be seen in a human prospective placebo-controlled clinical trial, which studies a small number of patients.[25] Because of the rarity of drug-induced ALF, randomized placebo-controlled clinical trials would not necessarily be feasible to establish a connection between acetaminophen and ALF.[26]

The experts in this case recognize that the types of studies the defendants claim are needed to make an opinion reliable—human prospective placebo-controlled clinical trials—are not feasible or ethical.[27] During his deposition, Dr. Anthony Temple, former Vice President of Medical Affairs at McNeil, also admitted that McNeil consulted with epidemiologists to design a statistically-significant controlled study which would prove

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acetaminophen-induced ALF, the defendants' argument on this point is unpersuasive. See A. Temple Dep., Mar. 20, 2014 at 91, 100, 185-86 (Doc. No. 154, Ex. 10).

[25] See Davern, T.J., et al, Drug-Induced Liver Injury in Clinical Trials: As Rare as Hen's Teeth (editorial), Am. J. Gastroenterol., 2009: 104: 1159-1161 (Doc. No. 154, Ex. 8).

[26] See N. Kaplowitz, Dep., Jun. 3, 2014 at 138-142, 164, 214-215 (Doc. No. 154, Ex. 9)(Lyles Deposition). See also A. Temple Dep., Mar. 20, 2014 at 91, 100, 185-86 (Doc. No. 154, Ex. 10).

[27] See N. Kaplowitz Dep., Jun. 3, 2014 at 138-42, 164, 214-15 (Doc. No. 154, Ex. 9)(Lyles Deposition) and at 139 ("I mean, there's no -- first of all, there is no scientific evidence that it does not because the studies are not powered to exclude it. And so, as one always has to do in the setting of rare events, is you have to see an accumulation of rare events. If this happened once in history, you know, one case report in the world's literature, obviously -- or two, even – we wouldn't be sitting here. But there are -- there's enough smoke here, enough case reports, coupled with all the other things that I've just been talking about that I won't repeat that I don't agree with."). See also S. Flamm Dep., May 5, 2015 at 94, 98 (Doc. No. 154, Ex. 4)(admitting that he cannot name one hepatotoxic drug which has statistically significant proof to show liver injury causation); R. Brown Dep., Apr. 30, 2015 at 105-09 (Doc. No. 154, Ex. 3)(same); A. Temple Dep., Mar. 20, 2014 at 84-85 (Doc. No. 154, Ex. 10)("Q. And because it would be inappropriate and unethical to prospectively expose a patient to a drug with the intent of trying to measure harm? A. Well, yeah. That's been an issue with giving overdoses of acetaminophen, yes. You wouldn't do it -- if you knew that giving a drug in a certain dose produced harm, then you wouldn't want to give it to someone.").

or disprove acetaminophen-induced ALF; they found such a study was not feasible and/or was too expensive to conduct.[28]

Like the Fourth Circuit, I find the defendants' argument unpersuasive. Dr. Kaplowitz cites over fifty articles to support his general causation opinions; half of these sources speak directly to whether acetaminophen can cause liver injury at or near 4 grams.[29] As a leading expert in acetaminophen-induced liver injury, he relies on his own clinical experience and research in rendering his opinions. I see nothing wrong with his general causation methodology.[30]

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[28] See A. Temple Dep., March 20, 2014 at 91 (Doc. No. 154, Ex. 10)(under seal)("I don't think there was an easy way or even a way to look retrospectively. I mean, we just did another case series with -- he admitted that it's very hard to define ingestion of alcohol or fasting during this period of time. So his case series was what it was. So doing the kind of epidemiology series I think you're describing, we determined wasn't a feasible study, but we have evaluated whether to do that or not, yes."), at 100 ("[W]e talked -- we had talked with epidemiologists, and we had looked at that issue, and I don't know that they -- I don't recall them ever giving us an adequate proposal, but the answer is yes, we did talk to them about the dosing issues and about ways to conduct epidemiology studies."), and at 185-86 ("McNeil has not done an epidemiology study that way because we couldn't find a way to conduct that trial.").

I also note that two different databases (the ALFSG and FDA databases) showed a risk in some people at 4 grams and that the median daily dose for liver injury was 5-7 grams a day. FDA Working Group Report (2008) at 11, n. 41 (Doc. No. 154, Ex. 30).

[29] Among these references, Dr. Kaplowitz cites Larson, A.M., et al., Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study, Hepatology, 2005 Dec: 42(6): 1364-1372 (Doc. No. 154, Ex. 22). The defendants filed a separate motion to exclude the use of this article. See Motion to Exclude Opinion Testimony of Neil Kaplowitz based on Supplemental Data, Jan. 29, 2016 (Doc. No. 193). I denied that motion. See Memorandum and Order Denying Defendants' Motion to Exclude Plaintiff's Expert Testimony Based on Larson Article/ALFSG Data, Jul. 14, 2016 (Doc. No. 224, 225). I see nothing improper with how Dr. Kaplowitz has used the Larson article—along with other evidence—in rendering his opinion.

[30] The defendants argue that Dr. Kaplowitz cannot rely upon information contained in a 2008 report from the FDA's Acetaminophen Hepatotoxicity Working Group because it is not peer-reviewed and does not offer information to support Dr. Kaplowitz's opinions. See FDA Working Group Report (2008)(Doc. No. 154, Ex. 30). This is a weak argument. See Heller v. Shaw Industries, 167 F.3d 146, 155 (3d Cir. 1999)("Given the liberal thrust of the Federal Rules of Evidence, the flexible nature of the Daubert inquiry, and the proper roles of the judge and the jury in evaluating the ultimate credibility of an expert's opinion, we do not believe that a medical expert must always cite published studies on general causation in order to reliably conclude that a particular object caused a particular illness…. To so hold would doom from the outset all cases in which the state of research on the specific ailment or on the alleged causal agent was in its early stages, and would effectively resurrect a Frye-like bright-line standard, not by requiring that a methodology be 'generally accepted,' but by excluding expert testimony not backed by published (and presumably peer-reviewed) studies. We have held that the reliability analysis applies to all aspects of

b. Reliance on Clinical Experience and Case Reports is Appropriate

The defendants argue that Dr. Kaplowitz's methods are flawed because he relies on anecdotal evidence and his personal clinical experience.[31] It is true that case reports and anecdotal evidence alone may not be sufficiently reliable for an expert to support a causation opinion. See, e.g., Wade-Greaux v. Whitehall Labs., Inc., 874 F. Supp. 1441, 1483 (D.V.I. 1994)("…anecdotal human data, whether from published case reports, DERs or other litigation, have inherent biases that make them unreliable."). However, case reports considered in conjunction with other evidence may be an appropriate basis for an expert's opinion on causation.[32] Dr. Kaplowitz does not rely solely on case reports

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an expert's testimony: the methodology, the facts underlying the expert's opinion, the link between the facts and the conclusion, et alia.").

I see nothing inherently unreliable in a report prepared by a group of scientists, who are experts in this area of study, coming together to discuss, discern, and analyze possible concerns on this topic. Not only was the document produced with input from experts on the topic of acetaminophen-induced liver injury, including ones working for the defendants, but it was also sponsored by the FDA. The fact that the national regulatory agency convened a group of experts to discuss the issue of acetaminophen-induced liver injury, to collectively present and analyze the available information about acetaminophen-induced liver injury, provides the document with the indicia of reliability required under Daubert.

The Working Group Report stated that acetaminophen has a narrow therapeutic margin. It discussed cases of liver injury caused by acetaminophen at or near recommended doses. The Working Group considered ways to reduce the risk of unintentional overdose and liver injury to consumers, including decreasing the maximum daily dose from 4000 milligrams to 3250 milligrams. This information would be relevant to Dr. Kaplowitz's opinions.

[31] The defendants further argue that Dr. Kaplowitz's opinion on this point is flawed because it is based on self-reported patient histories. This argument is unpersuasive. Dr. Kaplowitz's opinions based on his clinical experience would, of course, need to be based on patient histories. This is how physicians in practice diagnose patients with certain conditions. Of course, each patient will have multiple factors to take into consideration in making this diagnosis. But Dr. Kaplowitz, as a practicing physician, will have weighed those factors and the other information available in making his diagnoses of his patients.

[32] See Wolfe v. McNeil-PPC, Inc., No. 07–348, 2012 WL 38694, at *3 (E.D. Pa. Jan. 9, 2012)("As for the use of AERs as bases for expert testimony, this Court has previously ruled that expert testimony that relies, in part, on case reports to establish causation satisfies the requirements of Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). See Wolfe v. McNeil–PPC, Inc., No. 07–348, 2011 WL 1673805, at *5 (E.D. Pa. May 4, 2011). The Court reiterates its conclusion that, because plaintiff's experts 'did not solely rely on case reports in forming their opinions on causation but used them to supplement their extensive review' of other evidence, such testimony is admissible."); Wolfe v. McNeil–PPC, Inc., No. 07–348, 2011 WL 1673805, at *5 (E.D. Pa. May 4, 2011)("In this case, the three doctors did not solely rely on case reports in forming their opinions on

in rendering his opinion. The case reports and case series he does cite also include controls on the information analyzed, which make them more reliable.[33]

In addition, case reports and case series are the types of information on which DILI experts often rely. See FED. R. EVID. 703; Wolfe v. McNeil-PPC, Inc., No. 07–348, 2012 WL 38694, at *3 (E.D. Pa. Jan. 9, 2012); FDA Working Group Report (2008) at p. 11, n. 41 (Doc. No. 154, Ex. 30)(explaining how members of the working group looked at two different databases of case reports/adverse event reports (AERs) in finding that there is a risk of liver injury for some people at 4 grams).[34] As explained above, epidemiological or case-controlled studies for acetaminophen-induced liver injuries are not available. In the absence of epidemiological data, case reports and case series serve as

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causation but used them to supplement their extensive review of plaintiff's medical records and deposition testimony of plaintiff's treating physicians. As with defendants' other objections, the three doctors' use of case studies in reaching their conclusion affects only the weight to be given their testimony, not its admissibility. Thus, the proposed testimony of the three doctors is based on sufficiently reliable methods."); Schedin v. Ortho–McNeil–Janssen Pharm., Inc., 808 F.Supp.2d 1125, 1139 (D. Minn. 2011)(explaining that AERs are commonly used by experts to determine causation in conjunction with other evidence), rev'd in part on other grounds, In re Levaquin Prods. Liab. Litig., 700 F.3d 1161 (8th Cir. 2012).

[33] See Caraker v. Sandoz Pharm. Corp., 172 F.Supp.2d 1046, 1050 (S.D. Ill. 2001)(explaining how "an overwhelming amount" of case reports/series with appropriate controls, analysis of alternative causes, temporal proximity may be a reliable basis for expert opinion"). See also Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 537-44 (W.D. Pa. 2003)(finding case reports to be unreliable and "unscientific" bases for causation opinion because are unpublished, not peer-reviewed, did not consider alternative causes, patients' medical history, etc.); McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1250 (11th Cir. 2005)(explaining that anecdotal information "without any medical controls or scientific assessment" is unreliable basis for expert opinion); Hollander v. Sandoz Pharms. Corp., 289 F.3d 1193, 1211 (10th Cir. 2002)(finding that exclusion of opinions based on case reports with little information about medical history appropriate but that case reports with more detailed information may be reliable source of expert opinion).

[34] Whether the case reports themselves may be admissible or disclosed to the jury is a separate question, which I will defer until I see how they may be used at trial. See FED. R. EVID. 703 ("An expert may base an opinion on facts or data in the case that the expert has been made aware of or personally observed. If experts in the particular field would reasonably rely on those kinds of facts or data in forming an opinion on the subject, they need not be admissible for the opinion to be admitted. But if the facts or data would otherwise be inadmissible, the proponent of the opinion may disclose them to the jury only if their probative value in helping the jury evaluate the opinion substantially outweighs their prejudicial effect."); Wolfe v. McNeil-PPC, Inc., No. 07–348, 2012 WL 38694, at *3 (E.D. Pa. Jan. 9, 2012).

valuable sources of information for DILI experts, doctors, and scientists in determining causation.[35]

c. Reliance on the Watkins study is Appropriate

The defendants argue the Dr. Kaplowitz's reliance on the study he co-authored with Dr. Paul Watkins is not appropriate because the article discusses elevated aminotransferase levels, not ALF.[36] See Watkins, P., et al., "Aminotransferase Elevations in Healthy Adults Receiving 4 grams of Acetaminophen Daily: A Randomized Controlled Trial," JAMA, 296:87-93, 2006 (Doc. No. 154, Ex. 17).

The Watkins article found that some adults had developed abnormalities in liver enzymes (e.g., aminotransferases or ALTs) after taking recommended doses of acetaminophen. ALF occurs when the liver is severely damaged. Elevated ALTs are markers of liver damage (i.e., liver cell death). Increased ALTs do not necessarily lead to ALF. However, elevated ALTs are one early indicator that ALF might occur.[37]

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[35] See, e.g., N. Kaplowitz Dep., Jun. 3, 2014 at 134-136, 139, 158, 194, 213 (Doc. No. 154, Ex. 9)(Lyles Deposition); Davern, T.J., et al., Drug-Induced Liver Injury in Clinical Trials: As Rare as Hen's Teeth (editorial), Am. J. Gastroenterol., 2009: 104: 1159-1161 (Doc. No. 154, Ex. 8)(explaining how multi-center reporting is important to understanding DILI); FDA Working Group Report (2008) at 3-5, 11, n. 41 (Doc. No. 154, Ex. 30).

[36] The defendants also point out the Watkins article's statements that "acetaminophen clearly has a remarkable safety record when taken as directed, and chronic treatment with 4 g daily has been confirmed to be safe." Watkins, P., et al., "Aminotransferase Elevations in Healthy Adults Receiving 4 grams of Acetaminophen Daily: A Randomized Controlled Trial," JAMA, 296:87-93, 93 (2006)(Doc. No. 154, Ex. 17). The mere fact that the article acknowledges that acetaminophen is typically safe at recommended doses does not mean that other findings in the article should be negated or reliance on the article is inappropriate.

[37] Dr. Temple also admitted that looking at elevated ALTs is one way to study the risk of ALF. See A. Temple Dep., Mar. 20, 2014 at 85 (Doc. No. 154, Ex. 10)("Q. Right. So the way in which you study risk in clinical trials is to look for surrogates for risk. Oftentimes you look for laboratory abnormalities. If there happens to be a patient reaction during the clinical trial, you look for measurements of blood pressure, liver function tests, those kinds of things as a predictor, potential predictor of clinical problems when a drug is more widely used, true? A. You can do that, yes."). McNeil considered liver abnormalities in its own studies. See N. Kaplowitz Dep., June 3, 2014 at 137 (Doc. No. 154, Ex. 9)(Lyles Deposition)(explaining how McNeil's studies showed increased level enzymes at recommended doses).

The defendants fail to acknowledge the fact that the Watkins study was stopped early because the authors were concerned about the harm being caused to study participants. It would not have found ALF because inducing ALF—a life threatening condition—would have been unethical. I see no problem with Dr. Kaplowitz's use of the Watkins data to support his opinions, along with the many other sources he cites.[38]

d. Use of Animal Studies to Support Opinions is Reasonable

The defendants argue that Dr. Kaplowitz's opinions are invalid because they rely on animal studies.[39] Given the ethical considerations in obtaining human studies, the use of animal studies in this instance would be appropriate.[40] Animal studies are what other scientists exploring acetaminophen toxicity rely on because these studies can offer useful information about human liver function.[41] See FED. R. EVID. 703; In re Paoli R.R Shipyard PCB Litig., 35 F.3d 717, 748, 779 (3d Cir. 1994). In fact, the defendants

[38] The defendants claim his reliance on data from the Acute Liver Failure Study Group (ALFSG), including Larson, A.M., et al., Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study, Hepatology, 2005 Dec: 42(6): 1364-1372 (Doc. No. 154, Ex. 22)(i.e., the "Larson article"), is not appropriate because this data is nothing more than case reports. The defendants filed a separate motion regarding the admissibility and validity of the ALFSG data. See Doc. No. 193. I explained in my decision on that motion why the ALFSG data is admissible and can be relied upon by experts in the field. See Memorandum and Order Denying Defendants' Motion to Exclude Plaintiff's Expert Testimony Based on Larson Article/ALFSG Data, Jul. 14, 2016 (Doc. No. 224, 225). I see no problems with the way Dr. Kaplowitz has used this data in forming his opinions.

[39] See N. Kaplowitz Dep., Jun. 3, 2014 at 86-88, 194-95, 213-14 (Doc. No. 154, Ex. 9)(Lyles Deposition); Kaplowitz Dep., Apr. 21, 2015 at 161, 173 (Doc. No. 123, Ex. B)(Hayes Deposition).

[40] See In re Levaquin Products Liab. Litig., No. MDL 08-1943 JRT, 2010 WL 8400514, at *4 (D. Minn. Nov. 8, 2010)("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….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.")(citations omitted).

[41] See T. Davern Expert Report, Feb. 16, 2015 at 4-5 (Doc. No. 155, Ex. 1)(explaining how acetaminophen poisoning in mice is similar to humans).

themselves point to an animal study about glutathione to support their point that ALF cannot occur at 4 grams.[42] Their argument is unpersuasive.[43]

IV. Dr. Kaplowitz's Causality Assessment Methodology (CAM) in Rendering His Specific Causation Opinion is Reliable

The defendants also move to exclude Dr. Kaplowitz's specific causation opinions because his methodology is not statistically significant or exacting. Dr. Kaplowitz uses a "science of causality assessment" (i.e., causation assessment methodology or CAM) to reach his opinions about Ms. Hayes' cause of death. This is a common methodology used by DILI clinicians and experts.

Because traditional epidemiological and case-controlled studies are not feasible, DILI experts developed the "science of causality assessment," or CAM, to assess DILI risk.[44] This methodology is used by the Drug Induced Liver Injury Network (DILIN),

[42] See Mitchell, J., et al., "Acetaminophen-induced hepatic injury: Protective role of glutathione in man and rationale for therapy," Clinical Pharmacology and Therapeutics, Vol. 16, No. 4, 676-84 (1974). See also T. Davern Dep., Mar. 28, 2015 at 147-49 (Doc. No. 155, Ex. 3)(defense attorneys questioning regarding animal studies on glutathione).

[43] The defendants' other arguments about Dr. Kaplowitz's prior testimony about the strength of his causation evidence (i.e., that association is not causation, that he has written that acetaminophen is generally safe, etc.) go to weight, not admissibility. They are most appropriately explored on cross-examination.

[44] See N. Kaplowitz Dep., Jun. 3, 2014 at 139 (Doc. No. 154, Ex. 9)(Lyles Deposition)("I mean, there's no -- first of all, there is no scientific evidence that it does not because the studies are not powered to exclude it. And so, as one always has to do in the setting of rare events, is you have to see an accumulation of rare events. If this happened once in history, you know, one case report in the world's literature, obviously -- or two, even – we wouldn't be sitting here. But there are -- there's enough smoke here, enough case reports, coupled with all the other things that I've just been talking about that I won't repeat that I don't agree with….And so we are left with, instead of the – you know, the typical experimental scientific method, we are left with the science of causality assessment, you know, which is not a randomized control trial but a kind of postmarketing assessment of cases that's done by experts in the field in every other situation.") and at 213-15.

sponsored by the NIDDK, and by drug-induced liver injury registries in other countries.[45] It has also been used to assess causation between ALF and other hepatotoxic drugs.[46]

While the CAM tool itself may vary, at the core of this methodology is a "differential assessment."[47] DILI causality assessments considers a combination of factors, including: temporal associations, the rate of improvement after cessation of the drug, the definitive exclusion of alternative causes, and the "signature" of the drug as revealed in clinical trials and experience.[48] This "science of [DILI] causality assessment" has been published by DILI experts in various forms since the 1980s.[49]

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[45] See id. at 142 ("But ultimately the approach in a situation like that, and it is the approach followed by hepatologists in practice, it is the approach followed by all the different drug-induced liver injury networks worldwide, including the DILIN Network, the Drug-Induced Liver Injury Network sponsored by NIDDK, which I participate in; the Spanish Registry, which I collaborate with; the Swedish registry; the British registry; the German registry; the Italian. Every country has a registry and follow this methodology to evaluate postmarketing cases of liver injury suspected as being caused by drugs. So that's the science of causality assessment at the present time. It is not the scientific method in the way that your experts describe. Their description of epidemiological methodology and so on is perfectly fine. I don't dispute that. It is just that I don't think it applies in this situation.").

[46] See N. Kaplowitz Dep., Jun. 3, 2014 at 134-36 (Doc. No. 154, Ex. 9)(Lyles Deposition)(explaining how DILI causation assessment was used in determining that Rezulin could cause ALF).

[47] While I cannot find any precedent speaking directly to the use of CAM (and the parties have offered none as well), differential assessment—which is at the heart of CAM—has been approved by the Third Circuit as a reliable method for showing causation. See In re Paoli R.R Shipyard PCB Litig., 35 F.3d 717, 758-9 (3d Cir. 1994); Heller v. Shaw Industries, 167 F.3d 146, 155 (3d Cir. 1999); Felt v. Great West Life and Annuity Ins. Co., 271 Fed.Appx. 246, 24-55 (3d Cir. Mar. 31, 2008). See also Wolfe v. McNeil-PPC, Inc., No. 07–348, 2011 WL 1673805, at *4-5 (E.D. Pa. May 4, 2011); Benedi v. McNeil-P.P.C., Inc., 66 F.3d 1378, 1384 (4th Cir. 1995)(discussing how the use of medical history, examination, lab and pathology data, and peer-reviewed literature was reliable method to provide causation opinion); Baker v. Dalkon Shield Claimants Trust, 156 F.3d 248, 252-53 (1st Cir. 1998); McCullock v. H.B. Fuller Co., 61 F.3d 1038, 1043-44 (2d Cir. 1995); Zuchowicz v. United States of America, 140 F.3d 381, 285-87 (2d Cir. 1998); Glaser v. Thompson Med. Co., 32 F.3d 969, 978 (6th Cir. 1994); Ambrosini v. Labarraque, 101 F.3d 129, 140-1 (D.C. Cir. 1996); Kennedy v. Colligen Corp., 161 F3d 1226, 1228-30 (9th Cir. 1998).

[48] See Kaplowitz N., Causality Assessment verses Guilt by Association in Drug Hepatoxicity, Editorial, Hepatology, 33:308-310, 2001 (Doc. No. 154, Ex. 11). See also R. Brown Dep., Apr. 30, 2015 at 103-05 (Doc. No. 154, Ex. 3); S. Flamm Dep., May 5, 2015 at 69, 138-140 (Doc. No. 154, Ex. 4).

[49] See, e.g., Maria, V. & Victorino, R., Development and Validation of a Clinical Scale for the Diagnosis of Drug Induced Hepatitis, Hepatology, Vol. 26: 664-669, 1997; Aithal, G., et al., Clinical Diagnostic Scale: A Useful Tool in the Evaluation of Suspected Hepatotoxic Adverse Drug Reactions, J. Hepatology, 2000:33: 949-953; Danan G., et al., Causality Assessment of Adverse Reactions to Drugs – I. A Novel Method Based on the Conclusions of the International Consensus Meetings: Application to Drug Induced Liver Injuries [RUCAM], J. Clin. Epidemiol., 1993; 46:1323-1330; Benichou, C., et al., Criteria of Drug Induced Liver Disorders: Report of an International Consensus

Defense experts Drs. Brown and Flamm agree that DILI CAM is an acceptable methodology used by DILI experts to assess causation.[50] McNeil itself uses a differential assessment/CAM methodology in its acetaminophen hepatotoxicity causality data collection instrument.[51] In fact, Dr. Kaplowitz helped develop the CAM tool used by McNeil.[52]

In rendering his specific causation opinion, Dr. Kaplowitz used McNeil's "Causation Assessment Methodology (CAM)" instrument. Dr. Kaplowitz considered Ms. Hayes' medical records and her doctors' depositions.[53] He reviewed the available

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Meeting [CIOMS], J. Hepatol.,1990:11:272-276; Lucena, M., et al., Comparison of Two Clinical Scales for Causality Assessment in Hepatotoxicity, Hepatology, 2001: 33:123-130; Lee, W.M., Assessing Causality in Drug Induced Liver Injury, J. Hepatology, 2000, 33:1003-1005; Kaplowitz, N., Causality assessment versus guilt-by-association in drug hepatotoxicity, Hepatology, Vol. 33, No. 1, 308-10, 2001; Davern, T., Drug-Induced Liver Disease, in Clinics in Liver Disease, Vol. 13, No. 2, May 2012, 231-239 ("Diagnosis of DILI: Causality Assessment"]; Causality Assessment in Drug Induced Liver Injury, Presentation at the FDA, PhRMA, ASSLD Symposium by Robert J. Fontana, M.D. (Jan. 28, 2005).

[50] See R. Brown Dep., Apr. 30, 2015 at 104-05 (Doc. No. 154, Ex. 3)("Q. In other words, let me ask you this question: These are causation assessments for drug-induced liver injury. True? That's the standard methodology we've been talking about?...A. There isn't a standard methodology, but that is the methodology, yes."); S. Flamm Dep., May 5, 2015 at 69, 138-140 (Doc. No. 154, Ex. 4)("Q. [Have] you employed the same methodology that we have talked about before to assess the probable causation for a drug, in other words, what Dr. Davern and Dr. Kaplowitz have described in their literature as being a causation assessment? A. Yes. Again, I think what Dr. Davern described in[] his chapter in the book I edited, would be the protocol that one would follow to determine if there was drug induced liver injury.") and at 143. See also A. Temple Dep., Mar. 20, 2014 at 312-13 (Doc. No. 154, Ex. 10)("Q. That's right. And so this causation assessment methodology, or some version of it, is the standard way -- standard methodology used by experts in the field based on published medical literature for assessing causation in an individual case irrespective of dose, true? A. Irrespective of dose? You mean all-comers? Q. All-comers. A. Whether they had a dose or if it was the correct dose -- Q. Correct. A. Yes.").

[51] See Doc. No. 154, Ex. 1 (under seal); A. Temple Dep., Mar. 20, 2014 at 311-13 (Doc. No. 154, Ex. 10)(explaining McNeil's causality instrument, describing as one of differential assessment irrespective of dose).

[52] N. Kaplowitz Dep., Apr. 21, 2015, at 310-312 (Doc. No. 154, Ex. 5)(Hayes Deposition); Doc. No. 154, Ex. 1 (under seal)(McNeil CAM assessment with emails between Kaplowitz and Temple).

[53] See N. Kaplowitz Dep., Apr. 21, 2015 at 312-17 (Doc. No. 154, Ex. 5)(Hayes Deposition); History and Physical from Helen Keller Hospital, Aug. 29, 2010 (Doc. No. 154, Ex. 32). See also Kannankeril v. Terminex Int'l, Inc., 128 F.3d 802, 806-07 (3d Cir. 1997)("Depending on the medical condition at issue and on the clinical information already available, a physician may reach a reliable differential diagnosis without himself performing a physical examination, particularly if there are other examination results available. In fact, it is perfectly acceptable, in arriving at a diagnosis, for a physician to rely on examinations and tests performed by other medical practitioners.").

evidence about acetaminophen to determine acetaminophen's "signature" or track record.[54] He considered whether Ms. Hayes' liver injury had a temporal association with the use of acetaminophen which was consistent with the "signature" of the drug and whether there were other etiologies (i.e., viral hepatitis, cytomegalovirus (CMV), Epstein-Barr virus (EBV), ischemic hepatitis, Wilson's disease, illicit drugs, or sepsis) that could have caused her liver injury. He determined that acetaminophen at a dose of 3-5 grams a day for 5-6 days was highly likely the cause of Ms. Hayes' ALF. He indicated that the risk factors of malnourishment, fasting, and weight loss surgery likely contributed to her development of acetaminophen-induced ALF. From what has been presented, Dr. Kaplowitz appropriately applied the CAM methodology.

I see nothing suspect about Dr. Kaplowitz's specific causation opinion or his methodology is reaching this opinion.[55]

[54] See, e.g., Lee, W.M., Acetaminophen and the US Acute Liver failure Study Group, Lowering the Risk of Hepatic Failure, Hepatology, Vol. 40: 6-9 (2004)(Doc. No. 154, Ex. 19); Schiodt, F.V., et al., Acetaminophen Toxicity in an Urban County Hospital, N. Eng. J. Med., 1997 (Doc. No. 154, Ex. 20); Ostapowicz, G., et al., Results of a Prospective Study of Acute Liver Failure at 17 Tertiary Hospitals in the United States, Ann. of Internal Med, Vol. 137, 947-954 (2002)(Doc. No. 154, Ex. 21); Larson, A.M., et al., Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study, Hepatology, 2005 Dec: 42(6): 1364-1372 (Doc. No. 154, Ex. 22); Kurtovic, J. and Riordan, S.M., Paracetamol-Induced Hepatoxicity at Recommended Doses, J. Internal Med., 2003 Feb; 253(2):240-3 (Doc. No. 154, Ex. 23); Forget, P., et al., Therapeutic dose of acetaminophen may induce fulminant hepatitis in the presence of risk factors: A report of two cases, B. J. Anesthesia, Vol. 103, Issue 6; 899-900, 2009 (Doc. No. 154, Ex. 24); Eriksson, L.S., et al., Hepatoxicity Due to Repeated Intake of Low Doses of Paracetamol, J. Intern. Med., 231; 567-570, 1992 (Doc. No. 154, Ex. 25); Whitcomb, C., et al., Association of Acetaminophen Hepatotoxicity with Fasting and Ethanol Use, JAMA, Vol. 22, No. 2, 1994 (Doc. No. 154, Ex. 26).

[55] The defendants' other arguments about Dr. Kaplowitz's specific causation opinion (i.e., the strength of the sources he relied upon, etc.) go to weight, not admissibility. They are most appropriately explored on cross-examination.

V. Dr. Kaplowitz's Opinions About Fasting/Malnutrition and Gastric Bypass Surgery

The defendants move to exclude Dr. Kaplowitz's general opinion that fasting, malnutrition, and gastric bypass surgery are all risk factors which may make a person more susceptible to acetaminophen-induced liver injury.

Dr. Kaplowitz supports his general opinion about fasting and malnutrition with animal studies, case reports, and case series showing that fasting/malnutrition could be a significant risk factor.[56] Other evidence in the record shows that fasting/malnutrition was a known possible risk factor for acetaminophen-induced liver injury.[57] I see nothing unreliable about his fasting/malnutrition opinion. The defendants' arguments go to the

[56] See, e.g., James, L., Acetaminophen: Pathology and Clinical Presentation of Hepatotoxicity, at 336 (Kaplowitz, N. Ed.)("The role of fasting in the development of toxicity is widely appreciated by practitioners but has not been well studied in the clinical setting. In the rodent model, fasting reduced GSH stores and reduced the glucuronidation of acetaminophen by accelerating the development of toxicity. Anecdotal case reports have also associated fasting with the development of acetaminophen toxicity in humans."); Whitcomb, C., et al., Association of Acetaminophen Hepatotoxicity with Fasting and Ethanol Use, JAMA, Vol. 22, No. 2 , 1994 (Doc. No. 154, Ex. 26); N. Kaplowitz Expert Report, May 4, 2014 (Doc. No. 154, Ex. 15)(citing Faber, P.J., et al., The Effect of Rate and Weight Loss on Erythrocyte Glutathione Concentration and Synthesis in Healthy Obese Men, Clinical Science, Vol 102(5): 569-577 (2002); McLean, D., The Effect of Diet on the Toxicity of Paracetamol and the Safety of Paracetamol-Methionine, Clinical Therapeutics, Vol. 28, Issue 5, 755-760 (May 2006); Pessayre, D., et al., Effect of Fasting on Metabolite-Mediated Hepatotoxicity in the Rat Gastroenterology, (2), 264-71 (1979); Pessayre, W., et al., Addictive Effects of Inducers and Fasting on Acetaminophen Hepatotoxicity, Biochem. Pharmacol., 29(16): 2219-23 (1980); Price, J., et al., Mechanism of Fasting-Induced Suppression of Acetaminophen Glucoronidation in the Rat, Adv. Exp. Med. Biol., 197: 697-706 (1986); Whitcomb, C., et al., Association of Acetaminophen Hepatotoxicity with Fasting and Ethanol Use, JAMA, Vol. 22, No. 2, 1994).

[57] See, e.g., Kaplowitz, N., Acetaminophen Hepatoxicity: What we know, what we don't know and Where do we go?, Hepatology, Editorial, 40:23:26, 2004. See generally Memorandum Denying Defendants' Motion for Summary Judgment on Plaintiff's Failure-to-Warn Claim, Nov. 13, 2015 (Doc. No. 181)(discussing information presented by the FDA about fasting as a possible risk factor).

Dr. Anthony Temple, former Vice President of Medical Affairs at McNeil, testified that "McNeil has not done an epidemiology study that way because we couldn't find a way to conduct that trial." A. Temple Dep., Mar. 20, 2014 at 185-86 (Doc. No. 154, Ex. 10). Dr. Temple's comment was made specifically about a study to test whether fasting while taking acetaminophen could increase the risk of ALF, indicating that McNeil was aware that fasting may be a risk factor. See id. at 185 ("Had McNeil, to your knowledge, and this really is a yes or no question, ever asked any -- asked for any epidemiologist to prepare a protocol to study the fasting issue? A. I think this is the same question you asked me before, and you limited it to preparing a protocol. We've asked them to propose study designs and/or to conduct studies or that help us figure it out. So yes, that -- we've never asked them to write a protocol because we never got a recommendation that would -- we thought was useful to get the answer.").

weight, not admissibility. Any flaws in his opinion may be explored on cross-examination.

The defendants move to exclude Dr. Kaplowitz's opinion that Ms. Hayes was "susceptible" to ALF from recommended doses of acetaminophen because she had previously undergone weight loss surgery and was malnourished/fasting. They argue that this opinion is unreliable because Dr. Kaplowitz does not know the dose of acetaminophen that Ms. Hayes ingested and that no physician ever diagnosed her with malnutrition.[58] Dr. Kaplowitz reviewed and relied on Ms. Hayes' medical records in rendering his opinion. He cites evidence of acetaminophen being taken at the recommended dose and of limited food intake the week and half before her death.[59] The defendants' argument is unpersuasive.

The defendants also argue that Dr. Kaplowitz's opinion that gastric bypass surgery as a risk factor for Ms. Hayes is flawed. They claim it is only supported by one article, E. Holt, et al., "Acute Liver Failure Due to Acetaminophen Poisoning in Patients With Prior Weight Loss Surgery: A Case Series," J. Clin. Gastroenterol., Vol. 00, No. 00, 1-4 (2014)(Doc. No. 154, Ex. 29). Yet, as the defendants point out, Dr. Kaplowitz testified he did not rely on this article in rendering this opinion.[60] Gastric bypass has been linked to malnutrition and fasting because the surgery essentially restricts a person's caloric intake

[58] The defendants also argue this opinion is invalid because the decedent was not diagnosed with anorexia nervosa. I do not see malnutrition and fasting as necessarily analogous with anorexia nervosa. This argument is unpersuasive.

[59] See N. Kaplowitz Supp. Expert Report Regarding Ms. Hayes, Feb. 16, 2015 (Doc. No. 154, Ex. 13).

[60] See N. Kaplowitz Dep., Apr. 21, 2015, at 170 (Doc. No. 123, Ex. B)(Hayes Deposition)("Q. Are you relying on that study for your opinions in this case? A. No. I think it's an interesting study, and I think it -- it states -- it's an observation which I believe requires more study. Confirmation. But it's very provocative.").

and serves as a forced method of fasting. In this way, Dr. Kaplowitz's gastric bypass opinion relates to his opinion on fasting and malnutrition.[61] Assuming Dr. Kaplowitz is able to explain how gastric bypass is connected to malnutrition and fasting, his opinion will be admissible.

After hearing argument from the parties, I also am satisfied with Dr. Kaplowitz's methodology regarding his fasting, malnutrition, and gastric bypass opinions. Any weaknesses in his opinions relate to weight, not admissibility. They can be explored on cross-examination.

VI. CONCLUSION

For the reasons stated above, I will DENY the defendants' motion to exclude Dr. Kaplowitz's testimony.

An appropriate Order follows.

[61] See N. Kaplowitz Dep., Apr. 21, 2015, at 168-170 (Doc. No. 123, Ex. B)(Hayes Deposition)("Q. Was Ms. Hayes' prior weight loss surgery a factor in her illness and death? A. I would say it's reasonable to suspect that, yes. Q. Why do you say that? A. Because I think it affected her overall nutritional status.").