

# Vermin of Proof: Arguments for the Admissibility of Animal Model Studies as Proof of Causation in Toxic Tort Litigation

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## ABSTRACT

*Toxic torts is a body of law that aims to compensate individuals for harms they suffer from exposure to hazardous substances. To successfully bring a toxic tort claim, a plaintiff must prove the main elements of a general tort cause of action: duty, breach, causation, and damages. Causation in a toxic tort case is particularly challenging to prove given the nature of toxic substances. To prove the toxicant in question caused the damages alleged, plaintiffs often present expert testimony based on scientific studies. Animal model studies, in particular, can help factfinders understand the health implications of the toxicants at issue. However, judges, scholars, and other legal professionals are skeptical of the use of animal studies because of scientific and legal concerns, which range from interspecies disparities to prejudice of juries. These concerns are either unfounded or exaggerated. Animal model studies can be both reliable and relevant in toxic tort cases. Given the Federal Rules of Evidence, case law relevant to scientific evidence, and one of the goals of tort law—justice—judges should more readily admit these types of studies as evidence to help plaintiffs meet the burden of proof in toxic tort litigation.*

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## INTRODUCTION

Toxic torts is a powerful area of law that provides injured parties with an opportunity to recover monetary damages from disease, deformity, or death suffered by themselves or loved ones. These injuries result from exposure to substances (for example, pregnancy medications, herbicides, dielectric fluids) produced, processed, distributed, or otherwise controlled by another party. Often, the party is the toxicant's manufacturer but may also include safety equipment manufacturers, chemical or equipment distributors, or owners and lessors of a premises where the exposure occurred.

In all tort cases, the plaintiff bears the burden of proving the defendant caused the harm. In toxic tort cases, proving the substance in question more likely than not injured the plaintiff is challenging. Scientific evidence plays a key role in establishing the cause of an injury. The most common forms of scientific evidence in toxic tort cases are human clinical trials, epidemiological studies, chemical structure-biological activity studies, and animal model studies. The causation hurdle is heightened by judges' continued skepticism of a key form of scientific evidence: animal model studies.

Animal studies provide abundant information about toxic substances and can help us understand how those substances affect humans. Researchers use animal model studies—a type of controlled, experimental study—to make inferences about a substance's adverse effects on humans. Researchers also use animal studies to

understand basic anatomy and physiology, explore the impacts of environmental stressors, and test experimental treatments. Understanding human health through translational research using animal models is beneficial because experimentation involving animals is often more efficient (in both time and resources) than conducting human experiments or employing other forms of toxicity research, like epidemiological studies. And although there are ethical constraints, they are few compared to the ethical concerns arising in human experimentation studies. Importantly, these benefits do not come at the expense of result accuracy or translational capability, as skeptics suggest.

Skeptics of animal model studies articulate various scientific and legal concerns about this type of research, especially when it is used in the context of litigation. Some scientific concerns are interspecies disparities, artificial selection, and interpretation biases, which skeptics argue reduce the validity of the studies' results because the science is invalid; therefore, the animal studies should be inadmissible. Critics also argue that animal studies can unfairly prejudice, confuse, or mislead the jury, as well as waste time by needlessly presenting cumulative evidence. These critiques are unfounded and exaggerated. Critics misunderstand the science and overstate the limitations of the animal studies. The Federal Rules of Evidence, relevant case law, and foundational principles of tort law do not support the outright exclusion of animal studies in toxic tort cases. Yet courts frequently exclude animal studies for reasons that seemingly amount to an overall misunderstanding about how animal studies are conducted and interpreted, and an inherent bias against their relevance and reliability.<sup>1</sup>

Part I of this Article outlines the basic elements of a torts case and includes the specific causation challenges in toxic torts to illustrate where animal studies could

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1. See, e.g., *Brock v. Merrell Dow Pharm., Inc.*, 874 F.2d 307, 314 (5th Cir. 1989) (“... the very limited usefulness of animals studies when confronted with questions of toxicity.”); *In re Zolof (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 475 (E.D. Pa. 2014) (“... causation opinions based primarily upon *in vitro* and live animal studies are unreliable and do not meet the *Daubert* standard.”); *Sarkees v. E.I. DuPont de Nemours & Co.*, 2020 U.S. Dist. LEXIS 174889 (W.D. N.Y. Aug. 21, 2020) (granting in full defendant’s motion for summary judgment, disagreeing with the Report and Recommendation that “precise information concerning the exposure necessary to cause specific harm to humans and exact details pertaining to the plaintiff’s exposure are beneficial, such evidence is not always available, or necessary, to demonstrate that a substance is toxic to humans given substantial exposure” (quoting *Westberry v. Gislaved Gummi AB*, 178 F.3d 257 (4th Cir. 1999)) and that “some [animal] studies have showed stronger results than others, but the overall body of literature for several decades has tended in the direction of showing a statistically significantly higher incidence of tumors, bladder cancer, or other cancers for animals exposed to [the substance at issue.]”); *Pinares v. United Tech. Corp.*, 2019 U.S. Dist. LEXIS 230033 (S.D. Fla. Oct. 3, 2019) (only briefly stating in a footnote: “The animal studies relied upon by [the expert] are insufficient to show an association . . .”); *Pinares v. United Tech. Corp.*, 2019 U.S. Dist. LEXIS 230034 (S.D. Fla. Oct. 3, 2019) (only briefly stating in a footnote: “. . . [the experts] reliance on animal studies are insufficient to show causation.”); *In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1310 (N.D. Fla., Mar. 15, 2018) (stating that animal studies can support general causation opinions if the expert explains how and why the studies can be reliably extrapolated); *Martin v. Crown Equip. Corp.*, 2016 U.S. Dist. LEXIS 195737 (N.D. Ga. Jan. 5, 2016).

play an important role. Part II explains the role of scientific evidence in tort cases. The Article articulates the past and current principles of scientific evidence admissibility to help demonstrate the theories judges use (mostly inappropriately) to deem scientific studies, particularly animal model studies, inadmissible. Part III provides examples of other scientific studies available to prove causation before delving deeper into the practice of animal model studies. Part IV then explores skeptics' scientific and legal concerns about the use of animal model studies as evidence in litigation and refutes those concerns. This Article concludes by urging an expansion of animal study admissibility to aid plaintiffs in proving causation in toxic tort litigation. Animal model studies should be more readily admitted as part of a weight-of-the-evidence methodology (weighing of all available evidence to determine believability or persuasiveness of a given position) to prove causation in toxic tort cases because their inclusion is scientifically valid, legally permissible, and just.

## I. TOXIC TORTS

### A. BASICS OF A TOXIC TORT CASE

Torts provides relief to individuals who have suffered a loss within the scope of a legally recognized interest.<sup>2</sup> One of the foundations of tort law is justice; torts strives to make matters right and restore the person wronged to the condition they were in before the wrongdoing by way of monetary compensation.<sup>3</sup> Torts differs from other bodies of law, like criminal law, because tort law protects private interests, and actions are brought by individuals instead of by the government.<sup>4</sup>

A toxic tort arises out of exposure to chemical substances, emissions, or products that have allegedly caused physical or psychological harm.<sup>5</sup> Exposures to harmful or hazardous toxicants come in many forms, including consumer products, materials in the workplace, and discharges into the environment. For example, asbestos, a known carcinogen, was found in Johnson & Johnson baby powder. Use of the baby powder and other talc-based products was linked to thousands of reports of mesothelium mesothelioma and ovarian cancer.<sup>6</sup> In another prominent example, General Electric employees working with dielectric and coolant fluids were exposed to polychlorinated biphenyls, a proven animal—and probable human—carcinogen.<sup>7</sup> As recounted in Jonathan Harr's book, *A Civil*

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2. PAGE KEETON & WILLIAM L. PROSSER, PROSSER AND KEETON ON THE LAW OF TORTS 5–6 (W. Page Keeton ed., 5th ed. 1984); KAREN GOTTLIEB, 1 TOXIC TORTS PRAC GUIDE § 2:1 (2019).

3. See generally DAVID G. OWEN, THE PHILOSOPHICAL FOUNDATIONS OF TORT LAW (David G. Owen ed., 1997).

4. See KEETON & PROSSER, *supra* note 2, at 5.

5. KAREN GOTTLIEB, 1 TOXIC TORTS PRAC GUIDE § 2:1 (2019).

6. See, e.g., Tiffany Hsu & Roni Caryn Rabin, *Johnson & Johnson Recalls Baby Powder Over Asbestos Worry*, N.Y. TIMES, Oct. 18, 2019.

7. See, e.g., *Gen. Elec. Co. v. Joiner*, 522 U.S. 136 (1997).

*Action*, tanneries in Massachusetts contaminated a water supply through improper disposal of toxicants, especially trichloroethylene (also a known human carcinogen), that led to cancer and death of local children.<sup>8</sup> The examples are many and often heartbreaking.

Toxic torts often raise issues of environmental justice. Landfills, incinerators, polluting industries, and hazardous waste disposal sites are often zoned in predominantly poor, minority communities.<sup>9</sup> These communities bear the health, safety, and economic risks associated with residing next to and working in these industries and facilities while society reaps the benefits of the disposal and production services.<sup>10</sup> For example, a report from the late 1980s found that even in the same income bracket, sixty-eight percent of Black children had lead poisoning, compared to thirty-six percent for white children.<sup>11</sup> The rates were lower but still differed by race in higher income ranges as well.<sup>12</sup> A recent study found that even though there has been an overall decrease in child blood lead levels in the past thirty years, there still exists a disparity in the rates of lead exposure for immigrant children, low-income families, and children of ethnic and racial minorities.<sup>13</sup> These patterns are found throughout the field of toxic torts where minority and lower income communities are more likely to be exposed to toxicants, have less access to adequate health care to help navigate toxic harms, and can struggle to find and afford legal representation. Limiting the types of scientific evidence toxic tort plaintiffs can rely on exacerbates this disparity.

Several local, state, and federal laws work to limit our exposure to toxic substances, but common law tort actions still have an important role to play.<sup>14</sup> Although other regimes (usually regulatory) seek to prevent harm from hazardous and harmful substances, sometimes these regimes fail and exposures to these substances result in injury, illness, or death. Pre-market laws, like the Federal Food, Drug, and Cosmetic Act, attempt to identify and remove risks from products before they enter commerce and materialize into harm.<sup>15</sup> Some statutes regulate the distribution and use of toxic or hazardous substances. For example, the

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8. See, e.g., JONATHAN HARR, *A CIVIL ACTION* (1995).

9. See, e.g., Jon C. Dubin, *From Junkyards to Gentrification: Explicating a Right to Protective Zoning in Low-Income Communities of Color*, 77 MINN. L. REV. 739 (1993); Peter L. Reich, *Greening the Ghetto: A Theory of Environmental Race Discrimination*, 41 U. KAN. L. REV. 271 (1992).

10. Dubin, *supra* note 9; Reich, *supra* note 9.

11. AGENCY FOR TOXIC SUBSTANCES DISEASE REGISTRY, U.S. DEP'T OF HEALTH AND HUMAN RESOURCES, *THE NATURE AND EXTENT OF LEAD POISONING IN CHILDREN IN THE UNITED STATES: A REPORT TO CONGRESS 1-12* (1988).

12. *Id.*

13. M. Hauptman, R. Bruccoleri & A.D. Woolf, *An Update on Childhood Lead Poisoning*, 18 CLINICAL PEDIATRIC EMERGENCY MED. 181 (2017).

14. Mark P. Nevitt & Robert V. Percival, *Can Environmental Law Solve the "Forever Chemical" Problem?* 57 WAKE FOREST L. REV. (forthcoming 2022), <https://perma.cc/ZEN6-3UJC> (discussing how tort litigation for PFAS has been an important way to both fund research on PFAS and get any controls on the substance).

15. 21 U.S.C. §§ 301-399.

Federal Insecticide, Fungicide, and Rodenticide Act governs the registration and application of pesticides to ensure they will not cause unreasonable risk to human health or the environment.<sup>16</sup> Post-market laws seek to ensure products are not stored or disposed of in a way that they can become harmful.<sup>17</sup> For example, the Comprehensive Environmental Response, Compensation, and Liability Act instructs the removal and remedial actions in response to releases or threatened releases of hazardous substances into the environment.<sup>18</sup> However, even if individuals are able to bring successful claims for failure of these laws to protect them from harm, recourse usually involves remedial actions to prevent future harm from occurring—not restoration of the injured party to the condition they were in before the wrongdoing. So, even in this relatively well-regulated area, tort law plays an important role as a potential route to receive compensation for harms suffered.

Toxic tort cases begin when a person (or persons) believes they were exposed to some substance that has caused an injury or illness. The affected person files a complaint alleging facts showing that each element of a tort claim has been met. That is, they must show (1) the defendant owed the plaintiff a duty to not cause injury, (2) the defendant breached that duty, (3) the plaintiff is suffering an actual injury, and (4) there is a causal link between the defendant's breach of duty and the injury or illness alleged.<sup>19</sup>

The plaintiff in a tort case has the burden of producing evidence, called the burden of production.<sup>20</sup> She must present her legal theory and provide sufficient evidence to support that theory, which includes meeting all aforesaid elements.<sup>21</sup> The plaintiff also has the burden of persuasion, which means she not only has to produce evidence to support her theory, but that evidence must show more likely than not that her claims are true.<sup>22</sup> This evidentiary standard is called preponderance of the evidence.<sup>23</sup> The most challenging element to prove is causation, and this element is where animal studies can be of great importance.

#### B. THE CAUSATION HURDLE IN TOXIC TORTS

Plaintiffs must demonstrate two types of causation: general and specific.<sup>24</sup> General causation addresses whether products of the same nature as the

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16. 7 U.S.C. §§136–136y.

17. See CARL F. CRANOR, TOXIC TORTS: SCIENCE, LAW, AND THE POSSIBILITY OF JUSTICE 32 (Cambridge Univ. Press, 2d ed. 2016).

18. 42 U.S.C. §§ 9601–9675.

19. See FLEMING JAMES JR. & GEOFFREY C. HAZARD JR., CIVIL PROCEDURE 77 (2d ed. 1977).

20. *Id.* at 245.

21. *Id.* at 268.

22. See *id.* at 241.

23. *Id.* at 243.

24. CRANOR, *supra* note 17, at 38.

defendant's products can cause the type of injuries alleged.<sup>25</sup> For example, demonstrating that asbestos can cause cancer. Specific causation addresses whether the defendant's product more likely than not caused the plaintiff's injuries.<sup>26</sup> For example, whether the asbestos in Johnson & Johnson's baby powder caused a specific individual's cancer. General causation speaks to if the substance *can* cause the injury the plaintiff is alleging, and specific causation speaks to if the substance *did* cause the injury to *this* plaintiff. This type of bifurcated analysis is not required in other types of cases where causes and mechanisms of harm are usually more apparent. For instance, a truck speeding down a highway can cause damage (general causation). The resulting collision with another car (specific causation) is often more evident than the mechanisms of substance exposure and toxicity in toxic tort cases.<sup>27</sup>

Unlike negligence, libel, or trespass, which can be demonstrated in a somewhat more straightforward manner (a totaled car, a defamatory Facebook post, or security camera footage of a stranger on the property of another), toxic tort cases almost always rely on the compilation of comprehensive, technical, inferential, timely, and costly science.

Properties of toxic substances, mechanisms of toxicity, and the research complications they create make proving causation, particularly specific causation, more challenging than in other types of tort cases. Carcinogens, developmental toxicants, reproductive toxicants, and neurotoxicants make up a majority of the substances at issue in these cases, specifically asbestos, pesticides, dioxins, and pharmaceuticals.<sup>28</sup> For example, the drug Thalidomide was widely used in the 1950s and early 1960s as an antinausea treatment for pregnant women, but was later discovered to cause birth defects in their babies—primarily limb reduction anomalies, but also congenital heart disease, ear malformations, and ocular abnormalities.<sup>29</sup>

Proving that these substances are in fact toxic and caused the injuries alleged is challenging for multiple reasons.<sup>30</sup> Toxicants at issue in these cases often have long latency periods, meaning there is a long time between exposure, the start of

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25. *Heller v. Shaw Indus., Inc.*, No. Civ. A. 95-7657, 1997 WL 535163, at \*6 (E.D. Pa. Aug. 18, 1997).

26. *Id.*

27. CRANOR, *supra* note 17, at 38.

28. *Causation in Environmental Law: Lessons from Toxic Torts*, 128 HARV. L. REV. 2256, 2258–59 (2015); *see, e.g.*, *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993).

29. James H. Kim & Anthony R. Scialli, *Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease*, 122 TOXICOLOGICAL SCI. 1 (2011).

30. *See* Erin K.L. Mahaney, *Assessing the Fitness of Novel Scientific Evidence in the Post-Daubert Era: Pesticide Exposure Cases as a Paradigm for Determining Admissibility*, 26 ENV'T L. 1161, 1176 (1996); *see generally* Jean Macchiaroli Eggen, *Toxic Torts, Causation, and Scientific Evidence after Daubert*, 55 U. PITT. L. REV. 889, 896 (1994); Jeffrey D. Cutler, *Implications of Strict Scrutiny of Scientific Evidence: Does Daubert Deal a Death Blow to Toxic Tort Plaintiffs?*, 10 J. ENV'T L. & LITIG. 189, 198 (1995).



the illness, and development of clinical signs and symptoms.<sup>31</sup> These substances also do not always have signature effects, meaning the effects of the illness caused by the substance may be identical to effects of other illnesses caused by other substances or hereditary diseases.<sup>32</sup> A primary example is a person that develops small-cell lung cancer after having been a life-long smoker and having worked with polychlorinated biphenyls (PCBs), furans, dioxins, and other carcinogens.<sup>33</sup> Specific causation is challenging in these cases because it is nearly impossible to trace the lung cancer back to its true origin: cigarettes or PCBs. Even if it could be traced back to cigarettes, the plaintiff would, in many cases, still need to show that it was specifically the defendant's cigarettes that caused the cancer and not those of another company.<sup>34</sup>

Uncertainty about the mechanisms of transmission and harm of the substances in these cases makes it difficult to prove how much and through what mode of exposure the substance came in contact with the plaintiff (ingestion of a pharmaceutical drug, inhalation of toxic fumes, dermal absorption from hands-on work with hazardous liquids, etc.).<sup>35</sup> Further, once inside the plaintiff, the actual mechanism of toxicity might not be known.<sup>36</sup>

There are logistical research and diagnostic obstacles to proving causation in toxic tort cases as well. First, often there are limited—if any—studies on a particular substance or its components at the time of trial. For example, historians point out that the hazards of smoking cigarettes were common knowledge, even before there was scientific proof to substantiate the claims. This was in part because of the observed correlation between increased rates of lung cancer (a previously rare disease, estimated to be less than one percent of all cancers diagnosed in the nineteenth century)<sup>37</sup> and increased cigarette smoking (per capita consumption rose from 747 cigarettes per year in 1920 to 3,908 in 1960).<sup>38</sup> But common knowledge is not enough; if someone wanted to file a claim in the early 1950s and 1960s against a cigarette manufacturer for smoking-related health issues, their case would likely have been dismissed or the outcome have been in favor of the defendant because of a lack of sufficient scientific evidence demonstrating that

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31. CRANOR, *supra* note 17, at 92.

32. *Id.*

33. *See, e.g., Joiner*, 522 U.S. 136.

34. Unless a market share liability theory is employed. This legal doctrine permits the plaintiff to join multiple defendants that make up a substantial share of the market to apportion damages according to their market contribution at the time of the plaintiff's exposure. *See generally* David A. Fischer, *Products Liability—An Analysis of Market Share Liability—Introduction*, 34 VAND. L. REV. 1623 (1981).

35. CRANOR, *supra* note 17, at 92.

36. *Id.*

37. Otis W. Brawley, Thomas J. Glynn, Fadlo R. Khuri, Richard C. Wender & John R. Seffrin, *The First Surgeon General's Report on Smoking and Health: The 50th Anniversary*, 64 CA: A CANCER J. CLINICIANS 5 (2014).

38. ECON. RES. SERV., U.S. DEP'T OF AGRIC. CIGARETTE CONSUMPTION, UNITED STATES, 1900–2007 TOBACCO OUTLOOK REPORT (2007).



smoking causes cancer and other respiratory problems.<sup>39</sup> An example of this scenario is *Lartigue v. R.J. Reynolds Tobacco Company*, a Fifth Circuit case from 1963 in which the plaintiff's husband died of lung cancer.<sup>40</sup> She tried to prove causation through all existing scientific evidence, including animal experiments.<sup>41</sup> The jury, however, decided that the plaintiff had failed to prove the causation between her husband's smoking and his lung cancer; the defense's evidence, it felt, made a more convincing case for the lack of any causal connection between smoking and cancer.<sup>42</sup> The court upheld this decision stating that "the tobacco companies cannot be held liable for negligence on the basis of medical studies yet to be published."<sup>43</sup>

Second, plaintiffs are not likely to have the resources to conduct their own studies, and even if they do, defendants often put up roadblocks. One study found that the cost of the earliest phase of a clinical trial starts at over \$1 million.<sup>44</sup> When funding is available, defendants may refuse to provide samples or data. And even where evidence already exists, plaintiffs may have difficulty accessing it. Manufacturers, processors, and distributors often withhold information, research, or samples. For example, the makeup, methods, and results of vaccine development and testing are often considered proprietary information and therefore do not have to be shared or made public.<sup>45</sup>

Third, theories and methods to study the substance and/or pathology of a disease may be nonexistent or only in their infancy at the time of trial. For example, the creation of toxicity profiles for all pharmaceuticals did not begin until well after pregnant women taking the prescription drug Thalidomide began giving birth to babies with shortened or missing limbs, so initially there were limited ways to deduce the pathology of the congenital malformations.<sup>46</sup>

Fourth, the nature of some illnesses makes it hard for experts to make any definitive statement about causation. For example, a physician would not be able to conclude that a plaintiff's cancer was caused by cigarettes, some other substance, genetics, or is simply idiopathic.<sup>47</sup> This limitation is especially true for vulnerable populations where individuals are likely exposed to greater environmental

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39. See Robert N. Proctor, "Everyone Knew But No One Had Proof": Tobacco Industry Use of Medical History Expertise in US Courts, 1990–2002, 15 (Suppl IV) *TOBACCO CONTROL* iv117 (2006).

40. *Lartigue v. R. J. Reynolds Tobacco Co.*, 317 F.2d 19, 22 (5th Cir. 1963).

41. *Id.*

42. *Id.* at 23.

43. *Id.* at 41.

44. Aylin Sertkaya, Hui-Hsing Wong, Amber Jessup & Trinidad Beleche, *Key Cost Drivers of Pharmaceutical Clinical Trials in The United States*, 13 *CLINICAL TRIALS* 117 (2016).

45. See, e.g., Matthew Herder, Todd F. Hatchette, Scott A. Halperin & Joanne M. Langley, *Against Vaccine Assay Secrecy*, 11 *HUMAN VACCINES & IMMUNOTHERAPEUTICS* 498 (2015).

46. S. Parasuraman, *Toxicological Screening*, 2 *J. PHARMACOLOGY & PHARMACOTHERAPEUTICS* 74, 75 (2011).

47. See e.g., Julia Peebles, *Plaintiffs with Hopeless Causes: Idiopathic Causes in Toxic Tort Litigation—Analyzing How Courts Address Scientific Uncertainty*, *HOUS. J. HEALTH L. & POL'Y: HEALTH L. PERSPS.* (2018).

hazards in their neighborhood, jobs, and food. A plaintiff's ability to prove causation diminishes as alternative causal explanations are uncovered, meaning that the people most exposed to toxics may be the least able to get relief.<sup>48</sup>

Fifth, scientific research to sufficiently prove causation may outlast the trial. For example, Bendectin, an anti-nausea medication prescribed to pregnant women, caused a slew of birth defects (hence its nickname "The Second Thalidomide").<sup>49</sup> The drug was first introduced in the late 1950s. Some studies assessing the teratogenicity of Bendectin lasted from the 1970s through the 1990s.<sup>50</sup> The median processing time from filing to verdict or judgment in tort trials is estimated to be about two years.<sup>51</sup> This problem is compounded by statutes of limitations that range from one to six years from the manifestation of disease or injury, meaning plaintiffs have a limited timeframe to file a claim. Thus, plaintiffs often cannot wait for the conclusion of research that would bolster their allegations.<sup>52</sup>

These research and diagnostic obstacles make proving causation in toxic tort litigation particularly challenging.

## II. ADMISSIBILITY OF SCIENTIFIC EVIDENCE

Before evidence is presented to a jury, a judge must deem it admissible. Admissibility is the most challenging hurdle for scientific evidence and expert testimony aiming to demonstrate causation. Perhaps surprisingly, scientific evidence and reports are not themselves presented to the judge and jury. Instead, expert witnesses testify about scientific evidence. The admissibility determinations focus on what the expert witness is allowed to testify about.<sup>53</sup>

Regular witness testimony is the retelling of an event that the individual had firsthand knowledge of and observed.<sup>54</sup> Expert testimony, on the other hand, is

48. Allan Kanner, *Environmental Justice, Torts and Causation*, 34 WASHBURN L.J. 505, 511 (1995).

49. Jeffrey S Kutcher, Arnold Engle, Jacqueline Firth & Steven H. Lamm, *Bendectin and Birth Defects II: Ecological Analyses*, 67 BIRTH DEFECTS RESEARCH PART A: CLINICAL AND MOLECULAR TERATOLOGY 88 (2003).

50. See generally *id.*

51. THOMAS H COHEN, TORT BENCH AND JURY TRIALS IN STATE COURTS 2005 at 9 (U.S. Dep't of Just. 2009), <https://perma.cc/Y565-GDWX>.

52. See, e.g., ALA. CODE § 6-5-502(b); MINN. STAT. ANN. § 541.05.

53. See *In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. at 1305 (quoting *Hendrix v. Evenflo Co.*, 255 F.R.D. 568, 585 (N.D. Fla. 2009) ("The qualifications standard for expert testimony is 'not stringent' and '[s]o long as the witness is minimally qualified, objections to the level of [his] expertise [go] to credibility and weight, not admissibility.'")); *K.E. v. GlaxoSmithKline LLC*, 2017 U.S. Dist. LEXIS 13705, 2017 WL 440242, at \*30 (D. Conn. Feb. 1, 2017) ("of course, the fact that [the expert] is qualified to offer opinions does not mean that the opinions he offers are admissible."); *cf. Trilink Saw Chain, LLC v. Blount, Inc.*, 583 F. Supp. 2d 1293, 1304 (N.D. Ga. 2008) (citing *Lappe v. Am. Honda Motor Co.*, 857 F. Supp. 222, 227 (N.D.N.Y. 1994) ("However, a witness may not qualify—through reading and preparation—as an expert in an entirely different field or discipline. Instead, he must stay within the reasonable confines of his subject area.")).

54. FED. R. EVID. 602 (citing *McCormick* §10, p. 19).

testimony based on opinions from facts. To be considered an expert, the individual must have knowledge, skill, experience, training, or education in a scientific, technical, or other specialized area beyond that of the average person, that will aid the trier of fact in understanding the evidence or determining a fact at issue in the case.<sup>55</sup> Plaintiffs rely on expert witness testimony to demonstrate both general and specific causation.<sup>56</sup> In toxic tort cases, this reliance means the expert might testify to the ability of the toxic substance at issue to cause the injuries alleged by the plaintiff (general causation), or the actual exposure of the plaintiff to the substance resulting in the injury/illness (specific causation).

Parties usually challenge the admissibility of the opposing party's expert testimony. The judge determines if the evidence may be presented to the jury (or considered by the judge in a bench trial). Exclusion of scientific evidence can lead to termination of a case, leaving the plaintiff with no recourse for the harms suffered. Therefore, examining the process whereby judges, mostly untrained in any scientific or technical field, decide what scientific evidence to admit is vital. The guiding principles of these determinations are rooted in case law and codified in Rule 702 of the Federal Rules of Evidence. Therefore, studying the Federal Rules is also likely to give us a good understanding of the rules and interpretations employed in state courts.

For most of the twentieth century, expert testimony was admitted if (1) the expert was qualified, (2) the testimony was relevant to the issue, (3) the testimony would assist the jury, and (4) the methodology was not based on "novel" techniques or technology.<sup>57</sup> Admitted testimony went before the jury and adversarial features of litigation (for example, cross-examination) would help the jury decide how to weigh the various pieces of evidence.<sup>58</sup> The battle for many plaintiffs is not trying to convince the jury that its evidence is more persuasive (although that of course is not a trivial conversation), but trying to convince the judge that the jury should be able to hear the evidence.

In 1923, the D.C. Circuit in *Frye v. United States* articulated what would be coined the "*Frye* standard": the materials (studies, methods, techniques, technologies, etc.) that expert testimony relies on must be "sufficiently established to have gained general acceptance in the particular field in which it belongs."<sup>59</sup> This test was easy to administer because it only required that a person be "skilled in [the] particular science, art, or trade to which the question relates . . ." to be considered an expert, and the testimony not be informed by "novel" techniques or

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55. FED. R. EVID. 702.

56. Of course, provided all requirements are satisfied: the expert is qualified, the testimony has scientific basis, the testimony is relevant, and the testimony assists the jury.

57. See *Frye v. United States*, 293 F. 1013, 1014 (D.C. Cir. 1923).

58. CRANOR, *supra* note 17, at 40; see *Frye*, 293 F. at 1014.

59. *Frye*, 293 F. at 1014. (excluding expert testimony based on a precursor to the lie detector test, a "systolic blood pressure detection test," that was new at the time of trial).

technology.<sup>60</sup> The terms “sufficiently established” and “novel” were not defined by the court. Rather, the court stated that “when a scientific principle or discovery crosses the line between the experimental and demonstrable stages is difficult to define. Somewhere in this twilight zone the evidential force of the principle must be recognized . . .”<sup>61</sup>

The *Frye* test, though easy to administer, posed many problems. First, it was underinclusive regarding certain prongs. It essentially prohibited cutting edge methodologies or technologies by requiring some unknown amount of time for the method or technique to become “generally accepted.” Second, the test was too malleable because the “relevant field” could be defined in myriad ways for every expert, making the test either too generous or too strict depending on the judge’s interpretation of the field.

Despite its shortcomings, the *Frye* standard governed for many years and was mostly unquestioned until 1983. In that year, the Supreme Court issued its opinion in *Barefoot v. Estelle*.<sup>62</sup> The Court upheld the admissibility of the expert testimony, even with opposition from other experts in the relevant field (the American Psychiatric Association disagreed with the methodology used to examine the defendant)<sup>63</sup> and an acknowledgement that the testimony was somewhat unreliable.<sup>64</sup> The Court dismissed the argument that the jury should not have heard the evidence, stating that “the rules of evidence generally extant at federal and state levels anticipate that relevant, unprivileged evidence should be admitted and its weight left to the factfinder, who would have the benefit of cross-examination and contrary evidence by the opposing party.”<sup>65</sup> This ruling highlights the laxness of admissibility under *Frye* by overlooking the role of the judge and relying on other trial mechanisms to assist in evidentiary determinations.<sup>66</sup>

Seventy years after *Frye* came the Supreme Court case *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, which set a new standard for admissibility of expert testimony.<sup>67</sup> The parents of two children born with limb malformations sued Merrell Dow, alleging its product, an antinausea drug called Bendectin taken by the mothers while pregnant, was responsible for the congenital abnormalities.<sup>68</sup> The plaintiffs’ experts were going to testify that the drug could cause birth defects based on in vitro studies, animal model studies, chemical structure-biological

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60. *Id.*; see D.L. FAIGMAN ET AL., MODERN SCIENTIFIC EVIDENCE: THE LAW AND SCIENCE OF EXPERT TESTIMONY (2002).

61. *Frye*, 293 F. at 1014.

62. *Barefoot v. Estelle*, 463 U.S. 880, 899–901 (1983).

63. Brief for the American Psychiatric Association as Amicus Curiae, *Barefoot v. Estelle*, 463 U.S. 880, 899–901 (1983) (APA disagreed with the practice of using hypothetical questions, rather than in-depth psychiatric examination of a defendant, to predict likelihood of long-term future dangerousness).

64. *Barefoot*, 463 U.S. at 899–901.

65. *Id.* at 898.

66. *Id.*

67. *Daubert*, 509 U.S. at 579.

68. *Id.* at 582.

activity studies,<sup>69</sup> and reanalysis of published epidemiological studies.<sup>70</sup> However, the trial court judge considered the “vast body” of epidemiological studies on Bendectin that did not find a statistically significant association between the drug and birth defects and determined that the plaintiffs’ non-epidemiological studies were insufficient under the *Frye* general acceptance test. Therefore, the results of the non-epidemiological studies did not create a genuine issue of material fact.<sup>71</sup> Additionally, because the reanalysis of published epidemiological studies were not themselves published or subject to peer review, they were deemed unreliable and therefore inadmissible to establish causation.<sup>72</sup> Relying on *Frye*, the Ninth Circuit affirmed.<sup>73</sup>

When the Supreme Court considered the case, it considered Federal Rules of Evidence 702 (enacted in 1975, post-*Frye*), which provided:

If scientific, technical, or otherwise specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise.<sup>74</sup>

Rule 702 did not articulate a “general acceptability test” as in *Frye*, and it was unclear how these guiding principles would fit together until 1993 when the *Daubert* Court held that Rule 702 required scientific expert testimony to be admitted if “reliable and relevant.”<sup>75</sup>

Reliability is assessed by scientific validity. The *Daubert* Court offered five “general observations” to help trial judges assess reliability<sup>76</sup>:

- (1) whether the technique can be (and has been) tested;
- (2) whether it has been subjected to peer review and publication;
- (3) the known or potential rate of error;
- (4) the existence and maintenance of standards controlling the technique’s operation; and
- (5) general acceptance in the relevant scientific community

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69. Chemical structure-biological activity studies, or structure-activity relationship (SAR) analyses, assess the biological effects on organisms from certain chemical groups present in a compound to which the organisms are exposed. James D. McKinney, Ann Richard, Chris Waller, Michael C. Newman & Frank Gerberick, *The Practice of Structure Activity Relationships (SAR) in Toxicology*, 56 TOXICOLOGICAL SCI. 8, 8–17 (2000).

70. *Daubert*, 509 U.S. at 583.

71. *Id.*

72. *Id.*

73. *Id.* at 584.

74. Act of Jan. 2, 1975, Pub. L. No. 93-595, 88 Stat. 1937 (1975) (establishing the Federal Rules of Evidence).

75. *Daubert*, 509 U.S. at 589.

76. *Id.* at 593–94.

Justice Blackmun noted that these factors are not a “definitive checklist or test” but rather a “flexible” inquiry.<sup>77</sup>

Relevancy is assessed by determining whether the testimony would apply to the facts of the case.<sup>78</sup> The two prongs of a relevancy determination are whether the evidence is (1) probative (tends to prove or disprove a fact by making it more or less probable) and (2) material (bears on a fact of consequence in determining the action).<sup>79</sup>

This reliable and relevant approach was a course change from the “general acceptance” standard in *Frye*.<sup>80</sup> The goal of the Court in *Daubert* was to maintain the gatekeeping role of the trial judge by allowing judges to make preliminary determinations of relevancy and reliability but relax some of the traditional barriers to expert opinion testimony (that is, general acceptance), all while respecting the role of the jury to determine issues of fact.<sup>81</sup> This change was important and logical because, for example, experts could now rely on studies that employed new, cutting edge techniques and technologies. The Court highlighted the usefulness of the adversarial nature of litigation by noting “vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence.”<sup>82</sup>

Some courts (then and now) only allow evidence when it seems to definitively answer a specific question. Other courts are accepting of conflicting or less definitive evidence and agree to set it all before a jury to determine believability or persuasiveness of each piece of evidence—a weight-of-the-evidence-methodology.<sup>83</sup> Around the time the *Daubert* case began, another notable Bendectin case made its way through the courts. In *Oxendine v. Merrell Dow Pharmaceuticals*,

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77. *Id.*

78. *Id.* at 590–93.

79. FED. R. EVID. 401.

80. *Daubert*, 509 U.S. at 597–98.

81. CRANOR, *supra* note 17, at 50; *see Daubert*, 509 U.S. at 589 (“That the *Frye* test was displaced by the Rules of Evidence does not mean, however, that the Rules themselves place no limits on the admissibility of purportedly scientific evidence. Nor is the trial judge disabled from screening such evidence. To the contrary, under the Rules the trial judge must ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable.”).

82. *Daubert*, 509 U.S. at 596.

83. If using certain types of studies as part of the weight-of-the-evidence methodology, experts must identify an association between an exposure and a disease, consider a range of plausible explanations for the association, rank the rival explanations according to their plausibility, seek additional evidence to separate the more plausible from the less plausible explanations, consider all of the relevant available evidence, and integrate the evidence using professional judgment to come to a conclusion about the best explanation.

In re *Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp., at 1311; *see Milward v. Acuity Specialty Prods. Group*, 639 F.3d 11, 17–18 (1st Cir. 2011); *Jones v. Novartis Pharm. Corp.*, 235 F. Supp. 3d 1244, 1273 (N.D. Ala. 2017).



*Inc.*,<sup>84</sup> parents of a young girl born with a deformed hand and forearm sued Merrell Dow. At the first trial, Dr. Alan Done, the plaintiff's expert witness, testified that the antihistamine—doxylamine succinate—used in Bendectin had been shown to cause deformities through chemical structure-biological activity, animal model, in vitro, and epidemiological studies.<sup>85</sup> Dr. Done made clear that his opinion was not based on any one of the studies alone, but on all the studies put together taking a weight-of-the-evidence approach. However, the trial court did not subscribe to that logic.<sup>86</sup> Though the court granted the defendant's motion for judgment notwithstanding the verdict, the D.C. Court of Appeals reversed, stating that, "like the pieces of a mosaic, the individual studies showed little or nothing when viewed separately from one another, but they combined to produce a whole that was greater than the sum of its parts . . ."<sup>87</sup>

The *Oxendine* case went to the D.C. Court of Appeals three more times before the court found in favor of Merrell Dow after taking into account new Bendectin studies, the decisions of other Bendectin cases, and actions of the United States Food and Drug Administration ("FDA") and Canadian government.<sup>88</sup> Despite the eventual ruling, the *Oxendine* decision bodes well for scientific evidence because it is one of the first times a court supported the weight-of-the-evidence methodology when ruling on expert testimony admissibility, meaning the testimony may be sufficient when considered jointly with other evidence, even though it is insufficient to meet the requisite burden of proof on its own.<sup>89</sup> The court supporting a weight-of-the-evidence methodology in this case was an important step for scientific evidence admissibility in toxic tort litigation because it aligns the guiding principles of legal assessment of scientific studies with the assessment of scientific studies by scientists.<sup>90</sup> Scientists do not rely on one article or one experiment to draw conclusions. Instead, scientists consider many studies, reports, and experiments in formulating conclusions. As we would be skeptical of a scientist that only cited one paper, we should be nervous about a court that overly limits expert witness evidence.

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84. *Oxendine v. Merrell Dow Pharm.*, 506 A.2d 1100 (D.C. 1986).

85. *Id.* at 1104–08.

86. *Id.* at 1110 ("The trial court, however, granted appellee's motion for judgment notwithstanding the verdict on the ground that appellant's causation expert admitted in his testimony that each of the studies on which he relied could not, *by itself*, support a finding of causation. Where the court erred was in failing to consider the same expert's testimony that all of the studies, taken *in combination*, did support such a finding, as he carefully and repeatedly explained." (emphasis in original)).

87. *Id.*

88. SUSAN HAACK, EVIDENCE MATTERS: SCIENCE, PROOF, AND THE TRUTH IN LAW 211–12 (2014).

89. *Id.* at xxiii.

90. See, e.g., Glenn Suter, Susan Cormier & Mace Barron, *A Weight of Evidence Framework for Environmental Assessments: Inferring Qualities*, 13 INTEGRATED ENV'T ASSESSMENT & MGMT. 1038 (2017) (endorsing the synthesis and weighing of heterogenous evidence to determine, among other things, hazards posed by chemicals or other agents).



The second opinion in the *Daubert* trilogy is *General Electric v. Joiner*,<sup>91</sup> a toxic tort case where the Court excluded the plaintiff's expert witnesses, who were, in part, testifying to causation from animal studies. Joiner was an electrician often in contact with a dielectric fluid that contained chemicals banned less than ten years earlier, including polychlorinated biphenyls ("PCBs"), furans, dioxins, and other substances (some carcinogenic).<sup>92</sup> He alleged that his workplace exposure to these substances promoted his small-cell lung cancer.<sup>93</sup> His expert witness was going to rely on animal and epidemiological studies, but the district court excluded the testimony on the grounds that it did not rise above a "subjective belief or unsupported speculation,"<sup>94</sup> meaning it was not scientific knowledge as required under Rule 702. The Eleventh Circuit reversed and focused on determining the appropriate standard of review.<sup>95</sup> What is interesting for our purposes is how the Supreme Court subsequently regarded animal model studies. Unlike in *Daubert*, the Court discussed details of the evidence to justify upholding the district court's exclusion of animal testing.<sup>96</sup> The Court took this approach because it aimed to clarify the holding in *Daubert* that expert methodology should be the focus of the admissibility inquiry, not the conclusion.<sup>97</sup> But the Court also noted that "conclusions and methodology are not entirely distinct from one another" and that "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* [unsupported statement] of the expert."<sup>98</sup> It viewed differences between the mice in the study and the human plaintiff as significant and discrediting of the methodology (and the conclusion), based on the following points:<sup>99</sup>

- The models studied were infant mice while the plaintiff was an adult human.
- The substance at issue was injected directly into the stomachs of the mice while the plaintiff was exposed through skin contact and inhalation, and to a lesser extent, through contact with the eyes and mouth.
- The mice received a more concentrated dose compared to the plaintiff's exposure.

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91. *Joiner*, 522 U.S. 136.

92. *Id.* at 137–40.

93. *Id.* at 139–40.

94. *Id.* at 140.

95. The United States Supreme Court held that a court of appeals should not be applying a more stringent standard of review, no matter the outcome of the admissibility decision; an "abuse of discretion" review (whether the trial court judge abused her discretion in prohibiting the evidence) is the appropriate standard for evidentiary ruling. *Id.* at 141–42.

96. *Id.* at 145.

97. *Daubert*, 509 U.S. at 595; *Joiner*, 522 U.S. at 146.

98. *Joiner*, 522 U.S. at 146.

99. *Id.* at 144.

- The mice developed benign glandular tumors while the plaintiff developed carcinomas.

The Court did not say that animal studies can never be a proper foundation for an expert's opinion, but it did state, "a court may conclude that there is simply too great an analytical gap between the data and the opinion proffered," and in this case the dissimilarities (for example, species and exact tumor response) were too great to properly demonstrate causation.<sup>100</sup>

The third seminal opinion in the *Daubert* trilogy is a products liability case, *Kumho Tire v. Carmichael*.<sup>101</sup> The *Kumho Tire* Court held that the *Daubert* admissibility rules for scientific testimony also apply to expert testimony of other technical or specialized knowledge.<sup>102</sup> More importantly, the Court recognized that experts in the same field may disagree without rendering evidence inadmissible. As long as the expert opinion in question falls within the range of respectable disagreement, the testimony should be admitted and considered by the jury.<sup>103</sup> Additionally, the Court supported the liberal approach of admissibility first seen in *Daubert*: a departure from insistence on general acceptance in the relevant field, replaced with requirements of relevance and reliability.<sup>104</sup>

In sum, trial judges play a gatekeeping role but must embark on a searching review of proffered evidence.<sup>105</sup> A weight-of-the-evidence methodology may be considered.<sup>106</sup> And expert witnesses may disagree and still both be admitted, provided both their testimonies are based on permissible science.<sup>107</sup> Rule 702 was amended in 2000 to incorporate the principles of *Daubert*, *Joiner*, and *Kumho Tire*:

If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable

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100. *Id.* at 144–46.

101. *Kumho Tire Co. v. Carmichael*, 526 U.S. 137 (1999).

102. *Id.* at 147.

103. *See id.* at 153; *see also* *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 160 (3d Cir. 1999) (expert testimony cannot be excluded on the sole basis that another method exists, provided both tests are relatively equally accepted, and both reach reliable results).

104. *See Kumho Tire Co.*, 526 U.S. at 156.

105. *See Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1316 (9th Cir. 1995) ("Our responsibility, then, unless we badly misread the Supreme Court's opinion, is to resolve disputes among respected, well-credentialed scientists about matters squarely within their expertise, in areas where there is no scientific consensus as to what is and what is not 'good science,' and occasionally to reject such expert testimony because it was not 'derived by the scientific method.' Mindful of our position in the hierarchy of the federal judiciary, we take a deep breath and proceed with this heady task.").

106. *Oxendine*, 506 A.2d.

107. *Kumho Tire Co.*, 526 U.S. at 137.

principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.<sup>108</sup>

On paper, the new admissibility principles are more liberal and should result in a wider range of expert testimony in tort litigation. Novel techniques and technologies are no longer prohibited, and disagreement is no longer dispositive of unreliability.<sup>109</sup> However, judges retain some discretion regarding initial evidentiary rulings and are free to choose among permissible views of the evidence to determine admissibility. This discretion seems to have actually created stricter standards because judges, instead of admitting scientific evidence more liberally as expected, are more reserved in their admissibility determinations.<sup>110</sup>

Studies have found that judges are more likely to scrutinize and exclude expert testimony now than they were before *Daubert*.<sup>111</sup> After *Daubert* in 1993, civil plaintiffs, somewhat surprisingly, increased the rate at which they filed cases in state courts still adhering to the *Frye* standard.<sup>112</sup> When a *Frye* state changed to the admissibility standard used in federal courts (that is, to *Daubert*), plaintiffs' filing choices shifted again: the filing rate returned to the same general rate seen before other states adopted *Daubert*, which made the *Frye* state more favorable.<sup>113</sup> In other words, plaintiffs appear to prefer the *Frye* standard and will forum shop to take advantage of these expert testimony standards.<sup>114</sup> So even though *Daubert* does remove certain barriers of entry (for example, prohibition of novel techniques and technology), judges are, within their discretionary power, not admitting expert testimony more than they had under the *Frye* standard.

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108. FED. R. EVID. 702 (Advisory Committee Note on 2000 Amendments). The most recent version of FRE 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: (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; (b) the testimony is based on sufficient facts or data; (c) the testimony is the product of reliable principles and methods; and (d) the expert has reliably applied the principles and methods to the facts of the case."

109. CRANOR, *supra* note 17, at 55.

110. *Anderson v. City of Bessemer*, 470 U.S. 564, 574 (1985) ("Where there are two permissible views of the evidence, the factfinder's choice between them cannot be clearly erroneous"); *In re Paoli R. R. Yard PCB Litig.*, 35 F.3d 717, 744 (3d. Cir. 1994) (parties proffering expert witnesses "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 the evidence that their opinions are reliable . . . The evidentiary requirement of reliability is lower than the merits standard of correctness."); see, e.g., Andrew W. Jurs & Scott DeVito, *Et Tu, Plaintiffs? An Empirical Analysis of Daubert's Effect on Plaintiffs, and Why Gatekeeping Standards Matter (A Lot)*, 66 ARK. L. REV. 975, 977 (2013).

111. Carol Krafka, Meghan A. Dunn, Molly Treadway Johnson, Joe S. Cecil & Dean Miletich, *Judge and Attorney Experience, Practices, and Concerns Regarding Expert Testimony in Federal Civil trials*, 8 PSYCH., PUB. POL'Y, & L. 309 (2002); Lloyd Dixon & Brian Gill, *Changes in the Standards for Admitting Expert Evidence in Federal Civil Cases Since the Daubert Decision*, RAND INST. FOR CIV. JUST. (2001).

112. See Jurs & DeVito, *supra* note 111, at 976.

113. *Id.*

114. *Id.*; States currently still following *Frye* include California, Illinois, Maryland, New Jersey, New York, Pennsylvania, Washington, and Minnesota (*Frye*-hybrid).

Because admissibility rules after *Daubert* and related expert testimony cases are proving to be strict in practice, judges are often deeming scientific evidence, particularly animal model studies, inadmissible. Rule 702 does not appear to be the root of the problem, though. If admissibility rules required more evidence put before a jury, there is a risk that unreliable and irrelevant evidence could be presented. Conversely, if judges were given more judicial freedom, the current problem could be exacerbated. There is no perfect rule or foolproof method for distinguishing the scientific and reliable from the unscientific and unreliable;<sup>115</sup> there will always remain the requirement that, to some degree, judges make legal determinations about science. Familiarity with the studies and methods expert witnesses rely on—along with explanations of why concerns and skepticisms are unwarranted or misguided—will hopefully aid in making judges more comfortable with the use of scientific evidence, specifically animal model studies, as proof of causation in toxic tort litigation.

### III. SCIENTIFIC STUDIES USED TO MAKE CAUSAL CONNECTIONS

Given the characteristics of toxicants (for example, long latency periods, unknown mechanisms of toxicity, specific exposure requirements), plaintiffs usually rely on combinations of inferential and extrapolated science. A multitude of studies help researchers understand and infer causal properties of toxic substances. This section describes these studies and the benefits and shortcomings of each to highlight why animal model studies are an essential form of research as evidence in toxic tort litigation.

#### A. NON-ANIMAL STUDIES

Ideally, a plaintiff would be able to gather people of similar age, background, occupation, health, and lifestyle that she was at the time of her exposure, expose them to the exact same concentration of the substance in question via the exact same mode of exposure, and monitor disease progression over time to assess the effects of the substance. Obviously, this type of study is not possible. Instead, researchers use other types of studies to infer causal connections between substances and human harms. This inference is done through other methods of observational research and animal experimentation.

Clinical trials are the closest thing to a human dose-response experiment a researcher is likely to get.<sup>116</sup> In human clinical trials (for example, those used for prescription drug and vaccine testing), a large group of people are randomly assigned to an exposure or control group. They are then administered either a placebo or the drug being tested. Researchers then monitor the differences in effects

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115. Susan Haack, *An Epistemologist in the Bramble-Brush: At the Supreme Court with Mr. Joiner*, 26 J. HEALTH & POL. POL'Y & L. 217 (2001).

116. CRANOR, *supra* note 17, at 55.

between the groups. Clinical trials are commonly used for improving medical conditions. Researchers do not use them to test toxicants on people. Thus, the scientifically ideal types of studies for understanding how toxicants affect people are usually unavailable.

Epidemiological studies compare the health of different individuals exposed to the same substance.<sup>117</sup> There are three main types of epidemiological studies.<sup>118</sup> The first is a follow-up or cohort study in which a group exposed to a substance is compared to a group that has not been exposed.<sup>119</sup> For example, researchers studied the transport, deposition, and effects of radionucleotides following unintentional exposure from the Fukushima Daiichi Nuclear Power Plant accident.<sup>120</sup> Researchers monitored the exposed and nonexposed groups and compared the development and progression of any illnesses or other adverse effects.<sup>121</sup> The second type of epidemiological study is a case-control study in which researchers compare a group of individuals that have a given illness with an illness-free group and try to isolate factors or experiences that may have caused or contributed to the illness.<sup>122</sup> For example, when a cancer cluster is identified, researchers and doctors will try to find commonalities among those affected.<sup>123</sup> The third type is ecological or correlation studies in which researchers average exposure to a substance over a group and analyze the rates of illness and mortality.<sup>124</sup> For example, researchers and physicians wanting to know the effects of teen vaping may look at a population of young-adult vapers and assess the incidence of illness.<sup>125</sup>

All three types of epidemiological studies have limitations. First and foremost, all studies are nonexperimental, meaning the researcher has no control over the parameters of the study. They cannot control the mode or concentration of exposure, nor can they control the physical, mental, or occupational, characteristics of the individuals involved, all of which are factors that contribute to the results' reliability and evidentiary relevance.<sup>126</sup> This lack of control can also lead to the issue of confounding, which is a form of bias that occurs when the relationship with disease is skewed as a result of an association between the apparent causal factor and some other factor that is associated with either an increase or decrease

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117. KENNETH J. ROTHMAN, *MODERN EPIDEMIOLOGY* 51 (1st ed. 1986).

118. CRANOR, *supra* note 17, at 95.

119. *Id.*

120. See generally Abubakar Sadiq Aliyu, Nikolaos Evangelidou, Timothy Alexander Mousseau, Junwen Wu & Ahmad Termizi Ramli, *An Overview of Current Knowledge Concerning the Health and Environmental Consequences of the Fukushima Daiichi Nuclear Power Plant (FDNPP) Accident*, 85 *ENV'T INT'L* 213 (2015).

121. CRANOR, *supra* note 17, at 95.

122. *Id.*

123. See, e.g., HARR, *supra* note 8.

124. CRANOR, *supra* note 17, at 98.

125. See, e.g., Kathleen Raven, *Teen Vaping Linked to More Health Risks*, *YALE MED.* (2019).

126. See, e.g., *Joiner*, 522 U.S. at 146. One of plaintiff's epidemiological studies found a statistically significant increase in lung cancer deaths in a PCB-exposed group in Japan, but the study was excluded because the subjects of the study had also been exposed to other potential carcinogens.

in the incidence of the disease.<sup>127</sup> For example, it would seem likely that a smoker's lung cancer is the result of cigarette smoking, but it could also have been caused by long-term asbestos exposure in the workplace. Additionally, epidemiological studies often rely on follow-up and self-reporting, which pose problems of keeping track of individuals, maintaining participation, and recall bias (individuals over or underreport important factors like exposures and symptoms).<sup>128</sup>

Epidemiological studies can still be helpful in toxic tort cases. They can shed light on various aspects of toxicants and diseases that experimental studies might miss. A case-control study may reveal compounding factors (not to be confused with confounding factors)<sup>129</sup> that may have been overlooked in a research design. For example, studies of Thalidomide showed a greater likelihood of birth defects if taken in the mother's first trimester.<sup>130</sup> An experimental study may not have been designed to include women (or enough women) of all pregnancy stages, which may have resulted in missing this detail. And a cohort, or follow-up study, may reveal later-in-life effects not considered and unknown at birth or in early life stages.<sup>131</sup> An experimental study may not have been designed to include potential long-term effects.

The problem with epidemiological studies, in the legal context, is that they cannot predict the way an individual will respond to a given substance (that is, specific causation). The most help these types of studies can provide is an estimated probability of the risk of a given response following some level of exposure; these types of results are usually not enough to demonstrate, more likely than not, that a toxicant caused an injury in a specific case.<sup>132</sup> Additional problems inherent in the methodology of most epidemiological studies are limited sample sizes, chance exposures, and biases.<sup>133</sup> However, despite these shortcomings, courts seem to favor epidemiological studies over most other forms of

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127. WORLD HEALTH ORG. INT'L AGENCY FOR RSCH. ON CANCER, IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISK TO HUMANS: PREAMBLE 9 (2006).

128. CRANOR, *supra* note 17, at 96.

129. A compounding factor is a factor that also plays a role in the results. A confounding factor is one that skews the apparent relationship between the disease and the disease-determining variable.

130. See Neil Vargesson, *Thalidomide-induced Teratogenesis: History and Mechanisms*, 105 BIRTH DEFECTS RES. (PART C) 140, 144 (2015).

131. *Id.* at 141.

132. Jack L. Landau & W. Hugh O'Riordan, *Of Mice and Men: The Admissibility of Animal Studies to Prove Causation in Toxic Tort Litigation*, 25 IDAHO L. REV. 521, 531 (1989); Eggen, *supra* note 30, at 896–97; see MICHAEL D. GREEN, D. MICHAL FREEDMAN & LEON GORDIS, REFERENCE GUIDE ON EPIDEMIOLOGY 552 (2011) (“... an association is not equivalent to causation.”), <https://perma.cc/CBL9-VRNJ>.

133. Cutler, *supra* note 30, at 200; Michael D. Green, *Expert Witnesses and Sufficiency of Evidence in Toxic Substances Litigation: The Legacy of Agent Orange and Bendectin Litigation*, 86 NW. U. L. REV. 643, 644, 699 (1992); Troyen A. Brennan, *Causal Chains and Statistical Links: The Role of Scientific Uncertainty in Hazardous-Substance Litigation*, 73 CORNELL L. REV. 469, 491, 507 (1988).



scientific evidence, likely because they are the easiest to understand and most reliable for the average person.<sup>134</sup>

A second key type of study used to help ascertain causal properties of toxic substances is a chemical structure-biological activity study (“SAR”). These studies make predictions about a substance’s effects on biological and other systems based on the substance’s chemical structure, solubility, stability, pH sensitivity, electrophilicity, volatility, and chemical reactivity,<sup>135</sup> working under the assumption that the effects of chemicals are implicit in their molecular structures (referred to as toxicophores when they are associated with toxic effects).<sup>136</sup> These types of studies are commonly used by regulators and industry to more readily identify the hazard potential of various products, often in conjunction with other methods of research.<sup>137</sup>

These studies assess the biological effects of chemical compounds based on individual molecular structures using data about similar compounds. So these types of studies might be only marginally probative in a case involving oil exposure, for example, where this type of assessment might miss the synergistic and antagonistic effects of the complex combination of many compounds found in petroleum.<sup>138</sup> Additionally, though in some cases these studies may present evidence for a chemical’s hazard potential, they rely heavily on assumptions and inferences and are based on a refined, technical understanding of molecular and chemical structures and properties, areas of science less readily understood by persons not trained in the sciences (importantly, judges and juries) than others. For example, the court in *Oxendine* pointed out the defendant’s and trial court’s flawed recollections (or understanding) of these studies.<sup>139</sup> The defendant and trial court maintained that if an expert cannot look at the chemical makeup of a substance, like a pharmaceutical drug, and know if it is teratogenic (relates to or causes developmental malformations), the study is not helpful as evidence.<sup>140</sup> However, structure-activity studies do not work that way. Instead, researchers

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134. See *In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. at 1306 (“A general causation opinion that is not supported by at least one of these primary methodologies [epidemiological studies, dose-response relationship, and background risk of disease] is unreliable as a matter of law.”); *Chapman v. P&G Distrib., LLC*, 766 F.3d 1296, 1308 (11th Cir., 2014) (“Because these experts have failed to demonstrate the primary methods . . . their secondary methodologies, including plausible explanations, generalized case reports, hypotheses, and animal studies are insufficient proof of general causation.”).

135. CRANOR, *supra* note 17, at 111.

136. INST. OF MED. AND NAT’L RES. COUNCIL OF THE NAT’L ACADEMIES, DIETARY SUPPLEMENTS: A FRAMEWORK FOR EVALUATING SAFETY 205–06 (2005), <https://perma.cc/9TPY-VC94>.

137. CRANOR, *supra* note 17, at 112.

138. Petroleum is often a mixture of aliphatic hydrocarbons; polycyclic aromatic hydrocarbons and their alkylated derivatives; resin compounds including heterocyclic hydrocarbons, phenols, acids, alcohols, and monoaromatic steroids; as well as components of the source organic matter like steranes and terpanes. Joseph M. Bayona, Carmen Domínguez & Joan Albaigés, *Analytical Developments for Oil Spill Fingerprinting*, 5 TRENDS IN ENV’T ANALYTICAL CHEM. 26–34 (2015).

139. *Oxendine*, 506 A.2d, at 1104–05.

140. *Id.*



look at individual components of a substance and their interactions with each other to make probability determinations about the potential hazards from exposure based on what is known about those specific interactions in similar substances. Structure-activity studies are also not intended to be relied on in this way. They are meant to contribute to a collection of studies where each provides some insight into the hazard potential of the substance at issue. From a strategy perspective, this type of study will likely never be proffered as evidence alone, hence the need for other forms of research, particularly animal model studies, to be admitted as part of a weight-of-the-evidence methodology.

#### B. ANIMAL MODEL STUDIES

There are many benefits to conducting animal model studies over human studies like clinical trials and epidemiological studies. First, concerns with confounding factors are limited for animal studies because researchers can have full control over the experimental animals and their environment.<sup>141</sup> Additionally, animal testing is more affordable, efficient, and comprehensive—usually because animals have shorter life expectancies and generation times and quicker life stage turnover rates than humans, allowing for quicker study completion and transgenerational research.<sup>142</sup> Animal studies are amenable to experimental design to assess toxicants when epidemiological studies are unavailable or inconclusive. They can be particularly helpful where juries are considering multiple studies under a weight-of-the-evidence theory.

Researchers often use animal model studies to make inferences about a substance's adverse effects on humans.<sup>143</sup> Traditional animal models are mammals like rats, mice, and primates,<sup>144</sup> but models sometimes include seemingly less related species, including fish.<sup>145</sup> Unlike epidemiological studies, animal studies are controlled experiments where researchers can dictate exposure concentrations

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141. CRANOR, *supra* note , at 106; Landau & O'Riordan, *supra* note 133, at 533; Amanda Hungerford, *Back to Basics: Courts' Treatment of Agency Animal Studies after Daubert*, 110 COLUM. L. REV. 70, 75 (2010).

142. See, e.g., Anjana S. Narayanan & Adrian Rothenfluh, *I Believe I Can Fly!: Use of Drosophila as a Model Organism in Neuropsychopharmacology Research*, 41 NEUROPSYCHOPHARMACOLOGY 1439 (2016) (*Drosophila*, an increasingly employed animal model, has a generation cycle of <2 weeks and gives rise to large numbers of genetically identical progeny, which makes them effective and efficient models for studies like genetic screens. For genetic screens, large populations of genetically diverse flies are screened for a particular phenotype, then mutant genes are isolated and characterized. This screening allows for a relatively speedy understanding of molecular pathways, including things like drug responses).

143. See Landau & O'Riordan, *supra* note 133, at 535–36.

144. *Id.* at 533.

145. Adam Michael Stewart, Oliver Braubach, Jan Spitsbergen, Robert Gerlai & Allan V. Kalueff, *Zebrafish Models for Translational Neuroscience Research: From Tank to Bedside*, 37 TRENDS IN NEUROSCIENCES 264 (2014) (assessed PubMed publications in December 2013 for various model organisms, yielding more than 532,000 publications for mice, 361,000 for rats, 54,000 for dogs, 34,000 for fruit flies, 15,000 for zebrafish, and 13,000 for nematodes).

and other parameters of the study like ambient temperature, diet, and life stage of exposure. The methodologies of animal model studies are similar to human clinical trials, except these studies are conducted on animals and may be used to prove that suspected toxicants are in fact toxic at given concentrations (as opposed to human clinical trials that aim to prove the given substance, which is not a suspected toxicant, is safe).<sup>146</sup>

Researchers randomly assign the experimental animals to a control or exposure group. Sometimes there may be multiple exposure groups, in which case each group is exposed to a different concentration of the substance or some other variable such as duration of exposure or additional stressors. The researchers then monitor the development and growth of tumors (in the usual toxic tort case assessing carcinogenicity) or other adverse side effects, then compare the incidences and rates between control and exposure groups, and between different exposure groups. If the exposed group experiences a greater rate of tumor development and/or growth compared to the control group, the responses are extrapolated to humans through assumptions and mathematical and biostatistical models.<sup>147</sup>

There are many differences though between humans and laboratory animals, some as readily apparent as body size and some internal and unseen like tumor-induction and growth rates.<sup>148</sup> These differences may lead juries or judges to underestimate the validity, reliability, and relevance of animal studies to humans.

#### IV. ADMITTING ANIMAL MODEL STUDIES

Despite the efficiency and efficacy of using animal model studies, many people—problematically judges—remain skeptical about the relevancy and reliability of this type of translational research. Concerns with using animal model studies as evidence of causation in toxic tort litigation fall into three categories: scientific validity, relevance, and reliability. This section presents these concerns, but then demonstrates admitting animal model studies is scientifically valid, legally permissible, and just.

##### A. SCIENTIFIC VALIDITY OF ANIMAL STUDIES

Although many research organizations, like the FDA, accept animal model studies as a regulatory measure of risk assessment, judges do not always approve of the methodologies in the context of litigation.<sup>149</sup> Skeptics are most concerned

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146. CRANOR, *supra* note 17, at 107.

147. *Id.* (“This usually involves extrapolating from higher-dose effects in animals to lower-dose effects in animals and then from low-dose effects in animals to low-dose effects in humans in order to estimate the toxicity effects in humans.”); Landau & O’Riordan, *supra* note 133, at 534.

148. See CRANOR, *supra* note 17, at 107.

149. *Animal Model Qualification Program (AMQP)*, U.S. FOOD AND DRUG ADMIN. (2020), <https://perma.cc/V3MU-E8AV>.

with species disparities, housing and husbandry of test subjects, difficulties and subjectivity interpreting responses to exposures, lack of subsequent studies, and seemingly esoteric scaling and extrapolation calculations.<sup>150</sup>

### 1. Species Disparities

There are inherent differences between humans and animals: humans are bigger, humans have longer life expectancies, animals may process substances differently (for example, metabolic rates), and humans are more genetically heterogenous compared to select lineages of lab animals, just to name a few. These disparities are used to argue against the use of animal model translational research as evidence.<sup>151</sup> Cancer and public health specialist David Rall observes that “[t]he human population is different . . . the mouse doesn’t smoke or breathe hydrocarbons or sulfur oxides from fossil fuels, doesn’t drink, doesn’t take medicine, doesn’t eat bacon or smoked salmon, but man does.”<sup>152</sup> These characteristics can lead to both qualitative and quantitative differences in how humans and animals respond to toxicants.<sup>153</sup> Qualitative differences are those in which one species responds to a substance whereas another does not.<sup>154</sup> For example, arsenic

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150. Though beyond the scope of this Article, we acknowledge that some people believe that animal testing is never ethically justified. Although we agree that cruelty to animals should be a crime, to us potential benefits to human health justify animal testing. Cosmetic testing and related activities are unnecessary and should be prohibited, but medical testing on animals can benefit society. We would not have many of the cancer-fighting drugs we have today if not for translational animal research; chemotherapy was first developed by reducing tumors in mice with modified mustard gas. Animals have also been instrumental in the development of medications to treat mental illnesses; Abilify, an antipsychotic used to treat mood disorders such as bipolar disorder and irritability associated with autism spectrum disorder, was tested on mice and rats. Without the use of animal studies, people would suffer shorter life expectancies and poorer qualities of life from afflictions like smallpox, malaria, kidney disease, HIV, diabetes, epilepsy, and Alzheimer’s. We leave to others (or to another day) discussions over the contours of animal testing, but note federal laws are in place that set, define, and regulate the minimally acceptable standard for research animal treatment and care; the primary law is the Animal Welfare Act, administered and enforced by United States Department of Agriculture. See, e.g., *Top Five Reasons to Stop Animal Testing*, PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS, <https://perma.cc/XT9H-34YZ>; Frank E. Adair & Halsey J. Bagg, *Experimental and Clinical Studies on the Treatment of Cancer by Dichlorethylsulphide (Mustard Gas)*, 93 AM. SURGICAL ASS’N 190 (1931). See, e.g., Caroline Biojone, Plínio C. Casarotto, Leonardo B. Resstel, Hélio Zangrossi Jr, Francisco S Guimarães & Fabrício A. Moreira, *Anti-Aversive Effects of the Atypical Antipsychotic, Aripiprazole, in Animal Models of Anxiety*, 25 J. PSYCHOPHARMACOLOGY. 801 (2011); Thericia G Viana, Ana F. Almeida-Santos, Daniele C. Aguiar & Fabrício A. Moreira, *Effects of Aripiprazole, an Atypical Antipsychotic, on the Motor Alterations Induced by Acute Ethanol Administration in Mice*, 112 BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY 319 (2013); FOUNDATION FOR BIOMEDICAL RES.: ANIMAL TESTING AND RES. ACHIEVEMENTS; 7 U.S.C. § 2131.

151. CRANOR, *supra* note 17, at 107; Dije Ndreu, *Keeping Bad Science out of the Courtroom: Why Post-Daubert Courts Are Correct in Excluding Opinions Based on Animal Studies from Birth-Defects Cases*, 36 GOLDEN GATE U. L. REV. 459, 467 (2006); David E. Bernstein, *Getting to Causation in Toxic Tort Cases*, 74 BROOK. L. REV. 51, 62–64 (2008).

152. David P. Rall, *Thresholds?*, 22 ENV’T HEALTH PERSPS. 163, 164–65 (1978).

153. See Patricia E. Lin, *Opening the Gates to Scientific Evidence in Toxic Exposure Cases: Medical Monitoring and Daubert*, 17 REV. LITIG. 551, 579(1998); Hungerford, *supra* note 142, at 102–03.

is a carcinogen to humans but has not been shown to cause cancer in all laboratory animals.<sup>155</sup> Also, aflatoxin has been found to be toxic to rats and maybe humans, but not mice.<sup>156</sup> Differences can also occur across animals; dichlorodiphenyltrichloroethane (“DDT”), an insecticide, has been shown to cause cancer in some animals (mice) but not in other animals (monkeys and hamsters).<sup>157</sup>

Quantitative differences are those in which two species have similar adverse responses to a substance but with different sensitivity.<sup>158</sup> For example, early Thalidomide studies using rats did not initially reveal the same teratogenic effects (developmental malformations of an embryo or fetus) seen in humans; it was eventually discovered that rats are much less sensitive to Thalidomide.<sup>159</sup> Sometimes, animals can be more susceptible to illnesses than humans. For example, one study found the incidence of osteosarcoma (bone cancer) in dogs is around twenty-seven times higher than in humans.<sup>160</sup> These differences generate doubt over the validity of animal model studies as predictors of human health because it makes choosing an accurate animal model challenging.

The disparities problem is compounded by the intraspecies variations that may arise. Sometimes animals within different strains of the same species can have different sensitivities.<sup>161</sup> Skeptics of animal models studies use both these inter- and intraspecies disparities to argue that there is no definitive way to properly pick an animal model for translational research, and therefore, expert testimony based on animal model studies is neither reliable nor relevant and should thus be inadmissible.

Of course, there are differences between humans and some animals that would preclude their use as models in certain forms of toxicity testing. For example, fish would be an improper model to study mammary gland impacts and rats would be an improper model to study gallbladder toxicity. Yet, other than aesthetically, humans are not as different from model animals as many assume. Recent developments suggest that there are more physiological, biochemical, and metabolic similarities between model animals and humans than there are differences.<sup>162</sup>

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154. Bert P. Krages II, *Rats in the Courtroom: The Admissibility of Animal Model Studies in Toxic Tort Cases*, 2 J. ENV'T L. & LITIG. 229, 236 (1987).

155. L. Tomatis, *The Predictive Value of Rodent Carcinogenicity Tests in the Evaluation of Human Risk*, 19 ANN. REV. PHARMACOLOGY & TOXICOLOGY 511, 517 (1979).

156. Landau & O'Riordan, *supra* note 133, at 544.

157. EDWARD J. CALABRESE, PRINCIPLES OF ANIMAL EXTRAPOLATION 276–77 (1983).

158. Krages II, *supra* note 155, at 235–36.

159. *Id.*; CALABRESE, *supra* note 158, at 485–86.

160. Siobhan Simpson, Mark David Dunning, Simone de Brot, Llorenç Grau-Roma, Nigel Patrick Mongan & Catrin Sian Rutland, *Comparative Review of Human and Canine Osteosarcoma: Morphology, Epidemiology, Prognosis, Treatment and Genetics*, 59 ACTA VETERINARIA SCANDINAVICA (2017).

161. Krages II, *supra* note 155, at 236; Ndreu, *supra* note 152, at 467.

162. D. P. Rall, M.D. Hogan, J.E. Huff, B.A. Schwetz & R.W. Tennant, *Alternatives to Using Human Experience in Assessing Health Risk*, 8 ANN. REV. PUB. HEALTH 355, 356 (1987).

Processes of molecular, cellular, tissue, and organ functions are increasingly proven to be similar, if not the same, among mammalian and even non-mammalian, vertebrate species.<sup>163</sup> A close relationship in form and function of basic systems has been confirmed at levels as micro as genes and proteins in experimental animals like mice and fish.<sup>164</sup> For example, the Zebrafish is an important model animal in translational biomedical research.<sup>165</sup> The non-mammalian zebrafish—seemingly more dissimilar from humans than traditional model animals like mice and rats—has been and continues to be well-suited for study of the anatomy and physiology of basic fundamental systems common to most animals, including humans. The nervous and related sensory systems are examples of these fundamental systems conserved among almost all vertebrates.<sup>166</sup> And though there are some differences, in the context of basic toxicity testing, they are either negligible or able to be accounted for when translating results across species.<sup>167</sup> One commentator noted:

If a laboratory test on a rat shows a chemical to be carcinogenic to the rat at a high exposure level, the test will not prove carcinogenicity in humans if the expert cannot explain how rats and animals have a similar physiological makeup and rate of chemical absorption . . .<sup>168</sup>

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163. James Huff & David P. Rall, *Relevance to Humans of Carcinogenesis Results from Laboratory Animal Toxicology Studies*, in MAXCY-ROSENAU-LAST PUB. HEALTH & PREVENTATIVE MED. 434 (John M. Last and Robert B. Wallace eds., 13th ed. 1992).

164. See, e.g., Mark S. Boguski, *The Mouse That Roared*, 420 NATURE 515 (2002); Kerstin Howe et al., *The Zebrafish Reference Genome Sequence and its Relationship to the Human Genome*, 496 NATURE 498 (2013).

165. See, e.g., Allan V. Kalueff, Adam Michael Stewart & Robert Gerlai, *Zebrafish as an Emerging Model for Studying Complex Brain Disorders*, 35 TRENDS IN PHARMACOLOGICAL SCI. 63 (2014).

166. The anatomy of the central and peripheral nervous systems is similar: three main brain regions; sensory information processing area equivalents like the superior colliculus (humans) and optic tectum (zebrafish) essential for vision; comparable region-specific structures like the thalamus; a spinal cord that grades into the brain; neurons that convey information between sensory receptor organs, the brain, and target organs via chemical neurotransmission; etc. Victoria Rea & Terence J. Van Raay, *Using Zebrafish to Model Autism Spectrum Disorder: A Comparison of ASD Risk Genes Between Zebrafish and Their Mammalian Counterparts*, 13 FRONTIERS IN MOLECULAR NEUROSCIENCE 1 (2020) (describing brain regions); M.F. WULLIMAN, B. RUPP & H. REICHERT, *NEUROANATOMY OF THE ZEBRAFISH BRAIN: A TOPOLOGICAL ATLAS* (1st ed. 1996) (describing sensory processing areas, spinal cord characteristics, and neurotransmission); Thomas Mueller, *What Is the Thalamus in Zebrafish?* 64 FRONTIERS IN NEUROSCIENCE 1 (2012) (comparing the thalamus in zebrafish to that of humans); M.F. BEAR, B.W. CONNORS & M.A. PARADISO, *NEUROSCIENCE: EXPLORING THE BRAIN* (4th ed. 2020) (detailing spinal cord characteristics); *THE ZEBRAFISH IN BIOMEDICAL RESEARCH* (Samuel C. Cartner et al. eds., 1st ed. 2019) (describing issues related to neurons and neurotransmission). A noteworthy difference between this model animal and humans is that genetic coding of enzymes essential in neurotransmission are slightly different. For example, humans have two isoforms of a monoamine oxidase, but zebrafish only have one. See, e.g., Katherine A. Horzmann & Jennifer L. Freeman, *Zebrafish Get Connected: Investigating Neurotransmission Targets and Alterations in Chemical Toxicity*, 4 TOXICS (2016).

167. Horzmann & Freeman, *supra* note 167; BEAR, CONNORS & PARADISO, *supra* note 167.

168. Craig T. Smith, *Peering into the Microscope: The Rise of Judicial Gatekeeping After Daubert and Its Effect on Federal Toxic Tort Litigation*, 13 B.U. J. SCI. & TECH. L. 218, 233 (2007).

If an expert does not explain the similarities and differences in physiology and metabolism between humans and the model species, and how they are accounted for in the interpretation of study results, then that testimony should not be—and in many examples has not been—admitted.<sup>169</sup> However, this circumstance is a procedural deficit on the part of the expert because the physiology and metabolism of humans and model animals, especially rodents, is well known. If an expert overlooks this step, it is a failure of the expert, not the process of animal experimentation itself.

## 2. Housing and Husbandry of Test Subjects

Some of the benefits of animal model studies are (1) the quick progression through life stages, (2) the ability to isolate the animals from unwanted variables or external factors, and (3) the potential for transgenerational studies. However, these benefits also cause some trouble. In laboratory settings model animal colonies may be inbred after a couple generations.<sup>170</sup> If inbred too many times, there is the potential for unhealthy and nonviable populations that make the animals unfit to withstand experimentation.<sup>171</sup> Even if not inbred to this point, the question arises of how well the results of inbred strains of animals can be extrapolated to a genetically diverse and viable human population.<sup>172</sup> Inbreeding can lead to a variety of deleterious effects on general health and reproduction, which may skew study results.<sup>173</sup> Relatedly, laboratory animals used in these studies are often quick to reproduce so there may exist a rapid rate of artificial selection. This increased rate can lead to founder effects (reduced genetic variation when a population is established by only a small number of individuals) and genetic drift (random loss of alleles—alternative forms of a gene—in a small population over time).<sup>174</sup> If unaccounted for, artificial selection may affect the results and replicability of experiments conducted on different generations, or even the same generation separated in different housing.<sup>175</sup>

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169. Bernard Goldstein & Mary Sue Henifin, *Reference Guide on Toxicology*, REFERENCE MANUAL ON SCI. EVIDENCE 633 (3d ed. 2011); *See, e.g., In re Silicone Gel Breast Implants Prods. Liab. Litig.*, 318 F. Supp. 2d 879, 891 (C.D. Cal. 2004); *Fabrizi v. Rexall Sundown, Inc.*, No. 01-289, 2004 WL 1202984, at \*8 (W.D. Pa. June 2, 2004); *Sparling v. Doyle*, No. EP-13-CV-323-DCG, 2015 U.S. Dist. LEXIS 97204, at \*72 (W.D. Tex. July 27, 2015); *Martin*, 2016 U.S. Dist. LEXIS, at \*30–31.

170. *See* J. Casellas, *Inbred Mouse Strains and Genetic Stability: A Review*, 5 ANIMAL 1 (2011).

171. *See id.*; D. Charlesworth & B. Charlesworth, *Inbreeding Depression and Its Evolutionary Consequences*, 18 ANN. REV. ECOL. SYST. 237 (1987).

172. Krages II, *supra* note 155, at 236–37; *see* Thomas D. Brekke, Katherine A. Steele & John F. Mulley, *Inbred or Outbred? Genetic Diversity in Laboratory Rodent Colonies*, 8 G3: GENES, GENOMES, GENETICS 679 (2018).

173. *See, e.g.,* Lisa K. Bickley, Andrew R. Brown, David J. Hosken, Patrick B. Hamilton, Gareth Le Page, Gregory C. Paull, Stewart F. Owen & Charles R. Tyler, *Interactive Effects of Inbreeding and Endocrine Disruption on Reproduction in a Model Laboratory Fish*, 6 EVOLUTIONARY APPLICATIONS 279 (2012).

174. Krages II, *supra* note 155, at 237; Brekke, Steele & Mulley, *supra* note 171.

175. *See* Krages II, *supra* note 155, at 237.



Issues like genetic diversity and quality can be mitigated by following prescribed breeding schemes. Manuals provide protocols for preventing detrimental inbreeding and issues like genetic drift, including: obtaining new, genetically diverse animals from varying breeding sources; recording and referencing the genetic background of all animals before breeding; and using a number table or computer program to randomly select breeders.<sup>176</sup> For example, the Jackson Laboratory, an independent, nonprofit biomedical research institution founded in 1929, publishes a manual that describes breeding strategies and techniques for maintaining genetically well-defined colonies of laboratory mice.<sup>177</sup> The existence of these guidelines should make judges and others more comfortable with animal studies that follow these rules. Adherence to standard protocols should alleviate hesitation regarding the validity of animal model studies because of unhealthy animal populations.

Another concern related to the way the animals are housed is that the controlled environments in a lab cannot account for external influences on health, which may affect the results of a study. One study, for example, had results that varied by a factor of four because of different room temperatures.<sup>178</sup> Lab settings may overlook or be unable to replicate natural environmental factors that can have a role in health outcomes, like temperature,<sup>179</sup> light-dark cycles,<sup>180</sup> and ambient air pollution.<sup>181</sup> Critics also claim that protocols for housing in laboratories can skew results enough to make conclusions drawn from them unreliable.<sup>182</sup> Disturbances, diet, and space can exacerbate adverse effects. Unnatural noise, overcrowding, handling, storage size and location, humidity, lighting, and bedding content, can induce stress that magnifies the illness caused by the substance being studied.<sup>183</sup> Also, there may be unexpected inconsistencies in laboratory

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176. See, e.g., THE JACKSON LABORATORY, BREEDING STRATEGIES FOR MAINTAINING COLONIES OF LABORATORY MICE: A JACKSON LABORATORY RESOURCE MANUAL (2009), <https://perma.cc/JAA9-2VRY>.

177. *Id.*

178. Gary P. Carlson, *Factors Modifying Toxicity*, in TOXIC SUBSTANCES AND HUMAN RISK: PRINCIPLES OF DATA INTERPRETATION 47, 65 (Robert G. Tardiff & Joseph V. Rodricks eds., 1987).

179. *Id.*

180. See Kiichi Yoshinaka, Ai Yamaguchi, Ritsuko Matsumura, Koichi Node, Isao Tokuda & Makoto Akashi, *Effect of Different Light-Dark Schedules on Estrous Cycle in Mice, and Implications for Mitigating the Adverse Impact of Night Work*, 22 GENES TO CELLS (2017) (explaining that repetitive reversal of light-dark cycles triggers irregular estrous cycles in mice that remain for more than four weeks after return to regular light-dark cycles).

181. See Guangbiao Zhou, *Tobacco, Air Pollution, Environmental Carcinogenesis, and Thoughts on Conquering Strategies of Lung Cancer*, 16 CANCER BIOLOGY & MED. (2019) (describing how tobacco smoke and air pollution together—smohaze—can have hazardous effects on exposed populations, including induction of a large number of mutations in the genome, alternative splicing of mRNAs, abnormalities in epigenomics, initiation of tumor-promoting chronic inflammation, and facilitating immune escape of transformed cells).

182. Landau & O’Riordan, *supra* note 133, at 540; Hungerford, *supra* note 142, at 107; Ndreu, *supra* note 152, at 467–68.

183. Landau & O’Riordan, *supra* note 133, at 540.



settings that may affect the accuracy of a study. For example, aflatoxin, a naturally occurring toxicant, can sometimes make its way into commercial animal feed in varying concentrations, but the study might not account for it.<sup>184</sup> Another problem caused by artificial diets (often used in laboratory settings) is that the nutritional quality of animal food can vary seasonally, due to the variation in quality of the agricultural crops that go into the feed, which has been found to influence test results.<sup>185</sup>

These factors do not nullify the study results, provided the researcher is knowledgeable of and careful to limit these influences. An extensive body of research assesses how environmental variables like light-dark cycles, room temperature, and noise affect biology, physiology, and anatomy. An understanding of the impacts of altered environmental factors, combined with the proper equipment, lab conditions, and other procedures can mitigate, if not avoid, these issues. For example, researchers demonstrated that providing the animals with control or predictability can reduce the negative physiological effects of stressors associated with husbandry; they found that providing nesting materials so the laboratory mice could have control over their microclimate helped reduce stress in groups of three mice.<sup>186</sup> Another study cataloged the impacts of bedding volume on anatomical parameters, finding that mice housed on larger volumes showed a reduction in organ weights and increased body and tail lengths.<sup>187</sup> When these factors can be accounted for and corrected, the influences of housing and husbandry on results and translational capability are less of a concern.

### 3. Response Interpretation

The way individual animals respond to a toxic substance can vary. The magnitude and timing of responses to toxic substances can vary depending on features like genetics, life history, and overall health, which sometimes can lead to inaccurate reporting.<sup>188</sup> Additionally, diagnosis of certain responses like cancer or other tumor development, for example, is both difficult and subjective because the response to the toxicant is often a change in cell structure, which requires personal interpretation by the researcher through histopathological examination.<sup>189</sup>

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184. Landau & O'Riordan, *supra* note 133, at 540; See J.F. Robens, et al., *Methods in Testing for Carcinogenicity*, in PRINCIPLES AND METHODS OF TOXICOLOGY 81, 83 (A. Wallace Hayes ed., 1982).

185. Landau & O'Riordan, *supra* note 133, at 552; Off. of Sci. and Tech. Pol'y, Chemical Carcinogens: A Review of the Science and Its Associated Principles, 50 Fed. Reg. 10,372, 10,379 (Mar. 14, 1985).

186. Brianna N. Gaskill & Joseph P. Garner, *Stressed Out: Providing Laboratory Animals with Behavioral Control to Reduce the Physiological Effects of Stress*, 46 LAB ANIMAL 142, 144 (2017).

187. Jennifer Freymann, Ping-Ping Tsai, Helge D Stelzer, Reinhard Mischke & Hansjoachim Hackbarth, *Impact of Bedding Volume on Physiological and Behavioural Parameters in Laboratory Mice*, 51 LAB. ANIMALS 601, 604 (2017).

188. Krages II, *supra* note 155, at 237; see Ndreu, *supra* note 152, at 470–71.

189. Krages II, *supra* note 155. Histopathological examination is examination of diseased tissue specimens or cells through a microscope.

Another concern with interpreting responses following exposure, particularly in carcinogenicity studies, is the difficulty in deducing cancer incidence from tumor data.<sup>190</sup> Varying types of cancers and tumors can mean different things about the risk of the substance. No universal rules govern the methods to calculate cancer incidence in a way that leads to a definitive grouping of toxicants.<sup>191</sup> One option is to look at the total increase in tumor incidence, while another option is to assess the net incidence of tumor development and growth (some varieties of tumors increase but others decrease).<sup>192</sup> If different researchers use different methods of analysis, various conclusions may be drawn, making the risk assessment subjective. However, as discussed above, not only are humans and model animals similar anatomically, physiologically, and biologically in form and function, but also in carcinogenic processes.<sup>193</sup>

- All known human carcinogens that could be tested experimentally are likewise carcinogenic to some animal.
- Nearly one-third of human carcinogens were first discovered in animal bioassays.<sup>194</sup>
- For the substances known to be carcinogenic to both humans and animals, there is at least one common cancer-induced tissue/organ site.
- Findings from independently conducted bioassays on the same chemicals are relatively consistent.

Depending on the experimental animal and given exposure, some carcinogenic process and outcome inconsistencies remain. However, as renowned toxicologist James Huff points out in specific reference to bioassay animal studies,

[w]hile there are avowed uncertainties in the use and interpretation of long-term carcinogenesis bioassays [on animals], one should not take a single characteristic, or even collective instances, to mean automatically that particular bioassay results are meaningless or inappropriate for predicting potential human risks associated with exposure to chemical carcinogens. The tendency to do this seems to be increasing in those with vested interests, or those having relatively little knowledge or experience in the area of chemical carcinogenesis.<sup>195</sup>

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190. *Id.* at 238.

191. *Id.*

192. *See id.*

193. James Huff, *Predicting Chemicals Causing Cancer in Animals as Human Carcinogens*, 67 OCCUPATIONAL & ENV'T MED. 720, 721 (2010). Also notably, over 100 known animal carcinogens do not have valid or equivocal epidemiological studies.

194. This number would likely be even larger, but several carcinogens were discovered before standardization and popularity of bioassays and some human carcinogen exposure is through modes not readily testable on animals, like exposures through aluminum production.

195. James Huff, *Long-Term Chemical Carcinogenesis Bioassays Predict Human Cancer Hazards: Issues, Controversies, and Uncertainties*, 895 ANN. N.Y. ACAD. SCIS. 56, 59 (1999).

Like processes of carcinogenicity, mechanisms of toxicity are also similar between humans and model animals. Prominent scientists, the Environmental Protection Agency (“EPA”), and the Federal Judicial Center’s Reference Manual on Scientific Evidence, all assert that, as knowledge about the molecular structure and function of humans and other species increases, it becomes more certain that mechanisms of chemical toxicity are usually consistent between some species.<sup>196</sup> If mechanisms of toxicity are known to be the same, then animal model studies can be accurate and reliable predictors of human health following exposure to the same toxicant.

Even where the underlying mechanism may be the same, exposure responses may manifest differently among species. To account for these end-result differences, researchers have identified response patterns in model animals that help to more accurately predict responses in other species, here meaning humans.<sup>197</sup> For example, one study assessing the EPA’s suggested risk assessment factors found characteristics of exposure responses that increase the cross-species predictive value for carcinogenic responses: induction of uncommon tumors, tumors at multiple sites, and tumors in both sexes of one test species.<sup>198</sup> Chemicals that yield these responses in animal studies are considered potentially greater human hazards.<sup>199</sup> The ability to more accurately predict certain responses across species is the result of an increasing understanding about the similarities in cellular and organ function, particularly among mammals.<sup>200</sup> In addition to the concerns about species-to-species response differences, critics highlight the differences in the ways individuals of the same species respond following similar exposures, which lead to subjective identifications and interpretations by researchers.<sup>201</sup> This argument also applies to human medical diagnostics, yet critics do not argue that human oncology is as much of a shot in the dark. Continual development and validation of standardized terminology and tumor-assessment methods increasingly improves the accuracy of response characterization.<sup>202</sup> The identification and interpretation of exposure responses are not as subjective as critics would have others believe.

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196. See James Huff, *Chemicals and Cancer in Humans: First Evidence in Experimental Animals*, 100 ENV’T HEALTH PERSPS. 201, 204 (1993); see generally Proposed Guidelines for Carcinogen Risk Assessment, 61 Fed. Reg. 17960 (April 23, 1996); Goldstein & Henifin, *supra* note 170.

197. See CRANOR, *supra* note 17, at 109.

198. See generally George M. Gray, Ping Li, Ilya Shlyakhter & Richard Wilson, *An Empirical Examination of Factors Influencing Prediction of Carcinogenic Hazard across Species*, 22 REG. TOXICOLOGY & PHARMACOLOGY (1995).

199. *Id.*

200. *See id.*

201. See Krages II, *supra* note 155, at 238.

202. See, e.g., J. Kaijser, T. Bourne, L. Valentine, A. Sayasneh, C. Van Holsbeke, I. Vergote, A.C. Testa, D. Franchi, B. Van Calster & D. Timmerman, *Improving Strategies for Diagnosing Ovarian Cancer: A Summary of the International Ovarian Tumor Analysis (IOTA) Studies*, 41 ULTRASOUND OBSTETRICS & GYNECOLOGY 9 (2013).

#### 4. Subsequent Studies

Tenets of the scientific method are reproducibility and replicability; if a study can be reproduced or replicated, researchers can be more confident in the results.<sup>203</sup> Reproduction and replication are often hindered for animal studies, primarily because they require time and resources (though to a lesser extent than human clinical trials). Reproduction and replication are also challenging because researchers often have proprietary interests that require confidentiality of the study or key aspects of it, prohibiting independent, third-party studies of the substance (like with vaccines).<sup>204</sup> Without subsequent and impartial studies, it can be challenging to know what results are reliable and the actual range of uncertainty in animal studies, both of which are important for evidentiary purposes in toxic torts.<sup>205</sup>

Though reproducibility and replicability can bolster the results of any study, they are only two of multiple ways to substantiate findings. In one of the FDA's Draft Guidance for Industry documents, the agency acknowledges that although two studies may provide more convincing evidence than one alone, in some circumstances, there may not be a real difference in reliability between two replicate studies and one large, multifaceted study.<sup>206</sup> If one study is able to ensure a certain level of comprehensiveness and quality (for example, strict monitoring and limited biases), it is possible for that one study to yield results as reliable as two similar studies.<sup>207</sup> Lack of subsequent studies is important when considering reliability, but it is not dispositive.

#### 5. Scaling and Extrapolation Calculations

To apply animal studies to humans, researchers need to scale and extrapolate the doses and responses from the animals to humans. Critics of animal model studies assert that neither scaling nor extrapolation are reliable enough to predict actual human responses to the same substances.<sup>208</sup>

Scaling, in the context of animal studies, consists of adapting doses in the experimental animal studies to doses in humans that will elicit a comparable response.<sup>209</sup> Scaling relies on the presumption that different interspecies responses to substances are proportional to some common biological measurement, such as body surface area or target organ weight, the idea being that

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203. Remember, this factor is one of the “indicia of reliability” we are given in *Daubert*.

204. Krages II, *supra* note 155, at 239; *see, e.g.*, Herder et al., *supra* note 45, at 498.

205. Krages II, *supra* note 155, at 239.

206. *See* U.S. FOOD AND DRUG ADMIN., CTR. FOR BIOLOGICS EVALUATION AND RES., CTR. FOR DRUG EVALUATION AND RES., DEMONSTRATING SUBSTANTIAL EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS DRAFT GUIDANCE FOR INDUSTRY, Docket No.: FDA-2019-D-4964 (2019).

207. *Id.*

208. *See* Krages II, *supra* note 155, at 239–44; *see, e.g.*, *Sparling*, 2015 U.S. Dist. LEXIS 97204.

209. *See* Vijay Sharma & John H. McNeill, *To Scale or Not to Scale: The Principles of Dose Extrapolation*, 157 BRITISH J. PHARMACOLOGY 907 (2009).

biological and physiological system parameters will correlate, like blood volume and oxygen utilization.<sup>210</sup> For example, a proposed scaling calculation for dose translation between a mouse and human based on body weight and surface area might look like the following<sup>211</sup>:

$$\text{mouse dose } \left(\frac{\text{mg}}{\text{kg}}\right) \times \frac{\text{mouse } \frac{\text{weight}}{\text{surface area}}}{\text{human } \frac{\text{weight}}{\text{surface area}}} = \text{human dose } \left(\frac{\text{mg}}{\text{kg}}\right)$$

Skepticism exists around these calculations though because there are no industry standards and the results (that is, estimated doses or exposure amount to illicit the same response) can have an incredibly wide range depending on which biological basis is chosen. For example, if a researcher tried to scale the dose from the equation above using only a body weight ratio equation, the required dose would be different. Consider these parameters: mouse dose (22.4 mg/kg), mouse weight (0.02 kg), mouse surface area (0.007 m<sup>2</sup>), human weight (60 kg), and human surface area (1.6 m<sup>2</sup>).<sup>212</sup> Now consider these two different scaling equations<sup>213</sup>:

$$\text{mouse dose } \left(\frac{\text{mg}}{\text{kg}}\right) \times \frac{\text{mouse } \frac{\text{weight}}{\text{surface area}}}{\text{human } \frac{\text{weight}}{\text{surface area}}} = \text{human dose}$$

$$22.4 \times \frac{0.02}{\frac{0.007}{1.6}} = 1.82 \text{ mg for the human dose}$$

$$\text{mouse dose } \left(\frac{\text{mg}}{\text{kg}}\right) \times \text{human weight} = \text{human dose}$$

$$22.4 \times 60 = 1,344 \text{ mg for the human dose}$$

The first equation is a calculation based on the weight-to-surface area and the second equation is scaled by body weight alone; the two equations yield different results. Additionally, there may be unknown differences or sensitivities unaccounted for in a given scaling model.<sup>214</sup> For example, one study found that the presence of sulci, grooves on the surface of the brain, can have an influence on the mechanical response to accelerative impulses. Thus, models with lissencephalic or smooth brains—like mice and rats—cannot necessarily be scaled to humans by scaling to organ weight alone; researchers must account for the additional sensitivity.<sup>215</sup>

210. See Krages II, *supra* note 155, at 239–40; Shannon Reagan-Shaw, Minakshi Nihal & Nihal Ahmad, *Dose Translation from Animal to Human Studies Revisited*, 22 *FASEB J.* 659, 660 (2008).

211. Reagan-Shaw, Nihal & Ahmad, *supra* note 211.

212. Johnson Ho & Svein Kleiven, *Can Sulci Protect the Brain from Traumatic Injury?* 42 *J. BIOMECHANICS* 2074 (2009).

213. *Id.*

214. See *In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. at 1310 (citing biological differences like absorption and metabolism as significant disadvantages leading to considerable and unresolvable uncertainty).

215. *Id.*; Matthew B. Panzer, Garrett W. Wood & Cameron R. Bass, *Scaling in Neurotrauma: How Do We Apply Animal Experiments to People?*, 261 *EXPERIMENTAL NEUROLOGY* (2014).

Critics argue extrapolation is equally uncertain.<sup>216</sup> Extrapolation consists of mathematically adjusting responses from a high dose to responses at a low dose.<sup>217</sup> Researchers employ extrapolation methods because it is more efficient (in regard to both time and resources) to use a limited number of animals in a study and expose them to high doses of the substance than it is to use a large number of animals and expose them to multiple exposure variations.<sup>218</sup> A dose-response relationship is calculated based on these high-dose responses, and then researchers predict the dose-response relationship at lower doses through mathematical calculations.<sup>219</sup> These mathematical extrapolation calculations usually involve scaling the animal high-dose response to a human high-dose response. Then, that data is extrapolated downward to a human low-dose response through biostatistical models. Extrapolation in this context can also involve calculating from a high-dose animal exposure to low-dose animal exposure and then to low-dose human exposure.<sup>220</sup>

The problem with extrapolation is usually with the mathematical models chosen. There is a wide array of models that yield different results, so skeptics argue that choosing one is a guessing game that may or may not be an accurate predictor.<sup>221</sup> For example, a researcher may employ a linear extrapolation model that essentially calibrates the observed response to a high dose consistently down to a theoretical lower dose. However, this type of calculation does not allow for the presence of phenomena like unexpected thresholds.<sup>222</sup> In other words, a model like linear extrapolation assumes a steady correlation between dose amount and response severity, but some toxicants may be benign at lower doses yet reach a threshold dose (below the experimental high dose) that rapidly increases the response severity.

These concerns about scaling and extrapolation are unsupported by many national and international public health agencies.<sup>223</sup> The International Agency for Research on Cancer, for example, takes the position that

[i]t is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals also present a carcinogenic hazard to

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216. Krages II, *supra* note 155, at 243; Hungerford, *supra* note 142, at 104; Ndreu, *supra* note 152, at 467.

217. Krages II, *supra* note 155, at 239.

218. *Id.* at 242.

219. *Id.*

220. *Id.* at 242; CRANOR, *supra* note 17, at 107.

221. See Krages II, *supra* note 155, at 243.

222. See generally Matthew W. Wheeler & A. John Bailer, *An Empirical Comparison of Low-Dose Extrapolation from Points of Departure (Pod) Compared to Extrapolations Based Upon Methods that Account for Model Uncertainty*, 67 REG. TOXICOLOGY & PHARMACOLOGY (2013); Wout Slob, *Thresholds in Toxicology and Risk Assessment*, 18 INT'L J. TOXICOLOGY 259, 264–65 (1999).

223. Ronald L. Melnick, *A Daubert Motion: A Legal Strategy to Exclude Essential Scientific Evidence in Toxic Tort Litigation*, 95 AM. J. PUB. HEALTH S30, S31 (2005).

humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans.<sup>224</sup>

When much is known about physiologic characteristics (for example, blood flow rates) in the model animal, scaling and extrapolation are reliable.<sup>225</sup> The Federal Judicial Center's Reference Manual on Scientific Evidence also notes that even extrapolation from nonmammalian species to humans, though more difficult, is possible with sufficient information about absorption, distribution, metabolism, and excretion.<sup>226</sup> Issues only arise when there are qualitative differences between species, like the presence or absence of an enzyme that would affect metabolic capacity. But again, with increasing understandings of the similarities and differences among various model animals and humans, researchers account for these discrepancies and calibrate experiments to yield accurate results.<sup>227</sup> Additionally, many of these toxicity studies observe dose-response relationships, meaning researchers test a range of doses, further reducing the need to be concerned about high-to-low dose extrapolation.<sup>228</sup>

Using these critiques of the scientific methodologies employed by researchers, skeptics of animal model studies as evidence of causation raise issues of reliability and relevance.

#### B. ANIMAL STUDIES ARE LEGALLY PERMISSIBLE AS SCIENTIFIC EVIDENCE

The aforementioned skepticisms about the validity of animal model studies are the foundation for the legal concerns aired by critics and inadmissibility justifications articulated by judges.

Despite the potential usefulness of animal studies in toxic tort cases, judges frequently find expert testimony based on such studies to be inadmissible, preventing the evidence from getting before a jury to consider the persuasiveness as part of the weight-of-the evidence approach. This Section details how courts draw upon language from Rule 702 and *Daubert* to find evidence inadmissible. Together Rule 702 and case law require evidence to be both reliable and relevant. Yet, even when the evidence surpasses those thresholds, courts deem animal studies inadmissible. This pattern illustrates that some judges are just uncomfortable

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224. WORLD HEALTH ORG. INT'L AGENCY FOR RES. ON CANCER, IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISK TO HUMANS: PREAMBLE 12 (2006) (emphasis in original); *see also*, Jerry M. Rice & Julian D. Wilbourn, International Agency for Research on Cancer, *Tumors of the Nervous System in Carcinogenic Hazard Identification*, 28 TOXICOLOGIC PATHOLOGY 202 (2000) ("In the absence of adequate data on humans, it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence of carcinogenicity in experimental animals, usually rats and mice, as if they presented a carcinogenic risk to humans.").

225. Nat'l Res. Council Comm. on Risk Assessment of Hazardous Air Pollutants, Sci. and Judgment in Risk Assessment, *Appendix E, Use of Pharmacokinetics to Extrapolate from Animal Data to Humans* (1994), <https://perma.cc/874Q-7C4H>.

226. Goldstein & Henifin, *supra* note 170, at 646–47.

227. *Id.*

228. *Id.* at 641.



with animal studies and prevent juries from being able to consider experts relying on such studies as part of a weight-of-the-evidence approach.

Multiple examples from before *Daubert* and Rule 702 show courts have historically been skeptical of and quick to exclude animal studies. For example, in *In re Agent Orange*, the court rejected testimony based on animal model studies because the doses the animals were given were higher than the plaintiffs' exposure and because the studies were conducted on a different species. Because different species could respond differently, the court found the evidence potentially misleading and therefore inadmissible.<sup>229</sup> Similarly, in *Viterbo v. Dow Chemical Co.*, the Fifth Circuit affirmed the district court, finding the plaintiff's evidence insufficient because the rats' exposures were different than those of the plaintiffs.<sup>230</sup> Additionally, the rats' symptoms differed from those of the plaintiff.<sup>231</sup> In *Lynch v. Merrell-National Laboratories*, the court excluded evidence of animal studies because of the "several limitations inherent in the use of the animal . . . data."<sup>232</sup> Further, it felt that in that case "studies conducted on rats, rabbits, and monkeys are not helpful and are of little probative value," again mostly because the animal model and human exposures and outcomes were not identical.<sup>233</sup>

Like many evidentiary decisions regarding animal studies today, the inadmissibility determinations in these examples were unjustified. Interspecies discrepancies and unidentical responses should not be enough to deem a study invalid. Science is not perfect. All scientific studies available to toxic tort plaintiffs have some concerns; methodological shortcomings are not unique to animal studies. Yet, animal studies are more likely to be found inadmissible than other studies, primarily epidemiological studies.<sup>234</sup> It is hard to determine exactly how often scientific evidence is deemed inadmissible, and even harder to learn details of the studies excluded and the justifications for excluding them because of a lack of published information. In light of these limitations, we turn to the literature from scholars and practitioners in the field to understand the specific legal arguments.

## 1. Reliability

To assist courts in determining whether expert testimony is reliable under Rule 702, *Daubert* tells us that "in a case involving scientific evidence, *evidentiary*

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229. See *In re Agent Orange Prod. Liab. Litig.*, 611 F. Supp. 1223, 1241 (E.D.N.Y. 1985), *aff'd sub nom. In re Agent Orange Prod. Liab. Litig.* MDL No. 381, 818 F.2d 187 (2d Cir. 1987).

230. *Viterbo v. Dow Chem. Co.*, 826 F.2d 420 (5th Cir. 1987).

231. See *id.* at 424.

232. See *Lynch v. Merrell-Nat'l Labs. Div. of Richardson-Merrell, Inc.*, 646 F. Supp. 856, 865 (D. Mass. 1986).

233. See *id.* at 865–66.

234. See, e.g., *In re Zolofit Sertraline Hydrochloride Prods. Liab. Litig.*, 176 F. Supp. 3d at 493 (" . . . to successfully opine on general causation . . . any expert must account for the findings reached in the full universe of epidemiological studies.").

*reliability* will be based upon *scientific validity*.<sup>235</sup> Skeptics of animal model studies argue that they are never reliable for the reasons discussed above (species disparities,<sup>236</sup> housing and husbandry variations,<sup>237</sup> difficulties and subjectivity interpreting responses,<sup>238</sup> lack of subsequent studies,<sup>239</sup> and random scaling and extrapolation calculations<sup>240</sup>).<sup>241</sup> If studies are not reliable, expert testimony based on them is inadmissible.<sup>242</sup> As discussed above, these concerns about the science are largely unfounded. If the science is valid, it is reliable and should be admitted. This is especially true when the other evidence is proffered, and the animal studies will be used as part of a weight-of-the-evidence methodology.

Critics also claim the studies are unreliable when performed in the context of regulatory risk assessments.<sup>243</sup> In these types of assessments, researchers rely on estimates to predict some general margin of safety of the substance or ascertain the level of any toxicity response; it is not used to predict actual dose-response relationships over a span of different doses.<sup>244</sup> In the regulatory context (such as development and evaluation of FDA-regulated products ranging from medical devices to food ingredients<sup>245</sup>) relying on these estimated results is fine because researchers in those situations are only looking for the possibility of causation rather than actual proof of causation by a preponderance of the evidence.<sup>246</sup> In the context of tort litigation, the parties need to prove causation-in-fact; a suggestion

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235. *Daubert*, 509 U.S. at 590 n.9 (emphasis in original).

236. *See, e.g.*, CRANOR, *supra* note 17, at 107.

237. *See, e.g.*, Yoshinaka et al., *supra* note 181.

238. *See, e.g.*, Kranges II, *supra* note 155.

239. *See, e.g., id.* at 239.

240. *See, e.g.*, Ho & Kleiven, *supra* note 213.

241. The Eleventh Circuit has even gone so far to say that a general causation opinion that is not supported by epidemiological studies, dose-response relationship studies, or a background risk of disease is unreliable as a matter of law, and animal studies may only be used as “secondary” methodologies to bolster general causation demonstrated by these other forms of scientific evidence because their inherent flaws limit their reliability. In re *Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. at 1306; *see Chapman*, 766 F.3d at 1308.

242. *See, e.g.*, In re *Agent Orange Prod. Liab. Litig.*, 611 F. Supp. at 1241; *Lynch*, 646 F. Supp. at 865; *Viterbo*, 826 F.2d at 424.

243. Krages II, *supra* note 155, at 245–46.

244. *See, e.g.*, U.S. ENV’T PROT. AGENCY, CONSIDERATION OF THE FQPA SAFETY FACTOR AND OTHER UNCERTAINTY FACTORS IN CUMULATIVE RISK ASSESSMENT OF CHEMICALS SHARING A COMMON MECHANISM OF TOXICITY (2002), <https://perma.cc/4CKA-43JX>.

245. U.S. FOOD & DRUG ADMIN., PREDICTIVE TOXICOLOGY ROADMAP (2017), <https://perma.cc/K8DV-V22N>.

246. *See, e.g.*, *Yates v. Ford Motor Co.*, 113 F. Supp. 3d 841, 857 (E.D.N.C. 2015) (“... statements from regulatory and official agencies . . . are not bound by standards for causation found in toxic tort law.”); *Burst v. Shell Oil Co.*, No. 14-109, 2015 U.S. Dist. LEXIS 77751, at \*21 (E.D. La. June 16, 2015) (“[T]he conclusions and guidance of regulatory and advisory bodies that a substance is carcinogenic . . . alone, do not provide a reliable basis for establishing legal causation.”); *Allen v. Pennsylvania Eng’g Corp.*, 102 F.3d 194, 198 (5th Cir. 1996) (“The agencies’ threshold of proof is reasonably lower than that appropriate in tort law, which ‘traditionally makes more particularized inquiries into cause and effect’ and requires a plaintiff to prove ‘that it is more likely than not that another individual has caused him or her harm.’”).

or estimation is not reliable as an assertion of a dose-response relationship. Therefore, it is not even likely that results of regulatory risk assessments of the given substance will be admissible, though they might be readily available.

This argument essentially concedes that animal models are suitable predictors of human health; they can predict margins of safety (general causation) just not dose-response relationships (specific causation). In other words, studies conducted in these regulatory contexts are falling short methodologically (according to the legal standards of proof), but the basic use of animal models is accepted.

## 2. Relevance

*Daubert* adds to Rule 702's reliability requirements by also requiring scientific evidence to be relevant.<sup>247</sup> Rule 401 provides the relevancy standard, explaining evidence is relevant if "it has any tendency to make a fact more or less probable than it would be without the evidence; and the fact is of consequence in determining the action."<sup>248</sup> However, Rule 403 states that "[t]he court may exclude relevant evidence if its probative value is substantially outweighed by a danger of one or more of the following: unfair prejudice, confusing the issues, misleading the jury, undue delay, wasting time, or needlessly presenting cumulative evidence."<sup>249</sup> This Section assesses the Rule 403 exceptions in the context of animal studies.

The balance between Rules 401 and 403 is tricky. Critics argue, and some courts agree, that animal model studies should be excluded both for lack of general relevance but also for Rule 403 exceptions. The argument against Rule 401 relevancy stems from some of the methodologies employed in the studies: namely the species, age, and exposure differences. The logic goes that the facts of the studies are not sufficiently tied to the facts of the case, and if evidence is not sufficiently tied to the facts of the case, it is not relevant and will not aid the trier of fact in making an informed decision, and is therefore, inadmissible.<sup>250</sup> However, animals are not that different from humans in regard to many anatomical, physiological, and biological forms and functions; there are many overlaps with mechanisms of toxicity; and scaling and extrapolation are proper and prudent when any physiological processing discrepancies are known and accounted for.<sup>251</sup> For these reasons, animal studies are relevant as evidence of causation in toxic tort litigation.

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247. See *e.g.*, *Daubert*, 509 U.S. at 590–93.

248. FED. R. EVID. 401.

249. FED. R. EVID. 403.

250. Mahaney, *supra* note 30, at 1167; *United States v. Downing*, 753 F.2d 1224, 1242 (3d Cir. 1985).

251. See, *e.g.*, Boguski, *supra* note 165; Huff, *supra* note 194; World Health Org. Int'l Agency for Res. on Cancer, *supra* note 225.

*a. Unfair Prejudice, Confusing the Issues, and Misleading the Jury*

The first Rule 403 relevancy exception allows for the exclusion of relevant testimony if the court believes the evidence will unfairly prejudice the jury, confuse the issues presented, or actively mislead the jury.<sup>252</sup>

Skeptics argue that animal studies will prejudice the jury, meaning that they will incite a jury's emotions, sympathies, or weaknesses.<sup>253</sup> As previously noted, in the interest of conserving resources and limiting the number of animals experimented on, researchers use methods that involve high-dose exposures and genetically modified or specially bred animals, which result in high tumor rates.<sup>254</sup> Critics argue that the often-dramatic outcomes (such as high tumor rates and/or death) will incite the jury and influence opinions about the substance as a whole, not necessarily calibrating their opinions to the different responses following exposure to different doses<sup>255</sup> (even after description of the methodologies and explanation that the rates do not reflect normal conditions). For example, when explaining that high doses are given to limit the required number of animals used while also increasing the likelihood of identifying target organs and probable mechanisms of toxicity, some people worry that layperson jurors will not be able to comprehend or will ignore those facts.<sup>256</sup> Essentially, opponents suggest that jurors will see any impact on animals as likely occurring in humans, no matter the exposure amount, and will overestimate potential impacts.

As with the lack of reliability argument, some argue that these studies might mislead the jury about the validity of the results.<sup>257</sup> Although courts have not expressed this concern so much in the animal testing context, some courts have regarded mathematical methods with suspicion.<sup>258</sup> The fear is that layperson jurors will be "impressed by the mystique of the . . . demonstration but [be] unable to assess its relevance or value."<sup>259</sup> For example, studies have demonstrated that people presented with "bad" articles and explanations of neuroscience research and psychological concepts rate the studies more satisfactorily when accompanied by brain information and images, even when irrelevant.<sup>260</sup>

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252. For example, in a criminal trial, an excessive number of photographs of a murder victim, though somewhat relevant, may be deemed to only serve the purpose of inflaming the jury and can therefore be excluded. *See e.g.*, *State v. Bocharski*, 22 P.3d 43, 48–50 (Ariz. 2001).

253. Landau & O'Riordan, *supra* note 133, at 522.

254. Krages II, *supra* note 155, at 248.

255. *Id.*

256. *Id.*; Landau & O'Riordan, *supra* note 133, at 533.

257. *See* Krages II, *supra* note 155, at 240.

258. *Id.* at 240–41.

259. *People v. Collins*, 68 Cal. 2d 319, 332 (1968) (alteration in original).

260. Deena Skolnick Weisberg, Frank C. Keil, Joshua Goodstein, Elizabeth Rawson & Jeremy R. Gray, *The Seductive Allure of Neuroscience Explanations*, *J. COGNITIVE NEUROSCIENCE* 20(4): 470–77 (2008); David P. McCabe & Alan D. Castel, *Seeing is Believing: The Effect of Brain Images on Judgements of Scientific Reasoning*, 107 *COGNITION* 343 (2008).

Critics also argue that animal model studies may confuse the jury.<sup>261</sup> Legally, there are differences between the terms “risk” and “safety,” but the average person might use them synonymously. “Risk” refers to the rate at which a disease might occur, while “safety” refers to no disease development.<sup>262</sup> In toxic tort cases, the plaintiff needs to prove causation through assessments of risk, not safety.<sup>263</sup> It is not sufficient to say that a substance has on occasion or has some unknown potential to cause the disease in question. The concern is that if presented evidence showing a substance caused disease development in some animals, the jury might assume the substance is never safe and likely caused the plaintiff’s harm.<sup>264</sup> But it is not enough for the plaintiff to show the substance could cause the disease because it did so in some animals, but rather that the substance, at the level of the plaintiff’s exposure, more likely than not caused the illness alleged by the plaintiff.<sup>265</sup>

There is also the fear that the inferences and assumptions required to properly evaluate and critique the studies are beyond a juror’s knowledge. One skeptic of animal model studies notes that

[t]o allow the admission of non-probative evidence [like animal model studies] that is beyond the comprehension of a typical jury is inimical to justice since the resulting decision is not the product of the merits of the case but rather the uninformed impression of the jury.<sup>266</sup>

This argument suggests the initial presentation of animal model studies could confuse a jury with jargon, methodologies, and statistical analyses. Then when that evidence is challenged by just as technical evidence from the opposing party, the possibility for confusion could become significant. The concern is that a jury would base its decision on something other than an accurate understanding and interpretation of the evidence presented.<sup>267</sup>

These arguments underestimate the intelligence of the jury. To assert that jurors will be befuddled and unable to make sound judgments when presented with scientific evidence in the form of expert testimony about animal study results is unfair. Animal model studies are no more confusing than other technical or mathematical forms of evidence.<sup>268</sup> If we exclude animal model studies on these grounds, should we forego all expert testimony based on technical or specialized knowledge?

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261. Krages II, *supra* note 155, at 248–49.

262. *Id.* at 249.

263. *Id.*

264. *See id.*

265. *Id.*

266. *Id.* at 250.

267. *See* Landau & O’Riordan, *supra* note 133, at 552.

268. *Contra* Krages II, *supra* note 155, at 250; Landau & O’Riordan, *supra* note 133, at 553.

Additionally, it is circular to say that jurors are not versed enough in science so scientific expert testimony will be too confusing to admit, but to qualify as an expert witness one *must* have and present knowledge beyond the ken of the jury.<sup>269</sup> Causation is already stacked against plaintiffs. Defendants make things harder by suggesting evidence should be kept out essentially because juries lack intelligence or are too emotional.

### *b. Waste of Time*

Toxic tort cases are usually lengthy, with the median timeline estimated to be between two and three-and-half years from filing to disposition.<sup>270</sup> If scientific evidence is thorough, both sides will pick apart all aspects of protocols, methodologies, assumptions, limitations, and analyses.<sup>271</sup> People opposed to animal studies as evidence purport that animal model studies provide so little probative value, therefore, on balance, it is not worth the substantial amount of time it takes to present the evidence.<sup>272</sup>

The rebuttal to this concern is simple. Trial judges are only to exclude evidence if its probative value is substantially outweighed by its costs.<sup>273</sup> But in most cases the probative value of animal studies does outweigh the time required to present the related expert testimony. They can be reliable predictors of human health and essential to the plaintiff's demonstration of causation, making them probative and certainly not outweighed by the time it takes to present them.<sup>274</sup>

### *c. Needless Presenting Cumulative Evidence*

Another critique of animal studies is that the studies have no independent validity and must always be admitted with and compared to epidemiological studies.<sup>275</sup> Therefore, the probative value of animal model studies is "entirely

269. See generally Edward J. Imwinkelried, *The Taxonomy of Testimony Post-Kumho: Refocusing on the Bottomlines of Reliability and Necessity*, 30 CUMB. L. REV. 185, 194–96 (2000).

270. STEVEN K. SMITH, CAROL J. DEFANCES, & PATRICK A. LANGAN, CIVIL JUSTICE SURVEY OF STATE COURTS, 1992: TORT CASES IN LARGE COUNTIES (U.S. Dep't of Just Apr. 1995), <https://perma.cc/P9V2-478X>; COHEN, *supra* note 51.

271. See Landau & O'Riordan, *supra* note 133, at 554; Krages II, *supra* note 155, at 253.

272. Krages II, *supra* note 155, at 253.

273. FED. R. EVID. 403.

274. An example of when waste of time would outweigh probative value would be if a party attempted to proffer an excessive number of witnesses to testify about the same evidence—though the testimony itself is probative, it might be redundant after multiple witnesses, and therefore, a waste of time.

275. See Krages II, *supra* note 155, at 252; *Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 882 (10th Cir. 2005) (agreeing "with the district court that epidemiology is the best evidence of general causation in a toxic tort case."); *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1198 (11th Cir. 2002) ("Epidemiology . . . is generally considered to be the best evidence of causation in toxic tort actions."); *In re Zolofit Sertraline Hydrochloride Prods. Liab. Litig.*, 176 F. Supp. 3d at 493 (" . . . to successfully opine on general causation . . . any expert must account for the findings reached in the full universe of epidemiological studies.").



derived” from epidemiological studies.<sup>276</sup> If the animal model studies cannot add anything and merely restate the results of the epidemiological study, it is cumulative evidence (evidence that proves what has already been established by other facts or information) and should not be admitted.<sup>277</sup> In other words, epidemiological studies are thought of as more relevant. As an example, the Eleventh Circuit has held that a general causation opinion not supported by epidemiological studies, dose-response relationship studies, or a background risk of disease is unreliable as a matter of law.<sup>278</sup> This position demonstrates a misunderstanding about the aims of both epidemiological and animal studies. Inherent in the definition of each type of research is a different kind of conclusion. Epidemiological studies are nonexperimental studies of the frequency or pattern of health-related states and their connections to determinants (causes and risk factors).<sup>279</sup> Animal studies on the other hand are experimental studies that attempt to ascertain the development, progression, and mechanism of disease. Given the type of results researchers yield from these studies, animal studies cannot universally be deemed inadmissible cumulative evidence.

Relatedly, there will rarely, if ever, be one piece of evidence that meets the requisite standard of proof in toxic tort cases. Instead, scientific evidence is collectively viewed as part of the weight-of-the-evidence methodology, where all pieces come together to unveil the full picture, like a puzzle or mosaic.<sup>280</sup> This is especially true for nonexperimental epidemiological studies; they should be used in addition to, not instead of, animal model studies to ascertain true causation. It is the common practice of many national and international agencies that provide evaluations on human health risk to rely on multiple methods of evaluation when making health risk determinations.<sup>281</sup> Why should the legal field impart a different method for the same type of evaluation? Given the scientific field’s acceptance of animal model studies as predictors of human health, if the methodology of the study is valid,<sup>282</sup> expert testimony that relies on animal model studies should be admitted to serve as a puzzle piece. Any other course of action ignores the relevant Federal Rules of Evidence and case law.

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276. Krages II, *supra* note 155, at 252.

277. *Id.* at 252–53.

278. In re *Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp., at 1306; see *Chapman*, 766 F.3d at 1308.

279. U.S. DEP’T OF HEALTH & HUM. SERVS. & CTRS. FOR DISEASE CONTROL & PREVENTION, *PRINCIPLES OF EPIDEMIOLOGY IN PUBLIC HEALTH PRACTICE* (3d ed. 2012).

280. See *Joiner*, 522 U.S. at 152–53.

281. Melnick, *supra* note 224, at S32.

282. Methodology of both the individual studies and of the way the expert uses the studies collectively. Not to be confused though with using methodology and conclusions synonymously as the *Joiner* court erroneously does: “conclusions and methodology are not entirely distinct from one another.” *Joiner*, 522 U.S. at 146. But rather with the *Daubert* principle in mind: “the focus, of course, must be solely on principles and methodology, not on the conclusions that they generate.” *Daubert*, 509 U.S. at 595.

One commentator—opposed to the use of animal model studies as evidence—dismantles the argument in another way by noting, “[i]t is odd for courts to exclude animal tests when epidemiological studies either do not exist or disagree with the animal tests, yet claim that the animals tests can be useful when they agree with the epidemiological evidence.”<sup>283</sup> The discourse can be interpreted to mean that animal studies cannot only be cumulative evidence; either the evidence itself is reliable, or it is not. Under *Daubert*, it is not possible for a study to be deemed reliable (or unreliable) only as it relates to other evidence. Relatedly, the absence of epidemiological studies should never bar the admission of reliable animal studies as evidence.<sup>284</sup> This course of action “would be the same as considering ‘rational the decision by a mother to allow her child to drink a substance that had just killed her cat on the grounds that no human had yet been harmed by it.’”<sup>285</sup>

### CONCLUSION

All scientific studies present challenges and uncertainties. Human experimental studies, epidemiological studies, and chemical structure-biological activity studies (all commonly used in toxic tort cases) have shortcomings that are not, to the same extent, present in animal model studies—namely, the inability to intentionally expose humans and the limited likelihood that humans will be exposed to environmental toxicants in a manner that allows for quantification of damages.<sup>286</sup> Animal studies enable experimentation to fill the gaps in our knowledge related to toxic exposures. But despite their efficacy and efficiency in proving that certain exposures to given substances cause specific injuries, animal studies are often deemed inadmissible.

Nothing in the Federal Rules of Evidence or case law prevents plaintiffs from proffering animal model studies as proof of causation in toxic tort litigation. However, judges often deem animal model studies inadmissible. It is hard to know how often animal studies are excluded because evidentiary rulings rarely lead to published cases. But their lack of use in toxic tort cases (compared to their utility when explaining injury/illness from toxicants) and the weak and superficial justifications given when we do see courts explain why they are inadmissible, like taking the time to highlight that humans and rats are different species, suggest they are often and unwarrantedly excluded.<sup>287</sup> Given that evidentiary rules allow for admissibility of these relevant and reliable studies, the issue seems to lie with the inherent skepticisms that judges have regarding animal studies.

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283. Ndreu, *supra* note 152, at 483.

284. *Contra* In re *Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp., at 1306; *Chapman*, 766 F.3d at 1308.

285. Lin, *supra* note 154, at 579–80.

286. Goldstein & Henifin, *supra* note 170, at 639.

287. *See e.g.*, *Pinares*, 2019 U.S. Dist. LEXIS 230034 (only briefly stating in a footnote: “. . . [the experts] reliance on animal studies are insufficient to show causation.”).

Without an abundance of published explanations regarding judicial exclusion of animal studies, critiques by scholars and practitioners are useful guidance. Common critiques include species disparities, subjective interpretation of exposure responses, and inaccurate or misleading scaling and extrapolation calculations. These fallacious concerns are then used by the opposing party to craft legal challenges against the animal studies' admission as evidence, including lack of reliability and lack of relevancy, unfair prejudice, confusing the issues, misleading the jury, waste of time, and needlessly presenting cumulative evidence. The scientific concerns are exaggerated. Humans are more physiologically, biochemically, and metabolically similar to animals than skeptics assert. Additionally, carcinogenic processes and other mechanisms of toxicity are conserved between humans and many animal models. Researchers have and continue to identify response patterns to more readily make exposure response comparisons and predictions from species to species; accounting for any physiological process rate differences helps researchers choose reliable animal models and scaling and extrapolation calculations.

Relatedly, the legal concerns are unwarranted: skeptics undermine the intelligence and ability of the jury to understand and weigh all the evidence presented and make rational decisions; animal studies are not redundant of epidemiological studies because they are experimental and yield results relevant (in some cases arguably more relevant) than adventitious epidemiological studies; "justice is the leading virtue of the law" and preventing plaintiffs from using an efficient and effective form of evidence to prove causation in their case because of unfounded critiques and inherent bias is counter to this tenet.

The Federal Judicial Center's Reference Manual on Scientific Evidence, which is intended to assist judges in presiding over cases with complex scientific and technical evidence by describing the tenets of important scientific fields, not only explains the validity of animal model studies as evidence, but also repeatedly takes the position that both epidemiology and toxicology can be valuable in demonstrating causation, noting that "these sciences often go hand in hand . . ."<sup>288</sup> Judges often assert that epidemiological studies are of more value than animal studies, some going so far as to say animal studies cannot be admitted in the absence of epidemiological studies. However, given the methodological shortcomings of these studies—primarily the inability to accurately measure exposure, the often-small number of subjects in the studies, and the inability to isolate variables—results of epidemiological studies are no harder to apply to specific toxic tort plaintiffs than animal model studies. Animal studies make up for the shortcomings found in epidemiological studies. Animal studies allow for isolation of variables, assessments of dose-response relationships, exploration of mechanisms of toxicity, and guarantee a sufficient number of subjects. These factors help researchers observe and articulate causal links by describing the metabolic,

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288. Goldstein & Henifin, *supra* note 170, at 657–58.

cellular, and physiological effects of exposure.<sup>289</sup> Given the advantages and shortcomings of both sciences, and the absence of one perfect form of research, the Reference Manual supports the position that both should contribute to the weight-of-the-evidence methodology to demonstrate causation.<sup>290</sup>

One primary goal of tort law is to make matters right and restore the person wronged to the condition they were in before the wrongdoing.<sup>291</sup> This goal can never be accomplished if plaintiffs in toxic tort cases are prohibited from using the best means available to them to prove their case. This is not to say that there should be no rules or limitations to what can and cannot be brought into a courtroom. But as Justice Stevens notes in his *Joiner* concurrence “[i]t is not intrinsically ‘unscientific’ for experienced professionals to arrive at a conclusion by weighing all available scientific evidence—this is not the sort of ‘junk science’ with which *Daubert* was concerned.”<sup>292</sup> The collection of sound science, including animal model studies, to prove causation in these cases should not be prohibited by validity standards set in the legal field because, as Judge Posner points out, “the law lags science . . .”<sup>293</sup> It is illogical for the legal field, whose aim is justice and fair compensation, to set its own standards of scientific validity that are in conflict with the standards of the relevant scientific field. It is unjust to set these impossible standards that parties can rarely meet given the nature of scientific research: it is inferential, often open-ended, and collaborative and cumulative.<sup>294</sup>

If a judge excludes an expert witness whose testimony is within the range of normal scientific debate<sup>295</sup>—as animal model studies usually are—the judge inserts their bias into the admissibility determination, which could influence the outcome of the case.<sup>296</sup> Judges’ personal biases appear to be where the issue lies. The Federal Rules of Evidence, pertinent case law, Reference Manual on

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289. *Id.* at 637, 658.

290. *Id.*

291. See generally OWEN, *supra* note 3.

292. *Joiner*, 522 U.S. at 153.

293. *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996); see also Eggen, *supra* note 30, at 901 (“Modern science has moved beyond the fixed Newtonian universe of absolute cause-and-effect into a universe of changing possibilities, as evidenced by relativity theory and quantum physics, 56 but the law has been reluctant to follow suit.”).

294. CRANOR, *supra* note 17, at 206–07; see Cutler, *supra* note 30, at 197.

295. There exists a range of acceptable conclusions in science, especially in the field of environmental illnesses, because there usually exists some knowledge gap due to lack of study subjects, insufficient time to ascertain all information, etc.

296. Melnick, *supra* note 224, at S31; see *Kumho Tire Co.*, 526 U.S. at 153; see, e.g., *Sarkees*, 2020 U.S. Dist. at \*86 (Ignoring Report and Recommendation of the Magistrate Judge stating that “uncertainty always will exist when assessing the causal relationship . . . Nonetheless, plaintiffs’ experts have been careful not to oversell the conclusions in the research literature, and they have acknowledged the inferences required to form their opinions. So long as plaintiffs’ experts continue to avoid overselling research results, their opinions are scientifically reliable and may be heard by a jury at trial. The jury also will hear cross-examination of plaintiffs’ experts and direct testimony from defense experts; where the preponderance of the evidence falls regarding plaintiffs’ negligence and other claims will be for the jurors to decide.”).

Scientific Evidence, and reports and guidance of multiple agencies support the position that animal model studies are helpful as part of the weight-of-the-evidence methodology to prove causation in toxic tort litigation. However, there are still inadmissibility determinations with dismissive and unsupported justifications such as “. . . causation opinions based primarily upon *in vitro* and live animal studies are unreliable and do not meet the *Daubert* standard.”<sup>297</sup> When ignoring the available guidance and outright excluding animal model studies, the judge essentially usurps the role of the jury by exceeding his gatekeeping authority and making his own biased assessment of validity of the scientific evidence, a role explicitly left to the trier of fact in a case.<sup>298</sup> Exclusion of an expert vital to a plaintiff’s case by a judge with a misguided perception or misunderstanding of the relevant science “is inconsistent with our national principle of equal and impartial justice for all citizens.”<sup>299</sup> The better, fairer, and prescribed course of action would be to allow expert testimony—founded on studies within the boundaries of normal scientific debate—to be admitted and allow the jury to decide its persuasiveness based on the defense’s cross-examination and contradictory evidence and expert opinions.<sup>300</sup>

Lastly, toxic tort cases are often not dealing with isolated incidences. To meet the legal standards, many people would need to be exposed and suffer serious illnesses, injuries, or even death before a plaintiff could use one study—for example, an epidemiological study—to incontrovertibly meet the burden of proof in her case. However, this “body in the morgue” approach is not, or should not in practice be, part of our justice system.<sup>301</sup> In Justice Breyer’s *Joiner* concurrence, he notes that

It is . . . essential in this science-related area that the courts administer the Federal Rules of Evidence in order to achieve the ‘ends’ that the Rules themselves set forth, not only so that proceedings may be ‘justly determined,’ but also ‘that the truth may be ascertained.’<sup>302</sup>

In other words, a function of toxic tort law is to prevent harmful substances from continuing to injure people through the proper prescribed judicial procedures, but the rules are not to be so strictly interpreted to lose sight of the underlying aim of truth and justice for those harmed. Judges should not be overstepping

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297. In re *Zolof*, 26 F. Supp. 3d at 475.

298. Melnick, *supra* note 224, at S31.

299. *Id.*

300. *Id.*; see, e.g., *Barefoot*, 463 U.S. at 899.

301. See generally Rafael Moure-Eraso, *Primary Prevention and Precaution in Hazard Identification in the NIEHS/NTP: Body in the Morgue Approach*, 117 PUB. HEALTH REPS. 564 (2002); see James P. Leape, *Quantitative Risk Assessment in Regulation of Environmental Carcinogens*, 4 HARV. ENV’T L. REV. 86, 94 (1980) (“. . . prudence dictates that regulation to protect public health must not permit forty years of human exposure to potential carcinogens while regulators await epidemiological evidence.”).

302. *Joiner*, 522 U.S. at 148–49.

their gatekeeping role, especially not when unjustifiably excluding reliable and relevant animal model studies as scientific evidence. If done improperly or without attention to design and detail, animal studies may yield skewed and unreliable results, but these circumstances reflect failures of the researchers, not of animal studies themselves. Advancements in technology, methods, and understandings of animal-human biological, physiological, and anatomical comparability can yield scientific studies reliable and relevant enough to be admitted as scientific evidence in toxic tort cases.

The solution to this issue is an expansion of the familiarity and comfortability people, primarily judges, have with this form of research. The rules are appropriate in allowing judges to serve as gatekeepers to prevent “junk science” from entering the courtroom. However, this discretion has, inadvertently, come at the cost of judges being too strict with their admissibility determinations and letting their misguided skepticisms cloud their ability to recognize the reliability and relevancy of animal studies as evidence of causation in toxic tort litigation.