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Epigenetics and Toxic Torts: How Epidemiological Evidence Informs Causation

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I. Introduction

Consider the recent tragedy in Flint, Michigan, resulting from a contaminated water supply.[1] After Flint switched from Detroit's water supply to water from the Flint River, its water became tainted with high levels of lead, trihalomethanes, and copper—some exceeding the limits in federal regulations.[2] Flint is a poor city with a majority black population.[3] Indeed, financial need drove the decision to switch water supplies in the first place.[4] Instead of saving Flint money, this choice may now prove

1. *See* Yanan Wang, *In Flint, Mich., There's So Much Lead in Children's Blood that a State of Emergency Is Declared*, WASH. POST (Dec. 15, 2015), https://www.washingtonpost.com/news/morning-mix/wp/2015/12/15/toxic-water-soaring-lead-levels-in-childrens-blood-create-state-of-emergency-in-flint-mich/ (last visited Feb. 4, 2016) (reporting on the water contamination and lead poisoning affecting Flint) (on file with the Washington and Lee Law Review).

2. *See id.* (discussing the levels of contaminants in Flint's water); *see also* Ron Fonger, *City Warns of Potential Health Risks After Flint Water Tests Revealed Too Much Disinfection Byproduct*, M LIVE (last updated Jan. 17, 2015, 10:04 AM), http://www.mlive.com/news/flint/index.ssf/2015/01/flint_water_has_high_disinfect.html (last visited Feb. 4, 2016) ("[T]he state Department of Environmental Quality issued a notice of violation of the Safe Drinking Water Act for maximum contaminant levels for trihalomethanes—or TTHM—a group of four chemicals that are formed as a byproduct of disinfecting water.") (on file with the Washington and Lee Law Review).

3. *See* John Eligon, *A Question of Environmental Racism in Flint*, N.Y. TIMES (Jan. 21, 2016), http://www.nytimes.com/2016/01/22/us/a-question-of-environmental-racism-in-flint.html?_r=0 (last visited Feb. 4, 2016) ("But it is indisputable that in Flint, the majority of residents are black and many are poor. . . . For civil rights advocates, the health crisis in Flint smacks of what has become known as environmental racism.") (on file with the Washington and Lee Law Review).

4. *See* Kemi Fuentes-George, *Flint's Structural Racism: This Is Why Providing Poisoned Water to the City's Citizens Seemed Like a Reasonable Idea*, SALON (Feb. 7, 2016), http://www.salon.com/2016/02/07/flints_structural_racism_this_is_why_providing_poisoned_water_to_the_citys_citizens_seemed_like_a_reasonable_idea/ (last visited Apr. 3, 2016) ("In an effort to cut corners, the state had 'no choice' but to abandon any renovations of the dilapidated water

far more costly to both the city and the state of Michigan.[5] More importantly, it burdens the population with lead levels that are almost twice as high as they were before the switch, among other devastating impacts.[6]

Lead exposure causes irreversible damage, including behavioral change and neurological impacts, immunotoxicity, and "toxicity to the reproductive organs."[7] These harms are especially acute for children exposed to lead—like the children in Flint.[8] Recent scientific research shows that the children in Flint will face not only physical symptoms, but also changes to how their genetic code operates.[9] Lead exposure causes changes in gene expression that "may not only have immediate dire consequences for brain development, but may also have effects that persist after the initial exposure."[10] Flint's population now suffers from changes in gene expression predisposing them to neurological

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infrastructure, and use the cheapest source of water available, despite persistent questions about its suitability.") (on file with the Washington and Lee Law Review).

5. Estimates of the cost of cleaning the Flint water crisis have ranged from $60 million to $300 billion. *See, e.g.*, Matthew Dolan, *Flint Water Crisis Could Cost U.S. $300 Billion*, USA TODAY (Mar. 5, 2016), http://www.usatoday.com/story/news/nation-now/2016/03/05/flint-water-crisis-could-cost-us-300-billion/81359834/ (last visited Apr. 4, 2016) (discussing the costs of replacing water infrastructure and compensating injured plaintiffs) (on file with the Washington and Lee Law Review); Nick Stockton, *Here's How Hard It Will Be to Unpoison Flint's Water*, WIRED (Jan. 29, 2016), http://www.wired.com/2016/01/heres-how-hard-it-will-be-to-unpoison-flints-water/ (last visited Apr. 4, 2016) (estimating the cost of replacing Flint's lead pipes to be $60 million over fifteen years) (on file with the Washington and Lee Law Review).

6. *See* Wang, *supra* note 1 ("The proportion of infants and children with above-average levels of lead in their blood has nearly doubled since the city switched from the Detroit water system to using the Flint River as its water source, in 2014.").

7. *Lead Poisoning and Health*, WORLD HEALTH ORG. (Aug. 2015), http://www.who.int/mediacentre/factsheets/fs379/en/ (last visited Feb. 4, 2016) (on file with the Washington and Lee Law Review).

8. *Id.*

9. *See* Marie-Claude Senut et al., *Epigenetics of Early-Life Lead Exposure and Effects on Brain Development*, 4 EPIGENOMICS 665, 668–69 (2012) (discussing how early-life lead exposure changes gene expression, causing not only immediate impacts but also leading to late-onset neurological diseases like Alzheimer's).

10. *Id.* at 669.

diseases like Alzheimer's.[11] Sadly, the children exposed to lead in Flint may even pass this predisposition for disease to their grandchildren and great-grandchildren.[12]

To obtain compensation for these harms through the legal system, an exposed child in Flint—or her descendants—would face the obstacle of proving the causal chain between exposure and disease onset.[13] Toxic tort cases create unique challenges for the traditional tort causation model.[14] Plaintiffs often must prove factual cause in tort through "but-for" causation.[15] Yet in toxic tort cases, courts typically go beyond this standard to require proof of both general and specific causation.[16] General causation considers "whether the substance at issue had the capacity to cause the harm alleged."[17] Plaintiffs must prove general causation as a threshold matter.[18] Such proof typically relies on

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11. *Id.* at 669–70.

12. *See id.* at 670 ("[S]ome changes in epigenetic determinants can extend to the germline, raising the possibility that [lead]-induced alterations could be propagated transgenerationally."); *see also* Arko Sen et al., *Multigenerational Epigenetic Inheritance in Humans: DNA Methylation Changes Associated with Maternal Exposure to Lead Can Be Transmitted to the Grandchildren*, 5 SCI. REP. 1, 6 (2015) (concluding that lead exposure in a pregnant woman can change the gene expression patterns of her grandchildren); *infra* Part II.B (discussing the heritability of epigenetic harms).

13. *See infra* Part IV (summarizing how courts handle the causation issue in toxic tort cases).

14. *See* Steve C. Gold, *When Certainty Dissolves into Probability: A Legal Vision of Toxic Causation for the Post-Genomic Era*, 70 WASH. & LEE L. REV. 237, 244 (2013) ("A fundamental difficulty in proving such a claim is that exposure and disease usually do not correlate perfectly: some people get sick without exposure, and some people receive exposure without getting sick.").

15. *See* RESTATEMENT (THIRD) OF TORTS: LIAB. FOR PHYS. AND EMOT. HARM § 26 cmt. b (AM. LAW INST. 2010) ("[A]n act is a factual cause of an outcome if, in the absence of the act, the outcome would not have occurred.").

16. *See* Henricksen v. Conoco Phillips Co., 605 F. Supp. 2d 1142, 1155 (E.D. Wash. 2009) ("Courts in toxic tort cases often separate the causation inquiry into general causation and specific causation."); *see also* Loren Peck, *How Sound Is the Science? Applying* Daubert *to Biomechanical Experts' Injury Causation Opinions*, 73 WASH. & LEE L. REV. 1063, 1083–86 (2016) (elaborating on the difference between general and specific causation and applying *Daubert* to evidence in personal injury cases).

17. Hanford Nuclear Reservation Litig. v. E. I. Dupont, 292 F.3d 1124, 1133 (9th Cir. 2002).

18. *See* Gold, *supra* note 14, at 245 ("Courts initially demand proof of 'general causation,' asking whether the exposure in question is ever a sine qua non for the plaintiff's disease, or whether the existence of cases of disease after

epidemiological data at the population level rather than data specific to an individual plaintiff's injury.[19] Epidemiological data results from population-level studies that determine the connection, if any, between diseases and environmental exposures or conditions.[20]

In contrast, specific causation "refers to whether a particular individual suffers from a particular ailment as a result of exposure to a substance."[21] Once plaintiffs prove general causation, they must also prove their individual exposure to the substance and the causal chain leading to their resulting injury.[22] Toxic tort cases often fail to prove specific causation because the biological mechanisms of exposure and disease are unknown or uncertain.[23]

Epigenetics—an emerging scientific field—provides a new causal mechanism for connecting disease to environmental toxin exposures.[24] Epigenetics refers to the study of "heritable changes

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exposure is merely coincidental.").

19. *See* Merrell Dow Pharms., Inc. v. Havner, 953 S.W.2d 706, 715–17 (Tex. 1997) (summarizing the different standards that courts use to determine causation based on epidemiological evidence).

20. *Id.* at 715 ("Epidemiological studies examine existing populations to attempt to determine if there is an association between a disease or condition and a factor suspected of causing that disease or condition.").

21. *Hanford*, 292 F.3d at 1133.

22. *See* Mitchell v. Gencorp, Inc., 165 F.3d 778, 781 (10th Cir. 1999) ("It is well established that a plaintiff in a toxic tort case must prove that he or she was exposed to and injured by a harmful substance manufactured by the defendant."); Wright v. Willamette Indus., 91 F.3d 1105, 1106 (8th Cir. 1996) ("[A] plaintiff in a toxic tort case must prove . . . the plaintiff's actual level of exposure to the defendant's toxic substance before he or she may recover."); Allen v. Pa. Eng'g Corp., 102 F.3d 194, 199 (5th Cir. 1996) ("Scientific knowledge of the harmful level of exposure to a chemical, plus knowledge that the plaintiff was exposed to such quantities, are minimal facts necessary to sustain the plaintiffs' burden in a toxic tort case.").

23. *See* June v. Union Carbide Corp., 577 F.3d 1234, 1245 (10th Cir. 2009) (noting that the plaintiffs failed to present evidence that exposure to radiation "was either a but-for cause of any medical condition . . . or . . . a necessary component of a causal set that would probably have caused one of those conditions"); *see also* Gold, *supra* note 14, at 250–52 (discussing the nearly "impossible task" of proving but-for causation in toxic tort cases).

24. *See* Laura S. Rozek et al., *Epigenetics: Relevance and Implications for Public Health*, 35 ANN. REV. PUB. HEALTH 105, 107 (2014) ("Molecular epidemiology is a useful approach for linking exposures and disease in human populations.").

in gene expression that are not due to any alteration in the DNA sequence."[25] A variety of chemicals and environmental conditions cause adverse health effects through epigenetic mechanisms.[26] These changes therefore provide an intermediate causal link between exposure (and risk creation) and the onset of disease.[27] Epigenetics provides an opportunity for courts to reframe the causation issue for toxic torts, particularly when considering liability for increased risk of disease.[28] This Note argues for courts to accept epigenetic harm as present physical injury for an increased risk claim and recommends that courts submit epidemiological evidence to the fact-finders without arbitrary legal cutoffs for scientific rigor.

Part II of this Note provides a scientific background and summarizes the current state of epigenetics research. Part III summarizes the primary challenges of proving causation in toxic tort cases and how courts address these challenges by modifying the existing causation framework. Part IV discusses how epigenetics can inform the causation inquiry in toxic torts cases and argues for modifying the increased risk framework according to scientific development.

II. Scientific Background

A. Gene Expression and the Epigenome

"Gene expression" refers to the process of producing proteins from the underlying DNA sequence—which is also known as the genetic code or genome.[29] Epigenetics describes the regulation of

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25. Manel Esteller, *Molecular Origins of Cancer: Epigenetics in Cancer*, 358 NEW ENG. J. MED. 1148, 1148 (2008).

26. *See* Andrea Baccarelli & Valentina Bollati, *Epigenetics and Environmental Chemicals*, 21 CURRENT OP. PEDIATRICS 243, 244–49 (2009) (summarizing the epigenetic impacts of various environmental chemicals).

27. *See* Rozek, *supra* note 24, at 108 (describing how epigenetics can be used to "identify relevant markers for translational studies of disease prediction and treatment in human populations").

28. *See* Gold, *supra* note 14, at 299–302 (discussing how courts might reframe increased risk and causation as science reveals the cellular changes leading to disease symptoms).

29. *See* E.R. Gibney & C.M. Nolan, *Epigenetics and Gene Expression*, 105 HEREDITY 4, 4–5 (2010) (providing an overview of the steps involved in gene

this process.[30] Genes can be activated or silenced—turned "on" or "off"—meaning they do or do not produce protein.[31] Genes can also be up-regulated or down-regulated, meaning they generate more or less of their protein product.[32] These changes in gene expression can have positive, negative, or neutral effects on health.[33] For example, epigenetic changes can serve a protective function by allowing an organism to adapt quickly to environmental cues.[34] They can silence genes that are likely to cause disease.[35] Epigenetic change can, however, also lead to serious diseases—when silencing genes with a protective function, for example.[36]

Many different biological and chemical pathways regulate gene expression.[37] Although the underlying molecular DNA

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expression).

30. *See* David Rodenhiser & Mellissa Mann, *Epigenetics and Human Disease: Translating Basic Biology into Clinical Applications*, 174 CAN. MED. ASS'N J. 341, 341 (2006) ("[Epigenetics] is the study of heritable changes in gene function that do not change the DNA sequence but, rather, provide an 'extra' layer of transcriptional control that regulates how genes are expressed.").

31. *See id.* ("Changes to the structure of chromatin influence gene expression: genes are inactivated (switched off) when the chromatin is condensed (silent), and they are expressed (switched on) when chromatin is open (active).").

32. *See* Gerda Egger et al., *Epigenetics in Human Disease and Prospects for Epigenetic Therapy*, 429 NATURE 457, 460–61 (2004) (describing the up-regulation and down-regulation of different genes associated with cancers); Mark A. Rothstein et al., *The Ghost in Our Genes: Legal and Ethical Implications of Epigenetics*, 19 HEALTH MATRIX 1, 5 (2009) ("While epigenetic changes can result in changes in the expression of . . . traits, they do so not by changing the form or function of gene products, but by altering the timing and quantity of their production in tissues at key points in time.").

33. *See* Rothstein et al., *supra* note 32, at 7–21 (providing an overview of normal and abnormal epigenetic changes in cells).

34. *See id.* at 10 ("Such mechanisms allow a developing organism to adjust its phenotype to its anticipated environment, thereby increasing its fitness . . . .").

35. *See id.* at 8 (noting that a normal role of the epigenome is to silence "disruptive sequences" that are likely to mutate and cause cancer or other diseases).

36. *See* Randy L. Jirtle & Michael K. Skinner, *Environmental Epigenomics and Disease Susceptibility*, 8 NATURE REVS. GENETICS 253, 257 (2007) (describing how a single epigenetic change can silence a protective tumor-suppressor gene and result in higher cancer risk).

37. *See* Edith Heard & Robert A. Martienssen, *Transgenerational Epigenetic Inheritance: Myths and Mechanisms*, 157 CELL 95, 99 (2005)

sequence—*A*s, *T*s, *C*s, and *G*s[38]—remains the same, epigenetic changes shape an organism's traits, health, and development.[39] The more common epigenetic modifications involve chemical changes to the DNA sequence that tighten or loosen the DNA structure (known as chromatin) itself.[40] These structural changes affect the ease of creating protein product from the gene sequence.[41] With a more compact structure, the biological machinery needed to create proteins has more difficulty attaching to the DNA, creating less or no protein product.[42] A more open structure, however, allows for easier binding and "reading" of the DNA sequence, leading to more protein product.[43] The illustration below shows some different structures of DNA.[44]

(summarizing a variety of epigenetic mechanisms).

38. These letters refer to the nucleotide building blocks of DNA that pair to create the double-helix structure: adenine, thymine, cytosine, and guanine. *See generally* Leslie A. Pray, *Discovery of DNA Structure and Function: Watson and Crick*, 1 NATURE EDUC. 100 (2008), http://www.nature.com/scitable/topicpage/discovery-of-dna-structure-and-function-watson-397.

39. *See* Rothstein et al., *supra* note 32, at 5 ("Changes in determining which genes are expressed and their degree of expression can have dramatic effects on the development and characteristics of an organism.").

40. *See* Rodenhiser, *supra* note 30, at 341 (discussing the basic chemical modifications to DNA structure and their impacts on gene expression).

41. *See id.* (describing how the epigenome guides the process of creating protein from genes).

42. *See id.* (discussing the impacts of condensed chromatin on gene expression).

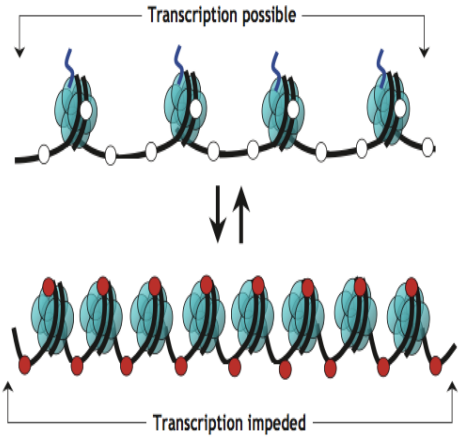
43. *See id.* (discussing the impacts of open chromatin on gene expression).

44. Figure reprinted from Rodenhiser, *supra* note 30, at 342.

Figure 1

Open chromatin structure, allowing for more transcription and protein product.

Condensed chromatin structure, slowing transcription and impeding the creation of protein.



The "epigenome" refers to all of the epigenetic changes in an organism.[45] Such changes explain why organisms with identical DNA sequences can exhibit different physical characteristics and "different susceptibilities to a disease."[46] The underlying gene sequence is analogous "to the hardware of a computer, whereas epigenetic information has been compared to computer software that controls the operation of the hardware."[47]

Epigenetic changes occur normally in cells.[48] Their most important role, for example, is controlling cell differentiation.[49] Although every cell in the human body has the same underlying

45. *See* Rothstein et al., *supra* note 39, at 6 ("Each epigenetic change is referred to as a 'mark,' and the total set of epigenetic marks in an organism is referred to as the epigenome.").

46. Esteller, *supra* note 25, at 1148.

47. Rothstein et al., *supra* note 39, at 3.

48. *See id.* at 7–11 (discussing the role of epigenetic programming in cells through normal development); *see also* Esteller, *supra* note 25, at 1148 ("DNA methylation has critical roles in the control of gene activity and the architecture of the nucleus of the cell.").

49. *See* Rothstein et al., *supra* note 39, at 7 ("The primary function of epigenetic programming is to control cell differentiation through differential gene expression.").

DNA sequence, different cells serve very different purposes through differential gene expression.[50]

From an evolutionary perspective, the epigenome also allows quick adaptation to environmental cues.[51] For example, rat pups with mothers who failed to nurse properly show an increased stress response later in life.[52] These mothers' nursing failures likely resulted from some environmental threat, and the pups face the same environment.[53] The rat pups inherited some epigenetic markers from their mother, and their mother's behavior further shaped their epigenomes.[54] These epigenetic changes create nervous offspring, who will be better prepared to react to environmental threats and should survive longer.[55] However, disease and other problems arise when epigenetic changes fail to match environmental stressors—usually as a result of mixed environmental cues or epigenetic modifications inherited from parents.[56] The rat pups, for example, may face a

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50. *See id.* at 7–8 ("Yet, different cell types, whether skin cells, muscle cells, bone cells, or nerve cells, display markedly different properties due to different sets of genes being turned on or off.").

51. *See* Graham C. Burdge & Karen A. Lillycrop, *Nutrition, Epigenetics, and Developmental Plasticity: Implications for Understanding Human Disease*, 30 ANN. REV. NUTRITION 315, 330–31 (2010) (discussing examples where epigenetic changes from environmental cues enhance organism fitness); Rothstein et al., *supra* note 39, at 9 ("[E]pigenetics provides a mechanism for a developing organism, either in utero or post-natally, to assess its environment and adjust its genetic response accordingly.").

52. *See* Burdge & Lillycrop, *supra* note 51, at 330 (summarizing epigenetic changes that likely increase evolutionary fitness).

53. *See* Ian C.G. Weaver et al., *Epigenetic Programming by Maternal Behavior*, 7 NATURE NEUROSCIENCE 847, 852 (2004) ("Such effects commonly follow from the exposure of the mother to the same or similar forms of threat and may represent examples whereby the experience of the mother is translated through an epigenetic mechanism of inheritance into phenotypic variation in the offspring.").

54. *See, e.g.*, I. Mendizabal et al., *Epigenetics and Evolution*, 54 INTEGRATIVE & COMP. BIOLOGY 31, 31 (2014) (noting that epigenetic changes include those that arise from environmental cues during an organism's lifespan and those transmitted through generations).

55. *See* Burdge & Lillycrop, *supra* note 51, at 330 ("More nervous offspring may be less susceptible to being stalked by predators.").

56. *See id.* at 317 ("[A]n incorrect prediction, such as may occur if maternal nutrition is adequate but placental function is suboptimal, would result in mismatch between the physiology of the offspring and the future environment. Such mismatch has been suggested to underlie cardio-metabolic disease in humans.").

different environment than their mother did—one where an overactive stress response becomes burdensome rather than advantageous.

B. Heritability of Epigenetic Change

Epigenetic changes have been shown to persist over many generations of offspring.[57] Unlike the underlying DNA sequence, a mammal's epigenome is subject to "reprogramming" or "resetting" in the embryo stage.[58] Most of the epigenetic marks are erased and reset early in development.[59] However, not all of the epigenetic changes are subject to this process, meaning that some are passed through generations.[60] The epigenome can have both transgenerational and intergenerational effects.[61] Intergenerational effects describe those passed along to organisms that were exposed to an environmental factor in utero—a mother and child have the same epigenetic change.[62] Transgenerational effects, however, describe those that persist beyond generations exposed to the environmental factor—an organism and its great-grandparent have the same epigenetic change.[63] Some epigenetic modifications have persisted for hundreds of years in plant species and for over forty generations in some animals.[64] Studies have shown epigenetic changes from toxin exposure persisting for up to four generations.[65] Most

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57. *See* Heard & Martienssen, *supra* note 37, at 95 (summarizing studies showing intergenerational and transgenerational effects of epigenetic change).

58. Mendizabal et al., *supra* note 54, at 37.

59. *Id.*

60. *See, e.g.*, *id.* (discussing studies of plants and animals which revealing that "some epigenetic marks escape epigenetic reprogramming").

61. *See* Heard & Martienssen, *supra* note 37, at 96 ("[I]t is important to distinguish [intergenerational] effects, such as the impact of in utero exposure to particular . . . environments . . . from truly transgenerational effects that are found in generations that were not exposed to the initial signal or environment that triggered the change.").

62. *Id.*

63. *Id.*

64. *See id.* at 103 (discussing examples of transgenerational effects in different types of organisms).

65. *See* Matthew D. Anway et al., *Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility*, 308 SCI. 1466, 1466 (2005) (noting that

human studies have focused on intergenerational impacts, and further research is needed on both transgenerational and intergenerational effects.[66] Even so, research firmly establishes the impact of environmental cues on individuals throughout all stages of development.[67] Because the science on intergenerational harms is still developing, this Note addresses epigenetic harms in only the generation exposed to a toxin.[68]

C. Epigenetics and Disease

A variety of chemicals and environmental conditions cause epigenetic changes that lead to adverse health effects.[69] Some toxins linked to specific epigenetic changes include: lead, arsenic, cadmium, nickel, chromium, methylmercury, air pollutants, benzene, BPA, trichloroethylene, arsenic, and persistent organic pollutants.[70] The study of epigenetics reveals a number of biological mechanisms connecting exposure to substances like these with disease symptoms.[71] For example, many different

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endocrine disruptors caused "transgenerational defects in spermatogenic capacity and sperm viability"); Mohan Manikkam et al., *Transgenerational Actions of Environmental Compounds on Reproductive Disease and Identification of Epigenetic Biomarkers of Ancestral Exposures*, PLoS ONE, Feb. 2012, at 5 ("[T]he current study has established the transgenerational actions of these compounds . . . .").

66. *See* Heard & Martienssen, *supra* note 37, at 105 (discussing the evidence for intergenerational and transgenerational effects in human populations).

67. *See id.* ("[D]ifferent nutritional cues during infancy and childhood can have adverse effects during adult life, and exposure to pollutants, alcohol, and tobacco can affect fetal programming. . . . [A] wide range of environmental conditions during embryonic development and early life determine susceptibility to disease during adult life.").

68. *See infra* Part V (discussing how epigenetic evidence can be used to prove causation in cases where a plaintiff is exposed to a toxin).

69. *See* Baccarelli & Bollati, *supra* note 26, at 244–49 (summarizing the epigenetic impacts of various substances, including heavy metals, air pollution, endocrine disruptors, and other environmental contaminants).

70. *See, e.g.*, *id.* at 247 (providing a table of the epigenetic effects of various environmental chemicals).

71. *See id.* at 249 ("Epigenetics holds substantial potential for developing biological markers to predict which exposures would put exposed individuals at risk and which individuals will be more susceptible to develop disease.").

cancer tumors show abnormal epigenetic marks.[72] Certain epigenetic changes can even be used to predict cancer patient outcomes and responses to treatment.[73] The table below provides a summary of some human diseases that have been linked to epigenetic abnormalities, with the "biological process" column indicating the type of epigenetic change that was found.[74]

72. *See* Esteller, *supra* note 25, at 1152 (listing "epigenetic aberrations" across thirteen types of cancers in Table 1).

73. *See id.* at 1155 (noting that certain epigenetic marks "can be indicators of the prognosis in patients with cancer" and act as "a predictor of the response to treatment"); Dieter Weichenhan & Christoph Plass, *The Evolving Epigenome*, 22 HUM. MOLECULAR GENETICS R1, R2 (2013) ("Cancer-specific DNA methylation can serve as a marker for early detection of a disease or as a prognostic marker that helps to classify tumor subgroups with different biological or clinical features.").

74. Table reprinted from Rodenhiser & Mann, *supra* note 30, at 344.

Table 1: Associations Between Epigenetic Modifications and Human Diseases and Conditions

Disease/condition	Gene	Biological process	Disease/condition	Gene
Cancer			**Neurologic**	
Bladder	Multiple genes	Hypermethylation[20]	Schizophrenia	*RELN*
Brain (glioma)	*RASSF1A*	Hypermethylation[28,29]	Bipolar disorder	*11p?*
Brain (glioblast)	*MGMT*	Hypermethylation[30]	Memory formation	Multiple genes
Breast	*BRCA1*	Hypermethylation[31]	**Lupus**	Retroviral DNA
Breast	Multiple genes	Hypermethylation[32,33]	**Cardiovascular**	
Cervix	*p16*	Hypermethylation[34]	Atherosclerosis	Multiple genes
Colon	Multiple genes	Hypermethylation[20]	Homocysteinemia	Multiple genes
Colorectal	L1 repeats	Hypomethylation[35]	Vascular endothelium	*eNOS*
Esophagus	*CDH1*	Hypermethylation[20]	**Imprinting and pediatric syndromes**	
Head/neck	*p16, MGMT*	Hypermethylation[20]	PWS or AS	15q11-q13
Kidney	*TIMP-3*	Hypermethylation[20]	BWS	11p15
Leukemia	p15	Hypermethylation[20]	SRS	Chromosome 7
Liver	Multiple genes	Hypermethylation[36]	UPD14	14q23-q32
Lung	*p16, p73*	Hypermethylation[20]	PHP, AHO, MAS	20q13.2
Lymphoma	*DAPK*	Hypermethylation[20]	Rett syndrome	*MECP2*
Myeloma	*DAPK*	Hypermethylation[37]	ICF syndrome	*DNMT3B*
Ovary	*BRCA1*	Hypermethylation[38]	ATRX	*ATRX*
Ovary	*Sat2*	Hypomethylation[39]	FraX	Triplet repeat
Pancreas	*APC*	Hypermethylation[20]	FSHD	3.3 kb repeat
Pancreas	Multiple genes	Hypomethylation[40]	**Reproductive**	
Prostate	*BRCA2*	Hypermethylation[20,41]	Ovarian teratoma	No paternal genome
Rhabdomyosarcoma	*PAX3*	Hypermethylation[42]	CHM	No maternal genome
Stomach	*Cyclin D2*	Hypomethylation[43]	BiCHM	Maternal genome
Thymus	*POMC*	Hypomethylation[44]	**Aging**	Chromatin
Urothelial	Satellite DNA	Hypomethylation[45]		
Uterus	*hMLH1*	Hypermethylation[20]		

Note: PWS = Prader-Willi syndrome; AS = Angelman syndrome; BWS = Beckwith-Weidemann syndrome; SRS = Silver-Russell syndrome; PHP = pseudohypoparathyroidism; AHO = Albright hereditary osteodystrophy; MAS = McCune-Albright syndrome; ICF = immunodeficien and facial anomalies; ATRX = α-thalassemia/mental retardation syndrome, X-linked; FraX = Fragile X syndrome; FSHD = facioscapuloh CHM = complete hydatidiform mole, BiCHM = familial biparental CHM.

This table summarizes just a few of the scientific studies linking epigenetic changes to disease.[75] Epigenetics therefore provides a scientific link between exposure to toxic chemicals and

75. *See* Arline T. Geronimus, *Deep Integration: Letting the Epigenome Out of the Bottle Without Losing Sight of the Structural Origins of Population Health*, 103 AM. J. PUB. HEALTH S56, S56 (2013) (discussing the relationships between epigenetic changes and population health).

disease onset.[76] The interplay between the genome and the epigenome provides another layer of complication, as certain *genes* may even create a propensity for abnormal *epigenetic* changes.[77] Scientific research, however, will continue to link toxins to epigenetic markers, and epigenetic markers to certain diseases. The legal issue, then, becomes how to consider these markers in the causation analysis.

III. Using Scientific Evidence to Prove Causation

A. Overview of Causation

Plaintiffs in toxic tort cases face great difficulty proving specific causation.[78] Most courts follow the but-for test for causation in tort cases: "Conduct is a factual cause of harm when the harm would not have occurred absent the conduct."[79] This test fits poorly with the factual progression of the typical toxic tort case—exposure, followed by a long latency period, only some of the exposed falling ill, and many possible contributing causes.[80] Environmentally caused diseases do not follow a simple but-for model of causation.[81] As a result, courts and scholars have suggested alternative tests for evaluating causation in toxic tort cases.[82]

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76. *See* Baccarelli & Bollati, *supr*a note 26, at 244–49 (noting chemicals that have been linked to epigenetic change and disease).

77. *See* Rodenhiser & Mann, *supra* note 30, at 343 ("People's sensitivity to diet or to environmental toxins may vary owing to pre-existing genetic variants that can challenge methyl metabolism and predispose a person to epigenetic change.").

78. *See* Gold, *supra* note 14, at 245–52 (discussing obstacles to proving causation in toxic injury cases).

79. RESTATEMENT (THIRD) OF TORTS § 26 (2014).

80. *See* Gold, *supra* note 14, at 244 ("[E]xposure and disease usually do not correlate perfectly: some people get sick without exposure, and some people receive exposure without getting sick. In marked contrast to traumatic injury cases, the disease process itself is unobserved and unobservable as it occurs, and inscrutable afterward.").

81. *See, e.g.*, Fazal Khan, *Preserving Human Potential as Freedom: A Framework for Regulating Epigenetic Harms*, 20 HEALTH MATRIX 259, 283 (2010) ("From a biological perspective, the concept of disease as a spectrum rather than a binary on/off event is logical.").

82. *See infra* Part IV (summarizing how courts have modified causation

Most tort cases require plaintiffs to prove causation by the preponderance of the evidence, meaning that plaintiffs must show a degree of certainty over fifty percent for the fact-finder to find for the plaintiff.[83] Different courts follow different approaches to reaching this proof threshold for the causation issue. Some states require evidence of both general and specific causation—sometimes referred to as a "strong" view of causation.[84] A minority of states allow a plaintiff to prove causation based solely on evidence of general causation—sometimes referred to as a "weak" view of causation.[85] How a court considers population-level data (as opposed to plaintiff-specific data) becomes a key difference between these approaches.

B. The Role of Epidemiological Studies and Scientific Parameters

Most scientific evidence in toxic tort cases involves epidemiological studies, which examine the relationship between environmental factors and disease.[86] Different states demand different standards for allowing epidemiological data to prove general or specific causation.[87] As with any evidence, epidemiological studies face the threshold legal issues of admissibility and sufficiency.[88] Admissibility refers to whether or

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doctrine to fit toxic tort cases).

83. *See* David Rosenberg, *The Causal Connection in Mass Exposure Cases: A "Public Law" Vision of the Tort System*, 97 HARV. L. REV. 851, 857–58 (1984) (discussing how different courts approach proof of causation in toxic tort cases).

84. *See In re* "Agent Orange" Prods. Liab. Litig., 611 F. Supp. 1223, 1261 (E.D.N.Y. 1985) (noting that a plaintiff must "offer both epidemiologic evidence that the probability of causation exceeds fifty percent in the exposed population and 'particularistic' proof that the conduct complained of caused him harm individually").

85. *See* Rosenberg, *supra* note 83, at 857–58 (noting that a "weak version" of causation "authorizes verdicts founded solely on statistical evidence").

86. *See* Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584, 590–91 (D.N.J. 2002) ("Epidemiological studies attempt to identify agents that are associated with an increased risk of disease.").

87. *See infra* Part IV (addressing the different approaches that courts use in considering epidemiological evidence).

88. *See* Michael D. Green, D. Michal Freedman & Leon Gordis, *Reference Guide on Epidemiology*, *in* FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 549, 610 (3d ed. 2011) ("Two legal issues arise with regard

not a court should consider the study as evidence, while sufficiency refers to how much weight a court gives a study when considering the plaintiff's case.[89]

Scientific evidence usually meets the admissibility standard more easily than it meets the sufficiency standard.[90] The admissibility of expert evidence in federal courts is governed by Federal Rule of Evidence 702 and the cases of *Daubert v. Merrell Dow Pharmaceuticals, Inc.*,[91] *Kumho Tire Co. v. Carmichael*,[92] and *General Electric Co. v. Joiner*[93].[94] Within these boundaries, though, some scholars and courts require only a low bar for admissibility: "An epidemiologic study that is sufficiently rigorous to justify a conclusion that it is scientifically valid should be admissible, as it tends to make an issue in dispute more or less likely."[95] Generally, plaintiffs do not face strict bars to the admissibility of epidemiological data.

Courts become stricter when dealing with the issue of sufficiency of evidence, often following bright-line cutoffs according to certain scientific parameters, such as relative risk or dose-response curves.[96] Relative risk represents the increased

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to the role of epidemiology in proving individual causation: admissibility and sufficiency of evidence to meet the burden of production.").

89. *Id.* at 610–11.

90. *See, e.g.*, *id.* ("[Admissibility] tends to receive less attention by the courts but nevertheless deserves mention."); Tumlinson v. Advanced Micro Devices, Inc., No. 08C-07-106 FSS, 2012 Del. Super. LEXIS 209, at *14 (Del. Super. Ct. Jan. 6, 2012) ("Some jurisdictions follow [a bright-line rule for admissibility]. Others accept the statistical significance requirements as a measure of evidentiary sufficiency, but not as a threshold for admissibility. And, others merely require a positive association, relying on the jury to determine the significance of the studies after proper instruction."); Ellis v. Int'l Playtex, Inc., 745 F.2d 292, 303 (4th Cir. 1984) ("Playtex's concern about the methodology of the studies should have been addressed to the relative weight accorded the evidence and not its admissibility.").

91. 509 U.S. 579 (1993).

92. 526 U.S. 137 (1999).

93. 522 U.S. 136 (1997).

94. A thorough discussion on the admissibility of scientific evidence under these rules and precedents is beyond the scope of this Note. For an overview of these issues, see 29 CHARLES ALAN WRIGHT & VICTOR JAMES GOLD, FED. PRAC. & PROC. § 6266 (Supp. 2012). *See also* Peck, *supra* note 16, at 1072–76 (summarizing the *Daubert* standard).

95. Green, *supra* note 88, at 610.

96. *See id.* at 612 (discussing how courts handle evidence related to relative

risk of disease faced by people exposed to a certain substance.[97] A dose-response curve represents how this risk changes with increasing exposure.[98] Texas, for example, requires a relative risk of 2.0 or greater before allowing epidemiological data to satisfy even general causation.[99] The relevance of these two parameters for toxic tort cases is explained further below.

1. Relative Risk

Epidemiological data typically yields a factor known as "relative risk"[100]:

> Relative risk indicates the difference in risk of contracting a disease in people exposed to a risk factor, as compared to those not exposed (but otherwise similar). Determining the relative risk is important in understanding the results of a study because virtually every disease associated with a risk factor also occurs, at some rate, in the general population not exposed to the risk factor.[101]

To calculate a relative risk factor, scientists divide the risk of developing a disease in a group exposed to an environmental factor by the risk of developing a disease in a similar group that is not exposed.[102] For example, if 9 out of 100 people develop a disease while taking a particular drug, but 6 out of 100 people *not* on the drug also develop the disease, the relative risk would be

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risk of disease).

97. Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584, 591 (D.N.J. 2002).

98. McClain v. Metabolite Int'l, Inc., 401 F.3d 1233, 1241 (11th Cir. 2005).

99. *See* Merck & Co. v. Garza, 347 S.W.3d 256, 265 (Tex. 2011) ("[W]hen parties attempt to prove general causation using epidemiological evidence, a threshold requirement of reliability is that the evidence demonstrate a statistically significant doubling of the risk.").

100. *See* Estate of George v. Vt. League of Cities & Towns, 993 A.2d 367, 374 (Vt. 2010) (noting that epidemiological data quantifies "the degree of association between a given substance and a disease by assigning a 'relative risk' factor to the association").

101. *Magistrini*, 180 F. Supp. 2d at 591.

102. *See id.* (noting that relative risk factors are "calculated by dividing the risk of developing a disease observed in an exposed group by the risk observed in an unexposed, but otherwise similar group").

.09/.06 = 1.5.[103] If both groups show the same occurrence of disease, then the risks are identical, the relative risk is 1.0, and the factor does not correlate with a higher incidence of disease.[104] A relative risk of 2.0, known as "doubling of the risk," means that the group exposed to a toxin showed twice as many individuals with disease as the unexposed group.[105] Therefore, courts have determined that a relative risk over 2.0 supports the assertion that a "plaintiff's disease was more likely than not caused by the implicated agent."[106] Accordingly, a number of courts require a relative risk of 2.0 or greater for a plaintiff to satisfy the burden of proof on general causation.[107] Courts that allow epidemiological data to satisfy specific causation—the "weak" view—may also require plaintiffs to meet a relative risk cutoff of 2.0.[108] The Third Restatement of Torts follows this model, requiring a relative risk of over 2.0 before an epidemiological study may be submitted to the jury for specific causation.[109]

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103. *See, e.g.*, Merrell Dow Pharms., Inc. v. Havner, 953 S.W.2d 706, 717 (Tex. 1997) (providing a sample calculation for relative risk).

104. *See* Magistrini v. One Hour Martinizing Dry Cleaning, 180 F. Supp. 2d 584, 591 (D.N.J. 2002) ("If the risks of the unexposed and exposed are the same, then the relative risk estimate (which mathematically is simply the former divided by the latter) is 1.0. This . . . indicates that exposure is not associated with the disease in that study.").

105. Green et al., *supra* note 88, at 612.

106. *Id.*

107. *See Havner*, 953 S.W.2d at 717 ("[W]e are persuaded . . . that there is a rational basis for relating the requirement that there be more than a 'doubling of the risk' to our no evidence standard of review and to the more likely than not burden of proof."); Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1403 (D. Or. 1996) ("In epidemiological terms, Oregon's standard of proof means that plaintiffs must be able to show a relative risk of greater than 2.0."); DeLuca v. Merrell Dow Pharms., Inc., 911 F.2d 941, 958 (3d Cir. 1990) ("[T]he relative risk of limb reduction defects arising from the epidemiological data Done relies upon will, at a minimum, have to exceed '2.'").

108. *See* Tumlinson v. Advanced Micro Devices, Inc., No. 08C-07-106 FSS, 2012 Del. Super. LEXIS 209, at *7 (Del. Super. Ct. Jan. 6, 2012) ("[S]cientists may not be able to determine exactly what caused the plaintiff's injury. But, scientifically reliable epidemiological studies may provide evidence of causation if they establish that exposure to the toxin more than doubles the risk of injury in the general population.").

109. *See* RESTATEMENT (THIRD) OF TORTS: LIAB. FOR PHYS. AND EMOT. HARM § 28(a) cmt. (c)(4) (AM. LAW INST. 2010) ("[W]hen there is group-based evidence finding that exposure to an agent causes an incidence of disease in the exposed group that is more than twice the incidence in the unexposed group, the evidence is sufficient to . . . permit submission of specific causation to a jury.").

Texas courts, for example, require a doubling of the risk for epidemiological data to satisfy either general *or* specific causation.[110] Additionally, Texas courts require that studies demonstrate this risk as statistically significant at a 95% confidence level, another statistical parameter for measuring scientific rigor.[111] In one Texas products liability case, plaintiffs sued for a wrongful death, alleging that it was caused by a prescription anti-inflammatory drug.[112] The court barred recovery because the plaintiffs failed to present epidemiological studies that met the Texas standard for "scientific reliability," namely, a relative risk over two and statistical significance at a 95% confidence level.[113] The court rejected the plaintiffs' offered studies after a lengthy discussion of their scientific rigor, concluding that none of the studies properly represented the decedent's dosage and duration of the drug.[114] The court went on to reject the plaintiff's argument that "the totality of the evidence" could be used to prove general causation even where individual scientific studies failed to meet Texas's rigorous standard.[115]

Depending on the evidence and facts of a specific case, this doubling of the risk standard may be an inappropriate barrier to proving a plaintiff's case: "[T]here are a number of reasons why reliance on a relative risk of 2.0 as a bright-line boundary would not be in accordance with sound scientific methodology in some cases. Careful exploration and explication of what is reliable

110. *See* Merck & Co. v. Garza, 347 S.W.3d 256, 265 (Tex. 2011) ("[W]hen parties attempt to prove general causation using epidemiological evidence, a threshold requirement of reliability is that the evidence demonstrate a statistically significant doubling of the risk.").

111. *See id.* ("We concluded that any study that did not find a doubling of the risk that was statistically significant at the 95% confidence level was unreliable.").

112. *See id.* at 259 ("Respondents contend that Vioxx, a prescription drug, caused their decedent's death.").

113. *See id.* at 267–68 (discussing the plaintiff's failure to present adequate scientific evidence supporting general causation).

114. *See id.* at 266–68 (summarizing the studies and emphasizing the "differences in dose and duration compared to [the decedent's] exposure").

115. *See id.* at 268 ("The totality of the evidence cannot prove general causation if it does not meet the standards for scientific reliability established by *Havner*. A plaintiff cannot prove causation by presenting different types of unreliable evidence.").

scientific methodology in a given context is necessary."[116] A certain relative risk cutoff may also be misleading when a plaintiff has a genetic or epigenetic susceptibility to a particular substance.[117] If a plaintiff has a genetic or epigenetic marker revealing susceptibility to a substance, then a study's relative risk may underestimate the risk that the individual plaintiff faces from exposure. On the other hand, if a plaintiff *lacks* a common genetic or epigenetic marker contributing to a disease, then a study's relative risk may underestimate the contribution that exposure had to that particular disease.[118] Because of these types of ambiguities, some courts take a more holistic approach to determining evidentiary sufficiency.[119] New Jersey courts, for example, will not exclude an expert's testimony merely because she relies on studies with a relative risk below 2.0.[120] The New Jersey Superior Court emphasized the importance of leaving the evidentiary weight issues to the fact-finder.[121] Following this precedent, the New Jersey Supreme Court further elaborated: "[A] relative risk of 2.0 is not so much a password to a finding of causation as one piece of evidence, among others, for the court to consider in determining whether the expert has employed a sound methodology in reaching his or her conclusion."[122] Other courts have similarly given the jury more discretion in determining causation, finding a specific cutoff to be entirely arbitrary.[123]

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116. Merrell Dow Pharms., Inc. v. Havner, 953 S.W.2d 706, 719 (Tex. 1997).

117. *See* Green, *supra* note 88, at 616–17 (noting the possible impact of genetic contributions to a plaintiff's risk).

118. *See id.* ("[G]enetics might be known to be responsible for 50% of the incidence of a disease independent of exposure to the agent. If genetics can be ruled out in an individual's case, then a relative risk greater than 1.5 might be sufficient . . . .").

119. *See id.* at 616 (discussing how some courts handle additional factors that may affect the causation inquiry).

120. *See* Grassis v. Johns-Manville Corp., 591 A.2d 671, 676–77 (N.J. Super. Ct. App. Div. 1991) ("In the case before us we need not, for the reasons stated earlier, set any risk factor limitation at 2.0 or any other arbitrary number. The total basis for the expert's opinion must be scrutinized.").

121. *See id.* at 676 (noting the importance of "the resolution of the issue by a jury").

122. Landrigan v. Celotex Corp., 605 A.2d 1079, 1087 (N.J. 1992).

123. *See, e.g.*, *In re* Joint E. & S. Dist. Asbestos Litig. v. U.S. Mineral Prods. Co., 52 F.3d 1124, 1134 (2d Cir. 1995) ("We believe that it would be far

2. Dose-Response Curves

Toxic tort cases also rely heavily on expert evidence regarding the dose-response curve, which shows the relationship between relative risk and exposure.[124] These curves demonstrate how "a change in amount, intensity, or duration of exposure to an agent is associated with a change—either an increase or decrease—in risk of disease."[125] If a plaintiff can prove exposure to a certain level of a substance, and a well-known dose-response curve exists, then this provides strong evidence for causation.[126] The figure below provides a sample dose-response curve, showing two different types of relationships between exposure and disease.[127] The straight line represents how the risk of disease increases steadily with each additional dose (exposure) of a particular agent.[128] The curved line shows the relationship for an agent with some threshold level of exposure.[129] People can be exposed to some dose without any risk, but once the dose meets a threshold, the risk increases sharply with additional exposure.[130] At some point, the dose becomes so high that a maximum level of risk has been reached, and the curve levels off again because

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preferable for the district court to instruct the jury on statistical significance and then let the jury decide whether many studies over the 1.0 mark have any significance in combination."); Allen v. United States, 588 F. Supp. 247, 418 (D. Utah 1984) ("The value of the available statistical data concerning radiation and cancer in off-site communities is not confined by arbitrary tests of 'statistical significance.' Nor is the court constrained by simplistic models of causal probability impressed upon the judicial 'preponderance of the evidence' standard."), *rev'd on other grounds*, 816 F.2d 1417 (10th Cir. 1987).

124. *See* McClain v. Metabolite Int'l, Inc., 401 F.3d 1233, 1241 (11th Cir. 2005) ("When analyzing an expert's methodology in toxic tort cases, the court should pay careful attention to the expert's testimony about the dose-response relationship.").

125. Green et al., *supra* note 105, at 622.

126. *See, e.g.*, Cano v. Everest Minerals Corp., 362 F. Supp. 2d 814, 848–49 (W.D. Tex. 2005) (discussing the usefulness of dose-response curves in proving causation and considering the plaintiffs' offered dose-response evidence).

127. Figure reprinted from Bernard D. Goldstein & Mary Sue Henifin, *Reference Guide on Toxicology*, *in* FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 633, 643 (3d ed. 2011).

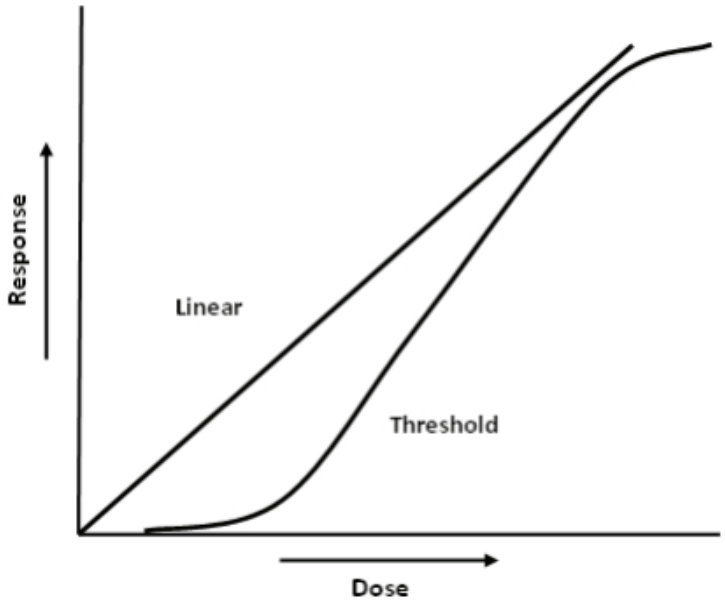
128. *Id.*

129. *Id.*

130. *Id.*

there is little more that additional exposure can cause.[131] For some substances, the dose response curves become very complex, and courts struggle with how to weigh expert opinions on dose-response relationships.[132]

Figure 2: Sample Dose-Response Curve



Although these curves are useful for quantifying disease risk, they can vary for each individual, depending on genetic, epigenetic, and environmental factors—and a combination of all three.[133] As with relative risk data, courts should consider dose-response curves in concert with all available evidence rather

131. *Id.*

132. *See id.* at 642 n.28 (discussing some of the controversy in evaluating dose-response curves for cancer causation); *see, e.g.*, Cano v. Everest Minerals Corp., 362 F. Supp. 2d 814, 849 (W.D. Tex. 2005) (summarizing case law regarding the particular dose-response relationship offered by the plaintiffs' expert).

133. *See* Jirtle et al., *supra* note 36, at 261 ("These epigenetic biomarkers will hopefully allow for the early diagnosis of individuals with a propensity for adult-onset disease. . . . Such an approach to human disease management could revolutionize medical care, which now mainly treats diseases only after they develop.").

than as determinative of any causation issue on their own.[134] Therefore, plaintiffs should not be barred from recovering solely because they have not proven that their dose of exposure is linked to a threshold risk of disease.[135]

IV. Alternative Models of Causation in Toxic Torts

A. Merging General and Specific Causation

One solution to the difficulty of proving specific causation is to allow general causation evidence to satisfy the specific causation inquiry as well.[136] This approach is "based on a policy determination that when the incidence of a disease or injury is sufficiently elevated due to exposure to a substance, someone who was exposed to that substance and exhibits the disease or injury can raise a fact question on causation."[137] General causation must, at a minimum, be supported by strong and consistent epidemiological data.[138] Courts can then presume specific causation from the statistical probabilities yielded by scientific data.[139]

Even with this approach, courts decide a standard for scientific rigor before epidemiological studies can be used to prove the plaintiff's case.[140] This determination shapes not only the

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134. *See* Gerald W. Boston, *A Mass Exposure Model of Toxic Causation: The Content of Scientific Proof and the Regulatory Experience*, 18 COLUM. J. ENVTL. L. 181, 240 (1993) (addressing the difficulties with determining an exact dose-response relationship for a particular environmental agent).

135. *Id.*

136. *See* Estate of George v. Vt. League of Cities & Towns, 993 A.2d 367, 374 (Vt. 2010) ("Notwithstanding this limitation, numerous courts have considered the role that epidemiological studies can play in establishing specific causation.").

137. Merrell Dow Pharms. v. Havner, 953 S.W.2d 706, 715 (Tex. 1997).

138. *See, e.g.*, *id.* at 715 ("Recognizing that epidemiological studies cannot establish the actual cause of an individual's injury or condition, a difficult question for the courts is how a plaintiff faced with this conundrum can raise a fact issue on causation and meet the 'more likely than not' burden of proof.").

139. *See* Rosenberg, *supra* note 83, at 858 (noting that this approach "converts the balance of probabilities into a conclusive presumption that the causal connection did or did not exist between the parties in the particular case").

140. *See* Tumlinson v. Advanced Micro Devices, Inc., No. 08C-07-106 FSS,

weight of scientific evidence but also whether or not certain experts and studies are even admissible.[141] For example, in *Estate of George v. Vermont League of Cities & Towns*,[142] the plaintiff offered eight epidemiological studies in order to support a workers' compensation claim that the claimant's years of firefighting caused his death from lymphoma.[143] The Vermont Supreme Court first recognized that epidemiological evidence can play a role in specific causation.[144] The court went on to discuss relative risk, concluding that the trial court's cutoff of 2.0 was proper.[145] Ultimately, the court upheld the trial court's grant of summary judgment to the defendant, partly because the plaintiff failed to offer epidemiological evidence that met the relative risk cutoff.[146] Legal standards for scientific evidence drastically affect a plaintiff's ability to satisfy the causation element of a toxic tort claim—regardless of a court's view of general versus specific causation.[147]

2012 Del. Super. LEXIS 209, at *7 (Del. Super. Ct. Jan. 6, 2012) (discussing what constitutes scientifically reliable epidemiological studies for evidence of causation).

141. *See, e.g.*, Andrew S. Lipton, *Proving Toxic Harm: Getting Past Slice and Dice Tactics*, 45 MCGEORGE L. REV. 707, 710–16 (2014) (discussing evidence issues associated with scientific studies and expert testimony).

142. 993 A.2d 367 (Vt. 2010).

143. *See id.* at 369 ("In 2003, claimant died of non-Hodgkin's lymphoma (NHL). His estate brought a workers' compensation action, alleging that his work as a firefighter caused him to develop NHL."); *id.* at 375 (noting that the experts offered eight epidemiological studies).

144. *See id.* at 374 ("[N]umerous courts have considered the role that epidemiological studies can play in establishing specific causation.").

145. *See id.* at 378 ("[W]e conclude that the trial court did not abuse its discretion in considering a relative risk greater than 2.0 as a reasonable and helpful benchmark under the circumstances presented here.").

146. *See id.* at 375 ("The trial court found that only two of the eight epidemiological studies relied upon by the experts in this case reflected a relative risk greater than 2.0 . . . ."); *id.* at 382 (concluding that summary judgment in favor of the defendant was proper).

147. *See id.* at 707 (noting the difficulty of proving causation with opposing experts and epidemiological studies).

B. Substantial Factor

Courts will also invoke the "substantial factor" test as an alternative to but-for causation.[148] Under this approach, legal cause is satisfied if "(a) [an actor's] conduct is a substantial factor in bringing about the harm, and (b) there is no rule of law relieving the actor from liability because of the manner in which his negligence has resulted in the harm."[149] New Jersey courts follow this standard for toxic tort cases, noting that "[t]here is no requirement in the law that a single cause be found and proven. All that is required is that the plaintiff show that a defendant's conduct or defective product was a proximate cause of the condition, *i.e.*, a substantial factor in bringing the condition about."[150]

In *Rutherford v. Owens-Illinois, Inc.*,[151] the California Supreme Court invoked the substantial factor test for proving causation in a suit for asbestos-related injuries and wrongful death.[152] Instead of requiring the plaintiff to prove that the defendant's exact fibers caused the onset of cancer, the court allowed the plaintiff to prove that "exposure to defendant's product was a substantial factor causing the illness."[153] The court elaborated that the plaintiff could satisfy this proof "by showing that in reasonable medical probability it was a substantial factor contributing to the plaintiff's or decedent's risk of developing cancer."[154]

However, the court reversed a lower court's decision to give a burden-shifting instruction on causation to the jury.[155] Lower courts in California allow for such a burden shift if "the plaintiff has proved that a particular asbestos supplier's product was 'defective,' that the plaintiff's injuries or death were legally

148. RESTATEMENT (SECOND) OF TORTS § 431 (1967).

149. *Id.*

150. Grassis v. Johns-Manville Corp., 591 A.2d 671, 677 (N.J. Super. Ct. App. Div. 1991).

151. 941 P.2d 1203 (Cal. 1997).

152. *See id.* at 1206 (summarizing the procedural and factual history of the case).

153. *Id.* at 1223.

154. *Id.*

155. *Id.* at 1217–18.

caused by asbestos exposure *generally*, and that he was exposed to asbestos fibers from the defendant's product."[156] The defendant then bears the burden of proving that its product did not cause the harm.[157] California's Supreme Court noted that such a burden shift is unnecessary when the fact-finders understand the limits of proving causation in such cases, noting that the substantial factor instruction was sufficient to accomplish this task.[158]

C. Sufficient-to-Have-Caused

A related, yet slightly different, test for causation is the "sufficient-to-have-caused" standard, which requires exposure to be of a level able to cause the harm, even if there is limited evidence connecting exposure to a particularized harm.[159] Although the Second Restatement of Torts used "substantial factor" language, the Third Restatement of Torts rejected that doctrine in favor of the sufficient-to-have-caused standard.[160] The Third Restatement, as well as several courts, has adopted this doctrine instead of the substantial factor test because of the likelihood for confusion over what constitutes a substantial factor.[161] For example, Virginia follows the sufficient-to-

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156. *Id.* at 1208.

157. *Id.*

158. *See id.* at 1217–18 ("[T]he most fundamental reason why a burden-shifting instruction is unnecessary to proving an asbestos-related cancer latent injury case becomes clear when the limits on the plaintiff's burden of proof on causation are properly understood.").

159. *See* Ford Motor Co. v. Boomer, 736 S.E.2d 724, 732 (Va. 2013) ("The exposure must have been 'a' sufficient cause . . . . Excluding other exposures from the pool of multiple sufficient causes will require competent medical testimony indicating whether the timing of exposure could possibly have caused the [disease]."); RESTATEMENT (THIRD) OF TORTS § 27 (2010) ("[C]ourts have long imposed liability when a tortfeasor's conduct, while not necessary for the outcome, would have been a factual cause if the other competing cause had not been operating.").

160. *See Boomer*, 736 S.E.2d at 730–31 (discussing the Restatement's approach to multiple contributing causes and ultimately using the sufficient-to-have-caused standard).

161. *See id.* at 730 ("[S]ubstantial contributing factor could be construed to mean any cause that is more than a merely *de minimis* factor. Conversely, the invocation of the term 'substantial' could be interpreted to raise the standard for

have-caused standard for mesothelioma cases where there may be multiple causes.[162]

D. Increased Risk

A minority of states allow plaintiffs a cause of action based on an increased risk of future disease, such as that resulting from an exposure to a carcinogen.[163] Because courts do not want to impose liability for harms that are merely speculative, these claims typically must prove some accompanying immediate harm, such as present physical injury, emotional distress, or medical monitoring.[164] Most courts also require that the harm is likely to occur based on a preponderance of the evidence and expert testimony.[165]

One common approach to allowing increased risk claims is for courts to require an accompanying present physical injury to

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proof of causation beyond a mere preponderance of the evidence to some more elevated standard.").

162. *See id.* at 732 ("We find that in concurring causation cases, the 'sufficient'-to-have-caused standard as elaborated above is the proper way to define the cause-in-fact element of proximate cause.").

163. *See, e.g.*, Lester v. Exxon Mobil Corp., 120 So. 3d 767, 781 (La. Ct. App. 2013) ("[T]he Louisiana Supreme Court acknowledged a cause of action for damages for increased risk of contracting cancer as a valid claim . . . ."); Gideon v. Johns-Manville Sales Corp., 761 F.2d 1129, 1137 (5th Cir. 1985) ("His claim includes, without limitation, all damages for future pain and suffering, inability to work in the future, reduced life expectancy, future medical expenses, and future disabilities and diseases that will probably develop from present injuries.").

164. *See* Schweitzer v. Consol. Rail Corp., 758 F.2d 936, 942 (3d Cir. 1985) ("If mere exposure to asbestos were sufficient to give rise to a F.E.L.A. cause of action, countless seemingly healthy railroad workers, workers who might never manifest injury, would have tort claims cognizable in federal court."); Merry v. Westinghouse Elec. Corp., 684 F. Supp. 847, 848 (M.D. Pa. 1988) (noting that the plaintiffs are not seeking a claim for increased risk of future illness but for emotional distress and medical monitoring).

165. *See Gideon*, 761 F.2d at 1137–38 ("Whether the district court should have excluded evidence that Gideon may develop cancer turns on epistemology. . . . Certainty, however, is not required: the plaintiff need demonstrate only that the event is more likely to occur than not."); Cudone v. Gehret, 821 F. Supp. 266, 270–71 (D. Del. 1993) (permitting a cognizable increased risk claim when experts showed that "it is more probable than not" that the plaintiff would experience a recurrence of cancer in her lifetime).

allow recovery.[166] In some courts, genetic mutation and chromosomal damage satisfy this standard, providing one possible analogy to how courts might deal with epigenetic changes.[167] In *Brafford v. Susquehanna Corp.*,[168] the plaintiffs lived near a uranium milling facility in South Dakota and sued for increased risk of cancer and other diseases as a result of radiation exposure.[169] The United States District Court for the District of Colorado, asserting diversity jurisdiction, considered increased risk claims to be cognizable only with present physical injury.[170] The court denied the defendant's motion for summary judgment based on expert testimony that concluded "with a reasonable degree of medical probability both that there has been chromosomal damage and that such damage was caused by the radiation."[171] The court noted the importance of plaintiffs' "experts of national renown," who agreed that subcellular damage

166. *See, e.g.*, Brafford v. Susquehanna Corp., 586 F. Supp. 14, 17 (D. Colo. 1984) ("[I]n order to recover future damages for enhanced cancer risk, plaintiffs must have suffered a definite, present physical injury."); Capital Holding Corp. v. Bailey, 873 S.W.2d 187, 194 (Ky. 1994) ("It is tangible injury that triggers the existence of a cause of action, and then, once a harmful change has occurred the plaintiff may sue for the increased risk of future consequences which are presently compensable as a part of the cause of action that has accrued.").

167. *See Brafford*, 586 F. Supp. at 17–18 (denying summary judgment for the defendant because the plaintiffs were exposed to high levels of radiation, which experts testified "with a reasonable degree of medical probability" caused chromosomal damage, satisfying the present physical injury requirement); *see also In re* Methyl Tertiary Butyl Ether Prods. Liab. Litig., 528 F. Supp. 2d 303, 315 (S.D.N.Y. 2007) ("Further, assuming that the model of carcinogenesis Dr. Mehlman describes is valid, as I must for the purposes of summary judgment, the physical manifestation of MTBE in plaintiffs' bodies is not benign, but can be the first step in the development of the disease they claim to fear."); Anderson v. W.R. Grace & Co., 628 F. Supp. 1219, 1227 (D. Mass. 1986) ("[T]he court did not distinguish between gross and subcellular harm. Instead, the court drew a line between harm which can be proven to exist through expert medical testimony based on objective evidence and harm which is merely speculative or based solely on a plaintiff's unsupported assertions.").

168. 586 F. Supp. 14 (D. Colo. 1984).

169. *See id.* at 15 (noting the plaintiff's possible tort claim based on increased risk of disease as a result of exposure to radiation).

170. *See id.* at 17 (discussing precedent in the jurisdiction for increased risk claims).

171. *See id.* at 17–18 (noting that such subcellular injury was sufficient to state a claim and survive a summary judgment motion from the defendant based on no present physical injury).

from radiation should be considered an injury.[172] The present cellular damage operated to "cock the trigger" of cancer in the future, thus "depriv[ing] plaintiffs of a degree of immunity which they had enjoyed prior to their exposure."[173]

Similarly, in *Werlein v. United States*,[174] the plaintiffs lived near a site contaminated by trichloroethylene[175] and were exposed to a contaminated water supply.[176] Minnesota requires a present physical injury for a cognizable increased risk claim.[177] The United States District Court for the District of Minnesota denied the defendant's motion for summary judgment based on the adequacy of subcellular injury for fulfilling the present physical injury requirement:

> Plaintiffs' experts have testified that plaintiffs who have been exposed to contaminated air and drinking water have suffered an actual physical injury in the form of chromosomal breakage, and damage to the cardiovascular and immunal systems. . . . These experts also have testified that the present injuries are the cause of the alleged increased future risk of disease. . . . Based on the record before it, this Court cannot rule as a matter of law that plaintiffs' alleged injuries are not "real" simply because they are subcellular. The effect of volatile organic compounds on the human body is a subtle, complex matter. It is for the trier of fact, aided by expert testimony, to determine whether plaintiffs have suffered present harm.[178]

Other courts, however, view subcellular injury as too speculative to sustain a claim for increased risk. In *Rainer v. Union Carbide Corp.*,[179] workers from a uranium-enrichment

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172. *Id.* at 18.

173. *Id.*

174. 746 F. Supp. 887 (D. Minn. 1990).

175. Trichloroethylene is an industrial solvent known to cause cancer, primarily causing damage to the human nervous system, liver, and kidneys. *See Trichloroethylene*, U.S. ENVTL. PROTECTION AGENCY (Apr. 1992), http://www.epa.gov/airtoxics/hlthef/tri-ethy.html (last updated Jan. 2000) (last visited Mar. 5, 2016) (summarizing the health risks of trichloroethylene) (on file with the Washington and Lee Law Review).

176. *Werlein*, 746 F. Supp. at 890.

177. *See id.* at 901 (discussing precedent in the jurisdiction allowing increased risk claims).

178. *Id.*

179. 402 F.3d 608 (6th Cir. 2005).

plant in Kentucky sued for exposure even though none had symptoms of clinical disease.[180] The court explicitly rejected the subcellular-damage precedents of *Brafford* and *Werlein*, noting that "the issue of whether chromosome damage constitutes a 'present physical injury' is essentially a legal question, not a factual one."[181] The court cited three public policy reasons for its decision.[182] First, the court wanted to avoid opening the door to endless litigation.[183] Second, the court noted that allowing this claim would bar future claims for injury given Kentucky's "one claim" rule for tort plaintiffs.[184] Last, the court discussed the difficulty of calculating damages where "the injuries claimed to date have caused no financial losses or impairments."[185] Advances in scientific research may, however, persuade more courts to follow the logic of *Werlein* and *Brafford* rather than the logic of *Rainer*.

E. Other Alternatives

Legal scholar Steve Gold argues that none of the existing causation frameworks fits the science of molecular epidemiology, and courts should instead adopt an entirely "probabilistic causal contribution model."[186] This approach would consider any exposure as a cause if it contributed to a disease.[187] Such a determination would require a plaintiff to prove by a preponderance of the evidence that the exposure added to the plaintiff's incremental risk of a disease from which the plaintiff

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180. *Id.* at 611.

181. *Id.* at 621.

182. *Id.*

183. *See id.* (discussing the high number of possible plaintiffs, given everyday exposure to possible toxins).

184. *See id.* (noting that plaintiffs may have a better chance of recovery if they wait until disease symptoms manifest).

185. *See id.* at 622 (noting that the only logical damages for subcellular injury are those for medical monitoring because no other harms have yet occurred).

186. Gold, *supra* note 14, at 338–39.

187. *See id.* at 281–82 (discussing the probabilistic causal contribution standard).

suffers.[188] Damages, then, would vary according to the proportion of risk created by the exposure.[189] Gold adapts an illustration from the Third Restatement of Torts for why his framework fits scientific evidence better than the existing doctrines.[190] His example involves three defendants—Able, Baker, and Charlie—who collectively push a car off a mountain.[191] He elaborates on how the fact pattern would change if it incorporated the uncertainties of subcellular harm and disease onset:

> Suppose, however, that Able, Baker, and Charlie could not be described by Newtonian physics but only by quantum mechanics. On a mountaintop ringed with cars, the three charge around blindfolded. What is more, they are joined by undetectable sprites that also impart momentum to any object they strike. Sometimes Able, Baker, and Charlie hit a car, and sometimes the impact is powerful enough to tip the car down the hill. But this is a quantum world: if we know what they hit, we cannot tell how hard they hit it. And we can't detect the sprite strikes at all. Every once in a while a car rolls down the hill. But the most science can tell us—if we can say whether Able, Baker, Charlie, or any combination of the three hit the car at some point before its descent—is the probability that they hit the car hard enough to make it move.
>
> If Able, Baker, and Charlie represent independent risk factors for a disease, and the invisible sprites represent unknown causes, then the probabilistic metaphor fits a wide range of toxic tort cases.[192]

Gold's approach would allow courts to determine causation according to scientific probabilities related to exposure and disease onset.[193]

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188. *See id.* (noting that the plaintiff's case "would be shown by a preponderance of the evidence . . . to have added incremental risk that the plaintiff would develop a disease that the plaintiff in fact developed").

189. *See id.* ("Damages should be apportioned to that contributing factor in proportion to its contribution to the plaintiff's risk.").

190. *Id.* at 283.

191. *See id.* (describing how the illustration would work using Newtonian physics—a certain amount of force pushes the car over the mountain, and each defendant contributes a portion of that force).

192. *Id.* at 283.

193. *See id.* at 303–04 ("Because such measures will continue to be the type of evidence that science can provide, it is time for a corresponding probabilistic contributing-factor model of causation.").

Yet another option is to take the legal analysis entirely out of the problem and present scientific issues to a "science panel" that would then decide scientific issues on behalf of the court.[194] Ontario, for example, uses an Industrial Disease Standards Panel for workers' compensation claims.[195] The Panel's role is to "investigate potential industrial diseases, make findings about the causal connection between disease and exposure, specify criteria for evaluation of claims, and advise compensation boards about eligibility rules."[196] In the United States, a few judges have appointed science panels when expert testimony on causation conflicted.[197] Like the probabilistic causal model, a science panel would be able to weigh scientific evidence regarding statistics and probabilities and come to a conclusion on causation.[198]

V. Adapting Causation Doctrine to Epigenetic Evidence

Scientific research is progressing quickly, and there are many epidemiological studies linking environmental conditions, epigenetic markers, and various diseases.[199] Legal scholarship addressing epigenetic harms focuses on broad impacts to tort liability and regulatory governance, particularly in the field of

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194. *See* Troyen A. Brennan, *Helping Courts with Toxic Torts: Some Proposals Regarding Alternative Methods for Presenting and Assessing Scientific Evidence in Common Law Courts*, 51 U. PITT. L. REV. 1, 10 (1989) ("The science panel . . . is a panel of scientists, possibly aided by lawyers and concerned citizens, who adjudicate a specific question regarding a technical dispute and formulate a consensus opinion. . . . [T]he science panel would provide a consensus opinion on a given causal dispute for the court.").

195. *See id.* at 16 (discussing ways in which scientists have played a role in the legal causation framework).

196. *Id.*

197. *See* Laural L. Hooper et al., *Assessing Causation in Breast Implant Litigation: The Role of Science Panels*, 64 LAW & CONTEMP. PROBS. 139, 140–41 (2001) ("[F]ederal judges appointed panels of scientific experts to help assess conflicting scientific testimony regarding causation of systemic injuries by silicone gel breast implants.").

198. *See* Brennan, *supra* note 194, at 19 ("[J]udges and most people are used to thinking about causation in terms of mechanistic causal chains. Scientists, however, rely to a large extent, especially in the science of toxicology, on probabilistic evidence of causation and statistical proof of propositions.").

199. *See supra* Part II (discussing the state of epigenetic science and its relevance for toxic tort cases).

transgenerational harms.[200] For example, legal scholar Christopher Weiner focuses on precedent allowing transgenerational liability for harm, particularly when dealing with a preconception tort.[201] University of Georgia Professor of Law Fazal Khan analyzes the potential regulatory issues that need to be addressed as science develops in this field.[202] Other scholars examine the public health and social justice impacts of transgenerational epigenetic harms—particularly those resulting from poor nutrition and stressful environments.[203] Although this scholarship provides an important overview of general legal issues associated with epigenetics, an in-depth analysis of each individual issue is necessary for preparing the legal system to deal with new scientific evidence.

Thus, this Note addresses how courts should handle epidemiological evidence of epigenetic harms in toxic tort cases. This Note argues that (1) rather than using a bright-line scientific cutoff for admissibility or sufficiency of evidence, courts should defer to the fact-finder for evaluating scientific evidence, and the fact-finder should weigh epidemiological evidence in the context of the other evidence available in a case; (2) epigenetic harms should be considered present physical injury sufficient to support a claim for increased risk of disease, following the model of the subcellular injury cases;[204] and (3) within such a claim, the

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200. *See generally* Christopher J. Weiner, *Transgenerational Tort Liability for Epigenetic Disease*, 13 DEPAUL J. HEALTH CARE L. 319 (2011) (proposing a framework for transgenerational tort liability for epigenetic harms); Khan, *supra* note 81 (analyzing how tort cases and regulations can be used to manage epigenetic harms and promote fairness and justice); Mark A. Rothstein, *Epigenetic Exceptionalism: Currents in Contemporary Bioethics*, 41 J.L. MED. & ETHICS 733 (2013) (discussing whether epigenetics should be regulated as its own field or whether existing regulations and doctrines addressing genetics should be modified to incorporate epigenetic science).

201. *See* Weiner, *supra* note 200, at 326–27 (discussing how preconception tort liability could evolve with epigenetic evidence).

202. *See* Khan, *supra* note 81, at 277 ("This article proposes a dynamic regulatory framework allowing for decisive actions against epigenetic threats without conclusive proof of harm, but requiring continual adaptation as new learning becomes available.").

203. *See* Geronimus, *supra* note 75, at S56 ("Ultimately, such findings offer new hope of identifying means to short circuit the processes—both social and biological—whereby membership in a racialized, gendered, and economically stratified society may lead to health inequalities.").

204. *See supra* Part IV.D.1 (discussing how courts have handled genetic and

general and specific causation inquiries should be merged when appropriate.

A. Evidentiary Issues

Although bright-line rules for admissibility and sufficiency of evidence simplify the judicial task, they can also unfairly and unreasonably bar recovery.[205] Scientific research and evidence simply do not follow the confines of legal causation doctrine.[206] The biological onset of disease after exposure is rarely, if ever, certain.[207] Even with a full understanding of the epigenetic mechanisms leading to certain diseases, proving the specific causal sequence for an individual plaintiff will remain difficult.[208] Most scientific research on epigenetic harms will be in the form of epidemiological studies and population-level data, yielding parameters such as relative risk and dose-response curves.[209]

Many courts deal with these evidentiary uncertainties by unnecessarily excluding or scrutinizing scientific data, requiring each individual study to meet arbitrary cutoffs before it can be admitted or considered sufficient for a plaintiff's case.[210] This

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chromosomal damage in increased risk cases).

205. *See supra* notes 116–123 and accompanying text (discussing courts that have chosen to avoid bright-line rules for expert testimony and epidemiological evidence).

206. *See* Gold, *supra* note 14, at 276 ("But the law must understand how science can best contribute. That understanding begins with acceptance of the fact that bringing toxicological understanding to the molecular level will not bring causation to the individual level.").

207. *See id.* at 280 ("At a molecular level, many of the processes associated with toxicity and disease are simply random.").

208. *See id.* at 276 ("Thus, finding that a plaintiff does or does not have a . . . susceptibility to the disease-causing effect of a substance to which the plaintiff was exposed will provide probabilistic but not deterministic evidence of causation or its absence.").

209. *See id.* ("The data will still be about relative risk, but risk will be parsed more and more finely. . . . [N]ew associations will be detected or known associations will be disaggregated in new ways. This process has already begun even for causal connections that were already relatively well-accepted.").

210. *See* Lipton, *supra* note 141, at 709 ("[C]ourts have aggressively exercised their gatekeeper roles to reject expert causation testimony . . . by taking an atomistic approach that examines individually and independently each piece of scientific evidence . . . .").

method is known as the "corpuscular approach" because it breaks down a holistic case into small, easily attacked segments.[211] This approach, however, ignores the evidentiary strength of aggregating multiple scientific studies with the specific facts of a plaintiff's case.[212] By attacking the scientific rigor of each individual study, a defendant can unfairly bias the court against a plaintiff's case.[213]

To avoid this unfair bias, courts should liberally admit epidemiological evidence regarding the links between epigenetic harms and disease. Furthermore, courts should allow the fact-finder significant discretion in weighing the totality of scientific evidence.[214] Ultimately, causation is a subjective legal inquiry, although scientific and legal guidelines can direct the analysis.[215] Scientific inquiries simply do not follow the linear, but-for causation demanded by the legal system.[216] The causation inquiry, then, should be left to the fact-finder rather than requiring an arbitrary threshold as a matter of law.[217]

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211. *Id.*

212. *See id.* at 710 ("[T]he well-recognized weight-of-the-evidence methodology . . . permits scientific opinions based upon conclusions drawn from the totality of the evidence, with no individual study or piece of data having to be sufficient on its own to prove causation.").

213. *See* Thomas O. McGarity, *Proposal for Linking Culpability and Causation to Ensure Corporate Accountability for Toxic Risks*, 26 WM. & MARY ENVTL. L. & POL'Y. REV. 1, 19 (2001) (noting that epidemiological studies almost always have flaws and uncertainties that can be used to defeat a plaintiff's case).

214. *See supra* notes 116–123 and accompanying text (discussing courts that have decided to allow the jury discretion in evaluating scientific evidence rather than deciding the weight based on arbitrary scientific parameters).

215. *See, e.g.*, King v. Burlington N. Santa Fe Ry. Co., 762 N.W.2d 24, 39 (Neb. 2009) ("But determining causation differs from the objective inquiry into relative risk. An assessment of a causal relationship is not a scientific methodology as that term is used to describe logic (like a syllogism) and analytic methods. Instead, it involves subjective judgment.").

216. *See supra* notes 205–209 and accompanying text (discussing the fundamental disconnect between scientific evidence and legal doctrines of causation).

217. *See, e.g.*, *King*, 762 N.W.2d at 46–47 (declining to set a minimum threshold for relative risk or other statistical measurements and noting that "the significance of epidemiological studies with weak positive associations is a question of weight, not admissibility").

B. Increased Risk Framework

Epigenetic evidence may address many of the law's concerns with increased risk claims in toxic tort cases, allowing these claims to proceed with more success.[218] One criticism of the increased risk approach is that it still operates within but-for causation: each exposure is a but-for cause of an increase in risk.[219] As scientific research progresses, links between exposure, increased risk, and disease onset will become more readily available for proving a plaintiff's case.[220] Epidemiological data should fill in many of the causal gaps between exposure and disease.[221] Applying but-for causation to the increased risk framework might become possible as certain epigenetic markers are connected to certain levels of exposure and disease.[222] This type of evidence, however, will only support general causation, meaning that courts will still need to grapple with how to analyze specific causation.[223]

Another criticism is that tort law cannot and should not compensate every individual exposed to a risk.[224] Otherwise,

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218. *See supra* Part III.C (discussing the increased risk framework and the primary reasons why courts are reluctant to allow such claims).

219. *See* Gold, *supra* note 14, at 298–99 ("With respect to causation doctrine, however, it implicitly retreated to the comfortable confines of but-for: each material exposure to asbestos, tautologically, was a but-for cause of the increment of risk associated with that exposure.").

220. *See* Brafford v. Susquehanna Corp., 586 F. Supp. 14, 18 (D. Colo. 1984) (describing the link between subcellular damage and disease onset as having the "trigger cocked" on cancer and as depriving the plaintiff of a level of immunity against disease); *see also supra* Part II (discussing the link between epigenetic markers and disease onset).

221. *See supra* Part II (discussing the state of epidemiologic data and how epigenetic studies are likely to reveal many more disease mechanisms than previously known).

222. *See supra* Parts II, III.C (discussing the progress of epigenetic science and the demands of the increased risk framework).

223. *See* Gold, *supra* note 14, at 278–79 ("[T]he enormous number of possible combinations of potentially interacting causal factors—genes, epigenetics, other individual characteristics, and exposures—makes it extraordinarily unlikely that complete risk characterization will ever be possible at an individual level.").

224. *See id.* at 299–300 ("The latter would invite the objection that many negligent or otherwise wrongful acts create risk of harm, but tort law ordinarily does not, and practicably could not, compensate every person exposed to such risks.").

individuals would receive compensation based on harms that may never materialize, creating unnecessary and unending liability for defendants.[225] Epigenetic changes, however, provide evidence of exposure (and harm) before disease symptoms occur and can even provide evidence of ancestral exposure to toxins.[226] Courts can therefore treat the epigenetic change either as harm itself (as in the genetic and subcellular damage cases) or as distinct evidence of risk exposure itself.[227] Either approach would limit the liability for increased risk because not every exposed individual would show the epigenetic abnormalities necessary for disease onset.[228] Courts could limit recovery by requiring plaintiffs to prove epigenetic abnormalities associated with both exposure and disease. Similarly, only defendants who created risks sufficient for epigenetic harm would be held liable—this standard would address the concerns over limitless liability for negligence without resulting harm. Therefore, this approach would limit liability while still compensating those harmed and serving the additional deterrent purpose of the tort system.[229]

C. Addressing General and Specific Causation

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225. *See* Stites v. Sunstrand Heat Transfer, Inc., 660 F. Supp. 1516, 1526 (W.D. Mich. 1987) ("Accepting plaintiffs' risk of cancer claim in this instance may allow plaintiffs to recover, from a jury, monetary relief for an injury they are not reasonably certain to suffer."); Hagerty v. L & L Marine Servs., Inc., 788 F.2d 315, 319 (5th Cir. 1986) ("[W]e conclude that a plaintiff can recover only where he can show that the toxic exposure more probably than not will lead to cancer.").

226. *See* Manikkam, *supra* note 65, at 5 ("[D]istinct epigenetic changes in differential DNA methylation regions (DMR) provide epigenetic biomarkers for ancestral environmental exposures. Each exposure had a distinct epigenetic signature that can be used as a biomarker. . . . [T]he current study provides the proof of concept that epigenetic biomarkers for environmental exposures exist.").

227. *See supra* Part III.C.1 (discussing case precedent allowing subcellular injury to fulfill the present physical injury requirement in increased risk cases); *see also* Erik S. Knutsen, *Ambiguous Cause-in-Fact and Structured Causation: A Multi-Jurisdictional Approach*, 38 TEX. INT'L L.J. 249, 275 ("An increased risk would be treated as a new compensable injury for which a defendant would be liable. Exposure to risk of harm would be considered a harm itself.").

228. *See supra* Part II (discussing how epigenetic change varies across individuals, even when exposed to the same environmental conditions).

229. *See* McGarity, *supra* note 213, at 35–38 (summarizing how the current toxic tort evidentiary standards inhibit the deterrence goals of the tort system).

Most uncertainty associated with causation in toxic tort cases falls into one of four categories: (1) trans-scientific uncertainty, when scientific relationships are inferred from existing studies but not yet proven by epidemiological data; (2) statistical uncertainty, when scientific evidence is ambiguous due to sample sizes and other experimental set-up issues; (3) individual attribution uncertainty, which deals with the issues surrounding specific causation; and (4) vocabulary or multiple causation uncertainty, when the scientific jargon and methodology create confusion for the court in applying legal doctrines to evidence.[230] Of these, individual attribution uncertainty and statistical uncertainty are typically key considerations for epidemiological evidence.[231]

When these uncertainties combine with the errors and biases inherent in scientific research, proving causation becomes extremely difficult for a toxic tort plaintiff.[232] Because of these challenges, courts should accept consistent, peer-reviewed epidemiological evidence as specific causation, leaving the weight of the evidence to be determined by the fact-finder.[233] In doing so, courts would follow the precedent of the states using a "weak" view of causation.[234] Plaintiffs should not recover solely on the basis of epidemiological data, but a lack of specific causation should not bar recovery when plaintiffs otherwise present a strong case.[235] Such evidence should at least allow a plaintiff to

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230. *See* Brennan, *supra* note 194, at 23–26 (summarizing how causal uncertainty in toxic tort cases relates to the challenges of using scientific evidence).

231. *See id.* (listing the circumstances under which these various issues are at play in the legal determination of causation).

232. *See supra* notes 205–213 and accompanying text (addressing how defendants can easily attack scientific evidence due to the uncertainties inherent in the scientific process).

233. *See supra* note 123 and accompanying text (discussing various standards for treating epidemiological data as specific causation).

234. *See supra* notes 84–85 and accompanying text (comparing the "strong" and "weak" approaches to causation).

235. *See* Allen v. United States, 588 F. Supp. 247, 418 (D. Utah 1984) ("Nor is the court constrained by simplistic models of causal probability impressed upon the judicial 'preponderance of the evidence' standard."), *rev'd on other grounds*, 816 F.2d 1417 (10th Cir. 1987); Merrell Dow Pharms., Inc. v. Havner, 953 S.W.2d 706, 720–21 (Tex. 1997) ("Courts should allow a party . . . to present the best available evidence . . . and only then should a court determine from a

survive a summary judgment motion in a toxic tort case, allowing the fact-finder to decide based on the full record of scientific and legal evidence.[236]

Evidence of epigenetic harm would still face the common problems with general and specific causation.[237] As science connects environmental factors, epigenetic change, and disease onset, epidemiological data will develop to support general causation.[238] Proving the specific instance of exposure that led to the epigenetic change, however, will remain difficult.[239] As a result, these two inquiries should be merged into one. In other words, strong epidemiological data—ideally peer-reviewed, consistent, and accepted by scientific experts—should satisfy specific causation as well.

D. Difficulties and Alternative Solutions

Alternatives to developing common law doctrine on causation include passing legislation or regulations addressing either the evidentiary issues or the factors that are known to cause epigenetic harms leading to disease. For example, one legal scholar suggests amending the Federal Rules of Evidence so that

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totality of the evidence, considering all factors affecting the reliability of particular studies, whether there is legally sufficient evidence to support a judgment.").

236. *See, e.g.*, *In re* Joint E. & S. Dist. Asbestos Litig. v. U.S. Mineral Prods. Co., 52 F.3d 1124, 1134 (2d Cir. 1995) ("We believe that it would be far preferable for the district court to instruct the jury on statistical significance and then let the jury decide whether many studies over the 1.0 mark have any significance in combination."); *see also supra* notes 205–217 and accompanying text (arguing for leaving most of the evidentiary decisions to the fact-finder).

237. *See* Gold, *supra* note 14, at 278–79 ("[T]he enormous number of possible combinations of potentially interacting causal factors—genes, epigenetics, other individual characteristics, and exposures—makes it extraordinarily unlikely that complete risk characterization will ever be possible at an individual level.").

238. *See id.* at 278 ("Toxicogenomics and molecular epidemiology are producing evidence about suspected exposure-disease links at finer and finer scales of resolution, but they have not altered the essential nature of that evidence.").

239. *See id.* at 279 ("For the most part, increased knowledge of toxicity at the genomic and molecular levels will simply provide an increasingly detailed description of probabilistic associations—population-based frequencies rather than deterministic certainties.").

judges no longer act as "super-scientists" who scrutinize every epidemiologic study.[240] Such an amendment would supersede the current precedent of *Daubert* and *Joiner*.[241] Furthermore, if factors causing epigenetic harm and disease were fully regulated (for example, if products causing epigenetic harm were banned), then courts would play a less important role in the toxic tort system.[242]

Even so, in the event that epigenetic harms were to be highly regulated, lawsuits would still arise, and courts would still need to address the causation and evidentiary issues.[243] Regulations and legislation both require extensive inputs of time, political energy, money, and scientific backing.[244] With the current rate of epigenetic research, courts will likely face these cases before legislators are able to fully regulate the field, and courts need to be prepared to handle both epigenetic evidence and epigenetic harms. Ultimately, however, protection from epigenetic harms and disease will require all three branches of government to work in concert.[245] Even as courts address these issues, regulations should be developed to minimize the health risks of the factors known to lead to the worst epigenetic harms—endocrine disruptors, for example. Indeed, California already includes epigenetic toxicity as a hazard in its state regulations.[246]

Calculating damages presents one difficulty with an increased risk approach to epigenetic harms, particularly if epigenetic damage is present but not causing any physical or

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240. *See* McGarity, *supra* note 213, at 42 ("One possible 'quick fix' to forestall the upcoming accountability crisis would be for Congress to amend the Federal Rules of Evidence to remove (or greatly reduce) the trial judge's screening role.").

241. *Id.*

242. *See* Khan, *supra* note 81, at 262–65 (discussing how dynamic regulation of epigenetic health risks is preferable to handling harms through the toxic tort system).

243. *See generally id.* (comparing how a comprehensive regulatory framework for epigenetic harms would interact with the tort system).

244. *See id.* at 310–14 (discussing barriers to establishing a comprehensive epigenetics regulatory framework).

245. *See* Khan, *supra* note 81, at 261–65 (discussing how to best protect populations from epigenetic harms).

246. CAL. CODE REGS. tit. 22, § 69403.4 (2012).

emotional symptoms.[247] The same courts allowing subcellular damage to support an increased risk claim have addressed this very issue, considering damages associated with medical monitoring and other harms.[248] This model should translate to cases dealing with epigenetic harms.

VI. Conclusion

Courts already struggle with the issue of causation in toxic tort cases.[249] As a result, courts, experts, and scholars have argued for many different approaches to proving causation in toxic tort cases.[250] Epigenetic research has the potential to assist courts by providing more nuanced scientific evidence on causal mechanisms.

Evidence of epigenetic change fits most closely within the increased risk framework of tort liability because it provides the intermediate causal link between environmental stressors and disease onset.[251] By relying on such evidence, courts can limit liability while compensating individuals with an increased risk of disease and incentivizing behaviors that limit environmental exposures likely to result in adverse epigenetic effects. Courts can either follow the precedent of subcellular damage as present physical injury or look to epigenetic evidence as proof of increased

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247. *See* Rainer v. Union Carbide Corp., 402 F.3d 608, 622 (6th Cir. 2005) ("[T]he plaintiffs have suggested no mechanisms for calculating losses resulting from subcellular damage. Indeed, the injuries claimed to date have caused no financial losses or impairments.").

248. *See, e.g.*, Brafford v. Susquehanna Corp., 586 F. Supp. 14, 17–18 (D. Colo. 1984) (discussing the defendant's arguments against damages on a summary judgment motion and acknowledging that the plaintiff should have the opportunity to prove damages at trial).

249. *See* Brennan, *supra* note 194, at 19 ("[J]udges and most people are used to thinking about causation in terms of mechanistic causal chains. Scientists, however, rely to a large extent, especially in the science of toxicology, on probabilistic evidence of causation and statistical proof of propositions.").

250. *See supra* Part III (documenting the varying approaches used to address the causation issue in toxic tort cases).

251. *See* Jirtle & Skinner, *supra* note 133, at 254 ("Environmental exposures to nutritional, chemical and physical factors have the potential to alter gene expression and modify adult disease susceptibility in various ways through changes in the epigenome.").

risk.[252] These approaches, however, still face difficulty in proving specific causation. Because of the unique characteristics of toxic tort cases, the causation inquiry should be merged and left to the jury if evidence of specific causation is lacking.[253]

Epigenetics presents a number of issues for the current legal system, and causation in toxic tort cases is but one. Some scholars argue that epigenetic harms should be regulated rather than litigated.[254] Moving forward, epigenetic harm will also require courts to deal with preconception torts and transgenerational liability.[255] Courts, therefore, must determine how to analyze epigenetic evidence. Even if epigenetic risks become highly regulated, courts will have to deal with related litigation. They will also become the intermediary "regulatory" bodies by mediating harms while the administrative and executive branches develop regulations. Some plaintiffs are already introducing epigenetic harm as evidence, and this process will only accelerate as scientific development continues.[256] Most importantly, the legal and regulatory system should be informed about scientific developments in epigenetics and prepare accordingly for cases and issues that are likely to arise.

In one court's own words, "Based upon the average American's exposure to chemically processed foods, toxic fumes,

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252. *See supra* note 167 and accompanying text (discussing cases accepting genetic and chromosomal damage as present physical injury).

253. *See, e.g.*, *In re* Joint E. & S. Dist. Asbestos Litig. v. U.S. Mineral Prods. Co., 52 F.3d 1124, 1134 (2d Cir. 1995) ("We believe that it would be far preferable for the district court to instruct the jury on statistical significance and then let the jury decide whether many studies over the 1.0 mark have any significance in combination."); *supra* Part III.B (discussing the role of scientific evidence in proving causation).

254. *See* Khan, *supra* note 81, at 264 ("[T]ort law appears incapable of limiting epigenetic risk.").

255. *See* Weiner, *supra* note 201, at 336 ("It would be unreasonable to expect that as our understanding progresses, aggrieved children would never seek to hold their parents liable for the risks and illnesses needlessly suffered because of the parents' tortious acts.").

256. *See* Snyder v. Sec'y of the Dep't of Health & Human Servs., No. 01-162V, 2009 WL 332044, at *47–50 (Fed. Cl. Feb. 12, 2009) (discussing the role of epigenetics in the development of autism in a case under the National Vaccine Injury Compensation Program); *see also* Allen v. Takeda Pharms. N. Am. Inc. (*In re* Actos (Pioglitazone) Prods. Liab. Litig.), No. 12-cv-00064, 2014 WL 46818, at *1 (W.D. La. Jan. 6, 2014) (discussing epigenetic harm as part of the evidence at issue).

genetically modified fruits and vegetables, mercury-laden fish, and hormonally treated chicken and beef, [plaintiffs] might encompass a very large percentage of the total population."[257] Perhaps instead of fearing "too many" plaintiffs, our legal system should be more concerned with protecting the public from the health risks of such exposures. By admitting and considering epidemiological evidence of epigenetic harm, courts can address public health while limiting liability to those harmed—even if the harm is limited to subcellular damage. Although compensation would not restore a plaintiff's health, it might provide some measure of assistance to those affected. The children in Flint, Michigan could seek recourse through our tort system armed with the most recent scientific research—without fearing arbitrary legal standards that might bar their claims or their evidence. This Note's recommendations solve one major challenge created by the disconnect between scientific evidence and legal doctrine, but many more obstacles remain for both the legal and public health fields.

257. Rainer v. Union Carbide Corp., 402 F.3d 608, 621 (6th Cir. 2005).