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Michael P. Vandenbergh
Vanderbilt University Law School

David J. Vandenbergh
Pennsylvania State University

John G. Vandenbergh
North Carolina State University

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Lamarck Revisited: The Implications of Epigenetics for Environmental Law

*Michael P. Vandenbergh**, *David J. Vandenbergh*** & *John G. Vandenbergh****

Abstract

For generations, a bedrock concept of biology was that genetic mutations are necessary to pass traits from one generation to the next, but new developments in genetics are challenging this fundamental assumption. A growing body of scientific evidence demonstrates that chemical alteration of the way a gene functions, whether through exposure to chemicals, foods or even traumatic experiences, may not only affect the exposed individual, but also the individual's offspring for two generations or more. This interaction between genes and the environment, known as epigenetics, has revolutionized the understanding of how genes are expressed within an individual and how they affect that individual's offspring. Epigenetics also presents novel challenges for chemical regulatory regimes in the United States and around the world. Chemical substances that do not cause mutations typically are not regulated based on their potential effects on future generations. They may be regulated based on their harms to living individuals, or perhaps to those exposed before birth, but until recently future generations were not thought to be at risk. We explore the implications of the new field of epigenetics for public and private regulation of toxics, and we suggest new legal strategies to reflect the new scientific understanding. We argue that new developments in public and private governance suggest optimism for the ability of the environmental regulatory regime to respond to new findings in the science of epigenetics.

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* David Daniels Allen Distinguished Chair of Law, Director, Climate Change Research Network, and Co-Director, Energy, Environment and Land Use Program, Vanderbilt University Law School. We thank Ellen Clayton, Owen Jones, Carol Kwiatkowski, Heather Patisaul, Ronald Sederoff, William Rawson, and David Sweatt for valuable comments. Madison Renner and Margaret Fowler provided excellent research assistance.

** Professor of Biobehavioral Health; The Penn State Institute for the Neurosciences, & Molecular Cellular & Integrative Bioscience Graduate Program, The Huck Institutes for the Life Sciences, The Pennsylvania State University.

*** Emeritus Professor of Zoology, North Carolina State University.

I. Introduction

Finland is remarkable not only for its cold temperatures, but also for its precise records of family histories that extend back for centuries. Aware of these records, Finnish geneticist Virpi Lummaa and her research team studied the Finnish Lutheran Church's family histories, which included data on over 700 twins born during the period from 1734 to 1888.[1] The conclusion was remarkable: a female with a male twin was far less likely to have children than was a female with a female twin or a male with a male twin.[2] Additionally, if the female twin did have children, her children were less likely to have children than those not descended from females with an op-

1. Virpi Lummaa et al., *Male Twins Reduce Fitness of Female Co-Twins in Humans*, 104 Proc. Nat'l Acad. Sci. 10915, 10916 (2007).
2. *Id.*

posite-sex twin.[3] Some effects on reproductive outcomes even appeared in the great-grandchildren of the twin pairs studied.[4] In other words, the presence of a male twin in utero affected the subsequent fecundity of the female twin, and this effect could be passed along to subsequent generations.

The environment – in the Finnish case the presence of a twin, but in many other cases toxic chemicals, common ingredients in food, or even stress – can alter genetic inheritance in ways that can affect health outcomes for multiple generations. This is one important aspect of the new field called epigenetics, which studies heritable changes in an organism that are not caused by direct changes to the sequences of the genes themselves. Although fascinating, what does this research in the new field of epigenetics mean for our understanding of law and policy? In this Article, we argue that epigenetics presents a challenge to two of the core functions of a rational risk regulatory regime: the ability to recognize new risks as scientific understandings shift and the ability to develop appropriate institutional responses. Environmental law draws on science to identify and characterize the threats posed to human health and the environment. The institutional responses and resources allocated to these threats are a matter of policy, but the underlying understanding of the threat is grounded in science. Debates on critical issues such as the appropriate role of the precautionary principle, the role of cost-benefit and risk-risk analysis, and the just distribution of environmental risks all assume that scientists can identify and characterize the underlying threat.[5] As a result, as the science evolves, so should the law.[6]

This is no easy process. For decades, scholars have noted that ossification and capture challenge the ability of the regulatory system to recognize

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3. *Id.*

4. *Id.* at 10917.

5. *See, e.g.*, CASS R. SUNSTEIN, LAWS OF FEAR: BEYOND THE PRECAUTIONARY PRINCIPLE 129 (2005) (precautionary principle); Michael A. Livermore & Richard Revesz, *Rethinking Health-Based Environmental Standards*, 89 N.Y.U. L. REV. 1184 (2014) (cost-benefit analysis); RISK VS. RISK: TRADEOFFS IN PROTECTING HEALTH AND THE ENVIRONMENT (John D. Graham & Jonathan Baert Wiener eds., 1995) (risk-risk analysis); Tseming Yang, *Melding Civil Rights and Environmentalism: Finding Environmental Justice's Place in Environmental Regulation*, 26 HARV. ENVTL. L. REV. 1, 30 (2002) (environmental justice).

6. We are paraphrasing Karl Llewellyn's statement that "the rule follows where its reason leads; where the reason stops, there stops the rule." KARL N. LLEWELLYN, THE BRAMBLE BUSH: ON OUR LAW AND ITS STUDY 157-58 (1951). We mean rational risk regulation in a broad sense, and in our view the need for the regulatory regime to address new scientific understandings applies regardless of the specific conception of rational risk regulation. *Compare* CASS R. SUNSTEIN, RISK AND REASON: SAFETY, LAW, AND THE ENVIRONMENT (2004) (identifying challenges to rational risk responses and emphasizing cost-benefit analysis) *with* DOUGLAS A. KYSAR, REGULATING FROM NOWHERE: ENVIRONMENTAL LAW AND THE SEARCH FOR OBJECTIVITY (2010) (noting limits of economic analysis and emphasizing normative judgments).

and respond to important threats,[7] and in recent years the roles of ideology, "alternative facts," and information overload have received more attention.[8] In this Article, we demonstrate why epigenetics challenges a core conceptual framework that underlies environmental law. We then demonstrate that toxics regulation has transitioned in recent years from a public regulatory regime to a public-private regime, and we argue that this new public-private regime may be surprisingly effective at adapting to conceptual shifts such as the emergence of epigenetics.

A. *The Addition to Standard Genetics*

A mainstay of modern biological science was the concept that genes, and only genes, determine heredity.[9] This foundational notion arose from the work of many, including Charles Darwin, Gregor Mendel, James Watson and Francis Crick, and it influences the toxicology, chemistry, health science, and ecology that underlie much of environmental law and policy.[10] For generations, biology students have been taught this standard genetic model by contrasting it with the thinking of Jean-Baptiste Lamarck, who argued that traits could be acquired during the lifetime of an individual and passed along to offspring.[11] The classic example used to debunk Lamarck and to support the standard genetic model was the idea that giraffes did not have long necks because adults stretch their necks to feed from tall trees, and then pass along these longer necks to their offspring. Instead, those offspring that had longer necks due to their specific combination of genes could reach more food and thus had more offspring. Federal statutes regu-

7. Thomas O. McGarity, *Some Thoughts on "Deossifying" the Rulemaking Process*, 41 DUKE L.J. 1385 (1992); RICHARD B. STEWART, *The Reformation of Administrative Law*, 88 HARV. L. REV. 1669 (1975); Michael A. Livermore & Richard L. Revesz, *Regulatory Review, Capture, and Agency Inaction*, 101 GEO. L.J. 1337 (2013).

8. *See* Dan M. Kahan, *Ideology, Motivated Reasoning, and Cognitive Reflection*, 8 JUDGMENT & DECISION MAKING 407 (2013); Jim Rutenberg, *"Alternative Facts" and the Costs of Trump-Branded Reality*, N.Y. TIMES (Jan. 22, 2017), https://www.nytimes.com/2017/01/22/business/media/alternative-facts-trump-brand.html?_r=0; Wendy E. Wagner, *Administrative Law, Filter Failure, and Information Capture*, 59 DUKE L.J. 1321, 1323–25 (2010).

9. *See* PETER H. RAVEN ET AL., BIOLOGY 301, 418-19 (7th ed. 2005)(textbook description that only mentions epigenetics in passing with respect to cancer); *see also* W. Wayt Gibbs, *Can We Inherit the Environmental Damage Done to Our Ancestors?*, SCI. AM. (July 15, 2014), http://www.scientificamerican.com/article/can-we-inherit-the-environmental-damage-done-to-our-ancestors-video/. We note that when we use the terms "standard genetic model" and "genetic determinism" we only mean the role that genes play in passing heritable traits to offspring. We are not using genetic determinism to refer to the relative role of genes and environment on behavior or other uses of the term "determinism."

10. *See generally* RAVEN ET AL., *supra* note 9 (discussing history of modern genetics).

11. *See* John Humphreys, *Lamarck and the General Theory of Evolution*, 30 J. BIOLOGICAL EDUC. 295, 295 (1996).

lating toxics, pesticides, foods, drugs, and cosmetics were all drafted and implemented in an era during which the genetic determinism of the standard genetic model was an underlying assumption.[12] Common law toxic tort doctrines developed and are still being implemented today under this conceptual framework as well.[13] Thus, the existing regulatory regime developed at a time when concern about toxic chemicals was limited to the individual exposed, including a fetus indirectly exposed in the womb, and included concern for subsequent generations only if the toxin could mutate the deoxyribonucleic acid (DNA) sequence of sperm and eggs.

B. *The Development of Epigenetics*

As the Finnish twin studies and others indicate, though, a new understanding has emerged in the last few decades that challenges genetic determinism as the only means by which change in a trait can be passed from one generation to the next. Epigenetics, which holds that cellular or environmental conditions around the genes influence heredity and can lead to inherited effects (and disease) for multiple generations without changing the genes themselves, has moved from a radical idea to one that is widely accepted.[14] It is also one of the most active areas of research in genetics laboratories around the world.[15] Early indications of the potential for

12. These statutes include: Toxic Substances Control Act, 15 U.S.C. §§ 2601–2697 (2006); Federal Insecticide, Fungicide, and Rodenticide Act, 7 U.S.C § 136 (2006); Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-399 (2006). Although little has been written about epigenetics in the environmental law and policy literature, Mark Rothstein has argued that epigenetics differs from genetics in several fundamental ways: compared to genetic mutations, epigenetic changes occur at higher frequencies, are more dose dependent, are more responsive to the life stage of exposure, are tissue dependent and species specific, and are more likely to be reversible. Mark A. Rothstein, *Epigenetic Exceptionalism*, 41 J.L. MED. & ETHICS 733, 734 (2013) [hereinafter Rothstein, *Epigenetic*]. Rothstein and colleagues also have identified a number of legal and ethical concerns raised by epigenetic science across a wide range of fields. *See* Mark A. Rothstein et al., *The Ghost in Our Genes: Legal and Ethical Implications of Epigenetics*, 19 HEALTH MATRIX: J.L. MED. 1 (2009) [hereinafter Rothstein, *The Ghost*].

13. Jamie A. Grodsky, *Genomics and Toxic Torts: Dismantling the Risk-Injury Divide*, 59 STAN. L. REV. 1671, 1673-74 (2007) [hereinafter Grodsky, *Genomics*]; *see also* Jamie A. Grodsky, *Genetics and Environmental Law: Redefining Public Health*, 93 CALIF. L. REV. 171, 196-97 (2005) [hereinafter Grodsky, *Genetics*]. For an example of the implementation of outmoded scientific understandings in tort cases, *see* Rothstein, *The Ghost*, *supra* note 12, at 37–41 (discussing court decisions limiting drug manufacturer liability to grandchildren of women exposed to diethylstilbestrol or DES).

14. Oliver J. Rando, *Ghosts in the Genome: How One Generation's Experience Can Affect the Next*, SCIENTIST, Dec. 1, 2015, http://www.the-scientist.com/?articles.view/articleNo/44628/title/Ghosts-in-the-Genome.

15. *Id.*

epigenetic effects in mammals arose in studies involving mice,[16] but as the Finnish studies also suggest, more recent research has demonstrated epigenetic effects in humans as well.[17] In isolation, these are just intriguing scientific findings; together, they represent a new conceptual framework – a new way to understand the role of genes and the effect of the environment on human health and behavior. Although epigenetics is a relatively young science, it has affected not only the understanding of reproductive performance,[18] but also diseases such as cancer,[19] cardiovascular problems,[20] and behavioral impairments.[21] In addition, it seems highly probable that environmental factors are particularly effective at creating epigenetic changes in organisms during early development,[22] and they can act at remarkably low levels of exposure.[23]

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16. For example, early research on mice demonstrated that the proximity of fetuses of different sexes in species has consequences for later genital anatomy, brain biochemical signaling, and behavior in the mouse. This effect of adjacent fetuses on later development has become known as the Intrauterine Position Effect. Frederick S. vom Saal et al., *Intrauterine Position Phenomenon*, *in* 2 ENCYCLOPEDIA OF REPRODUCTION 893, 895-97 (Ernst Knobil & Jimmy D. Neill eds., 1999); *see* Michael K. Skinner, *A New Kind of Inheritance*, 311 SCI. AM. 45 (2014) [hereinafter Skinner, *New Kind*] (demonstrating how environmental factors can affect epimutations several generations later).

17. *See* discussion *infra* Part II.

18. Philippe Grandjean et al., *Life-Long Implications of Developmental Exposure to Environmental Stressors: New Perspectives*, 156 ENDOCRINOLOGY 3408 (2015); Jorma Toppari et al., *Male Reproductive Health and Environmental Xenoestrogens*, 104 ENVTL. HEALTH PERSP. 741 (1996).

19. *See* Shikhar Sharma et al., *Epigenetics in Cancer*, 31 CARCINOGENESIS 27, 27 (2010) ("Disruption of epigenetic processes can lead to altered gene function and malignant cellular transformation. Global changes in the epigenetic landscape are a hallmark of cancer.").

20. *See* Johan M. Lorenzen et al., *Epigenetic Modifications in Cardiovascular Disease*, 107 BASIC RES. CARDIOLOGY 1, 7 (2012) ("Epigenetic modifications such as DNA methylation, histone modifications and RNA-based mechanisms represent the molecular substrate for detrimental environmental stimuli and may lead to disease initiation including cardiovascular disease.").

21. Lotte C. Houtepen et al., *Genome-Wide DNA Methylation Levels and Altered Cortisol Stress Reactivity Following Childhood Trauma in Humans*, 7 NATURE COMM. 10967 (2016); Peter D. Gluckman et al., *Effect of In Utero and Early-Life Conditions on Adult Health and Disease*, 359 NEW ENG. J. MED., July 2008, at 61.

22. Amy L. Non et al., *Genome-Wide DNA Methylation in Neonates Exposed to Maternal Depression, Anxiety, or SSRI Medication During Pregnancy*, 9 EPIGENETICS 964 (2014); Alicia K. Smith et al., *Prenatal Antiepileptic Exposure Associates with Neonatal DNA Methylation Differences*, 7 EPIGENETICS 458 (2012).

23. *See, e.g.*, Frederick vom Saal et al., *Prostate Enlargement in Mice due to Fetal Exposure to Low Doses of Estradiol or Diethylstilbestrol and Opposite Effects at High Doses*, 94 PROC. NAT'L ACAD. SCI. 2056, 2060 (1997); for reviews *see* Laura N. Vandenberg et al., *Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses*, 33 ENDOCRINE REVS. 378, 378 (2012) [hereinafter Vandenberg, *Hormones*]; Thaddeus T. Schug et al.,

C. *The Epigenetics of Chemical Exposure*

This new knowledge not only aids our understanding of natural processes such as the effects twins have on one another before birth,[24] but also raises concerns about non-mutagenic toxins that might alter outcomes in multiple generations without mutating DNA. In other words, it is becoming increasingly clear that chemical exposure in one generation can affect the health and behavior of the children, grandchildren and in some cases great-grandchildren of the exposed individuals even if no mutation has occurred.[25] The implications of this new epigenetic framework begin with the questions asked by scientists when they are designing studies. For some chemicals, a study that only examines the exposed individuals, not their children and grandchildren, may miss important epigenetic effects.[26] Scientists working under a pre-epigenetics framework did not have a reason to look for the effects of a non-mutagenic chemical in the next generations, but with the new understanding of epigenetics, scientists now often need to consider inter-generational effects in the experimental design when studying environmental life experiences, both chemical and behavioral.[27]

The emerging science of epigenetics not only has important implications for research on genetics, but also challenges the ability of the toxics regulatory regime to adapt to a shift in a core scientific understanding.[28]

Minireview: Endocrine Disruptors: Past Lessons and Future Directions, 30 MOLECULAR ENDOCRINOLOGY 833, 837 (2016).

24. *See* vom Saal et al., *supra* note 16, at 895-97.

25. *See* Mathew D. Anway et al., *Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility*, 308 SCI. 1466, 1468 (2005); Marcus E. Pembrey et al., *Sex-Specific, Male-Line Transgenerational Responses in Humans*, 14 EUR. J. HUM. GENETICS 159, 159 (2006); Marjolein V. Veenendaal et al., *Transgenerational Effects of Prenatal Exposure to the 1944–45 Dutch Famine*, 120 BJOG 548, 550 (2013).

26. For an overview, *see* Rothstein, *The Ghost*, *supra* note 12.

27. For example, one of us conducted some of the earliest research in the field of chemical signaling in the 1960s and 1970s, and another has conducted relevant scientific research more recently. In neither case did the pre-epigenetics conceptual framework under which we were working give us a reason to look at multi-generational effects. *See, e.g.*, John G. Vandenbergh et al., *Partial Isolation of a Pheromone Accelerating Puberty in Female Mice,* 43 J. REPROD. & FERTILITY 515, 515–23 (1975) (identifying the "Vandenbergh effect" but not examining whether it occurs in future generations); Joseph R. Lombardi & John G. Vandenbergh, *Pheromonally Induced Sexual Maturation in Females: Regulation by the Social Environment of the Male,* 196 SCI. 545, 545–46 (1977) (same); Marc A. Dingman et al., *Age-Specific Locomotor Response to Nicotine in Yellow and Mottled Yellow Avy/a Mice*, 6 BMC RES. NOTES 497 (2013) (identifying methylation effects but not effects on future generations).

28. The interplay between public and private regimes can be important for adaptive management and experimentalist governance. *See* Robin Kundis Craig & J.B. Ruhl, *Designing Administrative Law for Adaptive Management*, 67 VAND. L. REV. 1 (2014); Charles F. Sabel & William H. Simon, *Minimalism and Experimentalism in the Administrative State*, 100 GEO. L.J. 53 (2011).

For instance, the current regulatory test protocols might be missing subtle but multi-generational effects of chemical exposure. Epigenetics complicates the toxicology of new chemical substances we thought to be low risk because we now need to assess the effects of environmental exposures on future generations even for some chemicals that do not cause genetic mutations. Epigenetics also increases the need to re-evaluate the effects of existing chemical substances we already knew were problematic in light of the knowledge that epigenetic effects can be transferred to multiple generations of offspring.[29] Further, epigenetics increases the need to understand the effects of chemical exposure in the period before birth (in utero), since individuals may be most susceptible to epigenetic effects during this period.[30] Epigenetics also raises questions about the legal standards for regulatory action and for common law tort liability. Importantly, epigenetics also challenges the regulatory regime to account for the fact that epigenetic modifiers may provide new ways to treat or mitigate the risks of chemical exposures.

D. *Shifting the Focus of Toxics Regulation*

As we mentioned at the outset, the development of an appropriate response to epigenetics by the public toxics regulatory regime will not be easy. Scholars over the last several decades have noted that the public regulatory regime is a remarkably complex, slow-moving system.[31] This literature explains much of the gridlock between 1976 and 2015, a period during which Congress failed to update the principal federal toxics statute despite substantial developments in science and evidence of regulatory shortcomings.[32] This logjam was broken with a major statutory reform in 2016, but the implementation of the new statutory provisions will require a substan-

29. *See* Joceyln Kaiser, *Mom's Environment During Pregnancy Can Affect Her Grandchildren*, SCI. (July 10, 2014, 2:00 PM), http://www.sciencemag.org/news/2014/07/moms-environment-during-pregnancy-can-affect-her-grandchildren; *see also* Skinner, *New Kind*, *supra* note 16.

30. *See* Skinner, *New Kind*, *supra* note 16, at 51.

31. *See, e.g.*, Richard B. Stewart, *Madison's Nightmare*, 57 U. CHI. L. REV. 335, 355, 342-46 (1990) (discussing the iron triangle and the challenges of centralized government).

32. *See* discussion *infra* Part III. The gridlock was not limited to toxics: no major new pollution control statutes were enacted in the quarter century after the 1990 Clean Air Act Amendments. *See* Michael P. Vandenbergh, *The Emergence of Private Environmental Governance*, 44 ENVTL. L. REP. 10125, 10132 fig.1 (2014) [hereinafter Vandenbergh, *Emergence*]; David M. Uhlmann, *The Quest for a Sustainable Future and the Dawn of a New Journal at Michigan Law*, 1 MICH. J. ENVTL. & ADMIN. L. 1, 9 (2012); Richard J. Lazarus, *Congressional Descent: The Demise of Deliberative Democracy in Environmental Law*, 94 GEO. L.J. 619, 619 (2006) (describing congressional action as "effectively moribund").

tial amount of regulatory activity.[33] In addition to the other barriers facing the public toxics regulatory regime, the response to epigenetics confronts a psychological challenge: humans have a strong tendency to fit new facts into pre-existing mental models, accepting facts that fit and rejecting or re-shaping those that do not, rather than changing the underlying frameworks themselves.[34] This confirmation bias not only makes it difficult to appreciate the significance of new scientific information, but also impairs the ability to identify the new institutional arrangements that can respond to them.

Despite these challenges, we argue that the growth of private governance in the last decade provides room for optimism about the response to epigenetics.[35] Private environmental governance arises when private organizations perform traditionally governmental functions, such as reducing negative externalities and managing common pool resources or public goods.[36] Substantial uncertainty exists about the federal government's appetite to regulate toxics, but the toxics regulatory regime is no longer a purely public regulatory domain, and thus the impediments to a response may be less than they were in recent decades. In fact, we argue that what was once a public toxics regulatory regime is now better described as a public-private toxics regulatory regime.[37]

The private aspects of this new public-private toxics regulatory regime do not fit neatly into the public and collaborative governance models that dominate the legal literature,[38] but they are not marginal activities. Actions

33. Frank R. Lautenberg Chemical Safety for the 21st Century Act, Pub. L. No. 114-82, 130 Stat. 448 (2016). Although no major TSCA amendments were enacted prior to the Lautenberg Act, targeted provisions were added on asbestos (1986), radon (1988), lead (1992), schools (2007), and formaldehyde (2010). U.S. Envtl. Prot. Agency, *Toxic Substances Control Act (TSCA) and Federal Facilities*, https://www.epa.gov/enforcement/toxic-substances-control-act-tsca-and-federal-facilities (last visited Oct. 13, 2017).

34. *See, e.g.*, Raymond S. Nickerson, *Confirmation Bias: A Ubiquitous Phenomenon in Many Guises*, 2 Rev. Gen. Psychol. 175 (1998) (discussing research on confirmation bias). For a review of the implications of behavioral science for administrative law, *see* Michael P. Vandenbergh, Amanda R. Carrico & Lisa Schultz Bressman, *Regulation in the Behavioral Era*, 95 Minn. L. Rev. 715 (2011) [hereinafter Vandenbergh, *Regulation*].

35. Michael P. Vandenbergh, *The Private Life of Public Law*, 105 Colum. L. Rev. 2029 (2005).

36. Michael P. Vandenbergh, *Private Environmental Governance*, 99 Cornell L. Rev. 129, 141-47 (2013) [hereinafter Vandenbergh, *Private Environmental Governance*].

37. *See* discussion *infra* Part III.B. The new public-private toxics regulatory regime could also be described as a "regime complex," a term that has been applied to global climate mitigation efforts. Robert O. Keohane & David G. Victor, *The Regime Complex for Climate Change*, 9 Persp. on Pol. 7, 7 (2011); Charles F. Sabel & David G. Victor, *Governing Global Problems Under Uncertainty: Making Bottom-Up Climate Policy Work*, Climatic Change, Oct. 2015, at 15-16.

38. *See, e.g.*, Jody Freeman, *Collaborative Governance in the Administrative State*, 45 UCLA L. Rev. 1, 2 (1997) (discussing collaborative features of agency actions).

by retailers such as Walmart and Target, industry trade associations, advocacy groups, private disclosure organizations, and private standards and certification organizations respond to concerns about toxics by consumers, corporate customers, investors, and others, and their actions are not subject to easy control through the political process.[39] As one industry official stated in 2011, "[t]he loss of public confidence [in the public regulatory system means] we're going to increasingly have retailers that are regulators, like Walmart and Target."[40] This prediction has come true: Thousands of products and companies are now subject to private toxics requirements.[41] Corporations in the retail, electronics, automotive, food, and other sectors have worked with advocacy groups to reduce toxic chemical use through private regulatory initiatives and have extended private toxics standards to suppliers around the globe.[42] These private initiatives are not a substitute for government regulation, but they provide new ways to adapt to the new scientific understanding of epigenetics even if government is unable or unwilling to identify and address new threats.

In Part II of this Article, we explore the new understanding of epigenetics, and in Part III we examine the implications for the public-private toxics regulatory regime. In Part IV we identify other fields that will be affected by the new understanding of epigenetics, including the study of regulation generally, as well as toxic torts, pesticide and drug laws, and social services such as anti-hunger and child protection programs. Part V concludes by suggesting that although Lamarck may have been wrong to suggest that giraffes pass long necks to their offspring because they stretch to reach high places during their lifetimes, the underlying intuition that the experiences of an organism during its lifetime can affect the genetic inheritance of its offspring turns out to have more traction than anyone could have imagined at the time when policymakers constructed the modern toxics regulatory regime in the 1970s. Although it remains to be seen whether and how the toxics regulatory regime will adapt to epigenetics, the emergence of private governance in recent years provides a new institutional response that can fill gaps and create pressure for the evolution of the public regulatory regime. This is thus an auspicious time for testing the concept

39. *See* Vandenbergh, *Private Environmental Governance*, *supra* note 36 at 129, 136, 147, 156–57, 188, 191 n.260.

40. *Id.* at 136 n.32 (citing *Upcoming Lautenberg Bill Could Be Key Test for TSCA Reform this Congress*, INSIDE E.P.A. WKLY. REP., Apr. 1, 2011, at 6).

41. *See* discussion *infra* Part III.B.

42. *See, e.g.*, Michael P. Vandenbergh, *The New Wal-Mart Effect: The Role of Private Contracting in Global Governance*, 54 UCLA L. REV. 913, 916–17 (2007) [hereinafter Vandenbergh, *New Wal-Mart Effect*].

that environmental law is grounded in science, and when the science changes, so should—and can—the law.

II. The Emergence of Epigenetics

To examine the implications of epigenetics for environmental law, we begin with a very brief overview of the standard model of genetic inheritance that was worked out over the past century and that still explains most inheritance. We then introduce epigenetics by describing the newly-discovered mechanisms by which traits can change in the absence of genetic mutation, and we provide several examples of how epigenetic effects can arise.

A. *The Standard Genetic Model*

The dominant understanding in genetics has been that the characteristics, or traits, of plants, animals, and humans are passed down from generation to generation via transfer of DNA. In the standard model, if the sequence of DNA (i.e. the order of the bases) remains the same, there is no change in the genes (and thus the traits) that are passed down from generation to generation. Variability in the sequence is recognized to occur as a result of the combined inheritance from female and male parents, as well as through new mutations from exposure to background radiation, naturally occurring mutagenic chemicals and random errors during DNA replication. In the overall population, these processes result in very slow change in a trait—generally occurring only over many, many, generations.

The mechanism by which DNA could act as the agent for inheritance was revealed over the first half of the 20th century. The process started with the rediscovery of Mendel's work in the early 1900's[43] and with subsequent experiments demonstrating that DNA was the critical molecule that carried traits from one generation to the next.[44] In 1953, Watson and Crick showed that the structure of DNA is a two-stranded (double) helix.[45] Shortly thereafter, DNA and heredity appeared commonly in scientific publications capitalizing on the fact that DNA was the molecule of heredity,[46]

43. Jean Gayon, *From Mendel to Epigenetics: History of Genetics*, 339 Comptes Rendus Biologies 225 (2016).

44. Oswald Avery, Colin MacLeod & Maclyn McCarty, *Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by a Deoxyribonucleic Acid Fraction Isolated From Pneumococcus Type III*, 79 J. Experimental Med. 137 (1944).

45. James D. Watson & Francis H. Crick, *Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid*, 171 Nature 737 (1953).

46. H.E. Alexander & G. Leidy, *Nature of the Hemophilus Influenzae Cell Through Which Heritable Changes are Induced by Desoxyribonucleic Acid*, 86 Am . J. Diseases Child. 475, 475-77 (1953).

and is taught in general textbooks.[47] With Crick's proposal of the Central Dogma of Molecular Biology,[48] it was clear how the information received by offspring in the form of DNA could be "expressed" as ribonucleic acid (RNA), which in turn would serve as a messenger for the information needed to create proteins. It was the proteins, then, that were the workhorses of the cell, and the ability of various proteins to perform their intended tasks were traits one could measure in the organism or population.

This process of inheritance via DNA was extremely powerful for describing the generation of traits in single-celled organisms (e.g. bacteria), which were the species of choice for scientists carrying out molecular biology experiments. Research in this area led to an explosion of information about the basic biochemistry of life, not to mention creating a whole new industry (i.e., biotechnology) based on the understanding of how altering genetic sequences could create observable changes in traits. Although the theory and dogma also worked well for explaining the inheritance patterns of more complex multicellular organisms, some questions remained unanswered.

Two of these questions are important for the topic of this paper. First, it was recognized that something more than the passing of DNA to offspring was needed if identical twins inherited the same DNA sequences but differed from each other in some traits.[49] These differences in traits could not be explained adequately by mutations being inherited from the parents of the twins, which left the source of the differences yet to be identified.[50] Second, it was apparent that all cells in the body inherited a complete set of DNA, which included instructions for specialization to make any other type of cell; however, kidney cells were not found in the liver, or liver cells in the kidney. Thus, something other than the mechanisms by which DNA was replicated and transmitted must have been acting within an individual to explain the variability between genetically identical individuals and genetically identical cells, and that something—the concept of epigenetics—while giving an answer to both questions, brings with it a new set of concerns for environmental law and policy.

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47. RAVEN ET AL., *supra* note 9, at 15.

48. *See* F. H. C. Crick, *On Protein Synthesis*, 12 SYMP. SOC'Y EXPERIMENTAL BIOLOGY 138, 152 (1958).

49. Mario F. Fraga et al., *Epigenetic Differences Arise During the Lifetime of Monozygotic Twins*, 102 PROC. NAT'L ACAD. SCI. 10604, 10606 (2005).

50. *Id.* at 10609.

B. *Epigenetics*

The field of epigenetics arose, in part, from work on the second issue described above—the recognition that cells in the body can vary widely in structure and function (such as kidney and liver cells) despite each having the same complete set of genes to become any type of cell in the body.[51] The answer to the question of why dividing liver cells only produce more liver cells, and never kidney cells, came with discovery of a mechanism that could *repress* the kidney-related genes and allow only liver-related genes to be *expressed*. The mechanism involved chemical modification of the DNA, and the modification was subtle enough that the term epigenetics (meaning on, upon, or over, genetics) was an appropriate fit. Researchers found that although the base pair sequence of nucleic acids—the molecules of adenine, cytosine, guanine and thymine (often described as A's, C's, G's and T's) in the DNA comprising the repressed gene—was preserved, closer inspection showed that some of the cytosines were different.[52] They had not been replaced or deleted, but they had been modified by the addition of an extra part, known as a methyl group, that prevented the gene product they encoded from being expressed by the cell.[53]

This chemical modification, although subtle, is now recognized as a key factor in controlling gene expression, which in turn controls cell identity.[54] Genes that are not expressed (i.e. are repressed) in a particular cell tend to have methylation on more of the cytosines in and around them than do genes that are expressed. Methylation of DNA provides the examples we use to explain epigenetics in this Article, and methylation of DNA presents the strongest case for being the mechanism by which the chemical exposures or experiences of an individual may be passed to offspring.[55] More recent research, however, has identified additional mechanisms that play a role in epigenetics. We describe these other mechanisms in Section D, "Other Mechanisms of Epigenetic Effects?"

C. *The New Mechanism: Methylation of DNA as an Epigenetic Mark*

As described above, epigenetic effects depend greatly on the methylation of specific base pairs in the DNA sequence. The term methylation has

51. This concept is called totipotency. *See* John B. Gurdon, *The Egg and the Nucleus: A Battle for Supremacy*, 140 DEV. 2449, 2451 (2013).

52. Rudolf Jaenisch & Adrian Bird, *Epigenetic Regulation of Gene Expression: How the Genome Integrates Intrinsic and Environmental Signals*, 33 NATURE GENETICS 245 (2003).

53. *Id.*

54. *Id.*

55. *See id.*

its origins in chemistry, where one carbon and three hydrogen atoms are known as a "methyl group." Thus, methylation is the process of placing a methyl group on a molecule. The biological process of methylation occurs with the aid of a particular protein known as a methylase. As is the case for almost every biological process, methylation is balanced by demethylation (removal of a methyl group), which requires a protein known as a demethylase. Through adjustments to these proteins and processes, the organism's genome responds to environmental factors and ensures that there are the right number of cells of each type (e.g. liver cells and kidney cells) and that the cells are working optimally for a given environment because they are making enough RNA for sufficient amounts of proteins to be produced (liver cells producing liver proteins). Any environmental exposure, whether chemical or behavioral, that alters the numbers of a given cell type, or the proper function of cells, is a potential problem, with consequences for the organism that can range from subtle to disastrous (e.g., cancer).

As is often the case, the presence of methyl groups on DNA was well described long before the mechanism that acted to add or remove the methyl groups was well established. Even today, the complexities of this mechanism are not entirely understood. Research in mammals has described three distinct methylases with subtly different activities, but specific enzymes that demethylate DNA have not yet been well characterized. Research is now focused both on new sites of methylation in DNA and on the mechanisms that drive the placement or removal of methyl groups at these sites. Although methylation is still being explored and is just one of several potential mechanisms to account for epigenetic inheritance, it demonstrates how traits can be transmitted across generations without changing the sequence of DNA. DNA methylation patterns can be maintained across cell division and across generations because just like the DNA sequence itself, the associated cytosine methylation can serve as a template for specific methylation patterns to be (potentially) replicated when cells divide or an egg is fertilized. This idea contrasts with the widely accepted idea that methylation patterns are erased from DNA during very early embryonic stages and during reprogramming in germ cells and thus that there are no mechanisms to allow germ cells to be modified by the environment.[56] We now know that there are many sites that escape the erasure mechanisms.[57]

It is important to note, however, that when DNA methylation is not self-perpetuating, the epigenetic effects may not be passed down in full. In

56. Edith Heard & Robert A. Martienssen, *Transgenerational Epigenetic Inheritance: Myths and Mechanisms*, 157 CELL 95, 95 (2014).

57. Stefanie Seisenberger et al., *The Dynamics of Genome-wide DNA Methylation Reprogramming in Mouse Primordial Germ Cells*, 48 MOLECULAR CELL 849, 849 (2012).

such cases, specific gene methylation events that are passed on to offspring may decrease in intensity of effect by a factor of approximately one-half over each generation because each parent only contributes one-half of their DNA to offspring.[58] This phenomenon of decreasing or negligible effect in each generation is related to the sex of the exposed individual. A female child's eggs are generated before birth, so subsequent exposures to chemicals might have no effect on the eggs and thus leave the next generation unaffected. In contrast, sperm are replaced on a continuous basis (and only post-puberty) so it is unclear whether early life experiences will alter methylation of DNA in sperm that produce an offspring only many years later.[59] Thus, overall epigenetic effects due to environmental factors may be fully passed on to subsequent generations in some cases, but in other cases the methylation patterns may diminish with subsequent generations.

D. *Other Mechanisms of Epigenetic Effects?*

Although most research on epigenetics has focused on methylation of DNA,[60] at least three additional mechanisms also participate in epigenetic processes. Chemical modification of the protein scaffolding (histones) around which DNA is wound is also important in regulating gene expression. The modification of histones responds to the external environment as well as the internal environment of the cell to control gene expression.[61] There is evidence that patterns of histone modification are passed to subsequent generations,[62] and there is some limited evidence that traits can be influenced by paternal exposures via histones.[63]

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58. These effects might not persist into the third generation. Linda Titus-Ernstoff et al., *Offspring of Women Exposed in Utero to Diethylstilbestrol (DES): A Preliminary Report of Benign and Malignant Pathology in the Third Generation*, 19 EPIDEMIOLOGY 251, 256 (2008).

59. For instance, grandfathers who experienced malnutrition before puberty had grandsons with health effects. *See* discussion *infra* Part I.D.

60. *See* Michael K. Skinner, *What is an Epigenetic Transgenerational Phenotype? F3 or F2*, 25 REPROD. TOXICOLOGY 2, 3 (2008).

61. Jung Kyoon Choi & Sang Cheol Kim, *Environmental Effects on Gene Expression Phenotype Have Regional Biases in the Human Genome*, 175 GENETICS 1607, 1607 (2007).

62. Saher Sue Hammoud et al., *Genome-Wide Analysis Identifies Changes in Histone Retention and Epigenetic Modifications at Developmental and Imprinted Gene Loci in the Sperm of Infertile Men*, 26 HUM. REPROD. 2558, 2558-59 (2011); *see also* Keith Siklenka et al., *Disruption of Histone Methylation in Developing Sperm Impairs Offspring Health Transgenerationally*, 350 SCI. aab2006-1 (2015), http://dx.doi.org/10.1126/science.aab2006; Marta Teperek et al., *Sperm Is Epigenetically Programmed to Regulate Gene Transcription in Embryos*, 26 GENOME RES. 1034, 1034 (2016).

63. Christine van de Werken et al., *Paternal Heterochromatin Formation in Human Embryos is H3K9/HP1 Directed and Primed by Sperm-Derived Histone Modifications*, 5 NATURE COMM. 1, 7 (2014). For results in mice, *see* Siklenka et al., *supra* note 62, at aab2006-2.

In addition to transmission of modified histones across generations, two mechanisms of epigenetic influence on RNA have become apparent that may also be transmitted across generations. First, a specific class of RNA, known as long noncoding RNA (lncRNA), has been demonstrated to alter gene expression in a manner consistent with epigenetic effects.[64] Second, the activity of small RNAs, known as microRNAs (miRNA), in repressing gene expression is probably the oldest documented transgenerational epigenetic effect,[65] but one that only recently has been identified as acting in mammals.[66]

E. *Examples*

The discovery of epigenetic mechanisms and effects provides a new perspective on how environmental factors can affect heredity. Some of the specific factors that produce epigenetic effects have been identified, but much work remains to be done. We provide several examples below to demonstrate the wide range of epigenetic influences and how epigenetics challenges law and policy to adapt. We begin with several factors that do not involve toxic industrial or agricultural chemicals, including stress, diet, and chemical communication among prenatal siblings. Although these examples provide a sense of the breadth of environmental factors that act on epigenetics, and are important for a wide range of laws and policies, the factors that are of most interest for the chemical regulatory regime are industrial and agricultural chemicals, and we turn next to those chemicals. Considerable scientific evidence exists that several types of chemicals can affect reproduction and behavior in future progeny, suggesting that an epi-

64. Reinier Boon et al., *Long Noncoding RNAs: From Clinical Genetics to Therapeutic Targets?*, 67 J. Am. C. Cardiology 1214, 1215 (2016).

65. In plants, *see* Mario Alberto Arteaga-Vazquez & Vicki Lynn Chandler, *Paramutation in Maize: RNA Mediated Trans-Generational Gene Silencing*, 20 Current Opinion Genetics & Dev. 156, 157 (2010).

66. *See* Katharina Gapp et al., *Implication of Sperm RNAs in Transgenerational Inheritance of the Effects of Early Trauma in Mice*, 17 Nature Neuroscience 667 (2014); Miguel A. Brieño-Enríquez et al., *Exposure to Endocrine Disruptor Induces Transgenerational Epigenetic Deregulation of MicroRNAs in Primordial Germ Cells*, 10 PLOS One, Apr. 21, 2015, at 1. Details of these mechanisms, which involve epigenetics but do not involve DNA methylation, are beyond the scope of this Article, but the interested reader can learn more about epigenetic effects of histone modification, miRNA, and lncRNA by examining several recent review papers. *See generally* Adrian Bird, *Perceptions of Epigenetics*, 477 Nature 396 (2007); Agustina D'Urso & Jason H. Brickner, *Mechanisms of Epigenetic Memory*, 30 Trends in Genetics 230 (2014); Skinner, *New Kind*, *supra* note 16; Nadine Provençal & Elisabeth B. Binder, *The Effects of Early Life Stress on the Epigenome: From the Womb to Adulthood and Even Before*, 268 Experimental Neurology 16 (2015).

genetic mechanism involving changes in the regulation of genes can result in multi-generational effects in offspring.

1. Siblings, Stress, and Diet

The Finnish twin studies suggest that the conditions during pregnancy, including the sex of a twin, can be important influences upon reproductive success in adulthood.[67] Other findings have even greater significance for law and policy. For example, in addition to exposure to toxic chemicals, exposure to stressful conditions during fetal and early development can have long-term consequences for the exposed humans and for their offspring, in some cases for several generations.[68]

One form of stress is dietary. A rare opportunity to study the consequences of malnutrition and dietary stress during fetal development in humans and the effects on later adult disease risk was presented by the "Dutch Hunger Winter."[69] In 1944-1945, the population in western areas of the Netherlands was purposely deprived of food for several months by a Nazi-imposed food embargo.[70] Extensive records of food availability and of the population's medical care from that period to the present make this tragic event a useful epidemiological data set for studying the effects of food deprivation over multiple generations.

The epidemiological data from the Dutch Hunger Winter reveal that poor nutrition to fetal and newborn subjects has multiple adverse health effects lasting into adulthood.[71] Subjects exposed to the famine during gestation experienced higher rates of obesity, a twofold increase in incidence of cardiovascular disease, and a greater response to stress as adults.[72] In particular, women exposed as young girls (during fetal and early development) experienced elevated cholesterol and triglyceride levels,[73] as well as increased risk of breast cancer[74] in adulthood. One study sought to determine the underlying causes of these long-term effects on health. The study found

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67. *See* Lummaa et al., *supra* note 1.

68. *See* Bastiaan T. Heijmans et al., *Persistent Epigenetic Differences Associated with Prenatal Exposure to Famine in Humans*, 105 PROC. NAT'L ACAD. SCI. 17046 (2008); Veenendaal, *supra* note 25, at 548.

69. L. H. Lumey et al., *Cohort Profile: The Dutch Hunger Winter Families Study*, 36 INT'L J. EPIDEMIOLOGY 1196, 1197 (2007).

70. *Id.* at 1196.

71. *Id.* at 1201-02.

72. *See* Tessa Roseboom et al., *The Dutch Famine and Its Long-Term Consequences for Adult Health*, 82 EARLY HUM. DEV. 485, 487-89 (2006).

73. L.H. Lumey et al., *Lipid Profiles in Middle-Aged Men and Women After Famine Exposure During Gestation: The Dutch Hunger Winter Families Study*, 89 AM. J. CLINICAL NUTRITION 1737 (2009).

74. *See* Roseboom, *supra* note 72, at 489.

that exposed people, as compared to unexposed, same-sex siblings,[75] had less DNA methylation of the Insulin-like Growth Factor 2 gene (*IGF2*), which produces one of several insulin-like growth factors that play critical roles in human growth and development.[76] An effect of caloric restriction in a much shorter and less intense situation was demonstrated by Almond and colleagues.[77] They found academic performance at age 7 was reduced in children exposed in utero to fasting for religious purposes by their mothers.[78] This result is interesting in that the exposure was limited – fasting while pregnant only lasted for one month, and only occurred for half of each day. In short, epidemiological data indicating the lifelong harms of early dietary stress, coupled with the discovery of an epigenetic mechanism that may explain these harms at a molecular level, suggest that epigenetic changes made during early development can produce lifelong effects on gene expression and health.

In fact, the deleterious health effects of stress are not limited to a single lifespan. Epidemiological studies also have explored the effects of dietary stress across multiple generations, with startling results. Using health data and historical records of food availability, Bygren and colleagues found that a sharp change in childhood food supply for paternal grandmothers increased risk of cardiovascular problems in their granddaughters.[79] Similarly, Pembrey and colleagues linked restriction of food during the paternal grandfather's prepubertal slow growth phase with mortality risk in grandsons.[80] The researchers hypothesize that this transgenerational effect may result from epigenetic changes in the sperm cells of the grandfathers that are passed down the male line, and this hypothesis aligns with evidence from animal models that fathers can pass epigenetic effects to subsequent generations.[81]

These results are consistent with findings from animal studies. In rodents, changing the quality or amount of food given to a father at various developmental stages can affect male offspring. For instance, when male rats are deprived of nutrition during gestation but provided ample food

75. Heijmans et al., *supra* note 68, at 17046.

76. *See* F.M. Smith et al., *Regulation of Growth and Metabolism by Imprinted Genes*, 113 CYTOGENETIC & GENOME RES. 279 (2006).

77. *See, e.g.*, Douglas Almond et al., In Utero *Ramadan Exposure and Children's Academic Performance*, 125 ECON. J. 1501 (2014) (describing the effect on pregnant women who fast during Ramadan).

78. *Id.* at 1522-27.

79. Lars Olov Bygren et al., *Change in Paternal Grandmothers' Early Food Supply Influenced Cardiovascular Mortality of the Female Grandchildren*, 15 BMC GENETICS, 2014, at 3.

80. Marcus E. Pembrey et al., *Sex-Specific, Male-Line Transgenerational Responses in Humans*, 14 EUR. J. HUM. GENETICS 159, 159-60 (2006).

81. Rando, *supra* note 14.

throughout life, their offspring have lower birth weights and impaired glucose tolerance.[82] In addition, restricting food for a single day two weeks prior to mating causes mice to sire offspring with altered blood glucose and growth hormone levels.[83]

Initial studies also suggest that, like dietary stress, the stress from severe child abuse may alter an individual's DNA methylation patterns for decades.[84] As with other epigenetic effects, these patterns also may be transmitted to subsequent generations; in humans, methylation changes that produce significant differences in stress responsiveness and other behaviors have been associated with a history of childhood abuse and also have been shown to persist across generations.[85] Although the mechanism is not fully understood, some known genes may be targeted, including the glucocorticoid receptor[86] and serotonin transporter.[87] It is too early to draw firm conclusions, but this research emphasizes the long-term, and perhaps multigenerational costs of child abuse, and it suggests that it may be necessary to think in new ways about the optimal law and policy response.

Food also can affect DNA methylation and otherwise modify gene expression to create epigenetic effects. Although research into how different types of food may affect the human epigenome is limited, several isolated compounds and micronutrients have been extensively studied in animals and in vitro for their abilities to alter the levels of methylation on DNA. Organic compounds known as polyphenols, which are highly concentrated in certain plant-based foods such as teas, spices, and soy products, have been shown to change DNA methylation patterns in cancerous cells of human

82. Josep C. Jimenez-Chillaron et al., *Intergenerational Transmission of Glucose Intolerance and Obesity by* In Utero *Undernutrition in Mice*, 58 DIABETES 460, 466 (2009).

83. Lucy M. Anderson et al., *Preconceptional Fasting of Fathers Alters Serum Glucose in Offspring of Mice*, 22 NUTRITION 327, 329 (2006) [hereinafter Anderson, *Preconceptional*].

84. *See generally* P.-E. Lutz & G. Turecki, *DNA Methylation and Childhood Maltreatment: From Animal Models to Human Studies*, 264 NEUROSCIENCE 142 (2014).

85. For a review of stress and brain structures and behavior, *see* Bruce S. McEwen, *Stress and Anxiety: Structural Plasticity and Epigenetic Regulation as a Consequence of Stress*, 62 NEUROPHARMACOLOGY 3 (2012); *see also* EPIGENETIC REGULATION IN THE NERVOUS SYSTEM (J. David Sweatt et al., 1st ed. 2013, new edition forthcoming 2017) (discussing behavioral aspects of epigenetics).

86. For the glucocorticoid receptor (GR), the external stress signals release of cortisol, which binds to and activates GRs in the hippocampus. The activated GRs modify transcription of many genes that then modulate the methyl transferases and demethylases. *See* Patrick O. McGowan et al., *Epigenetic Regulation of the Glucocorticoid Receptor in Human Brain Associates with Childhood Abuse*, 12 NATURE NEUROSCIENCE 342 (2009).

87. The mechanism is unclear for the serotonin transporter. *See* Steven R.H. Beach et al., *Methylation at SLC6A4 Is Linked to Family History of Child Abuse: An Examination of the Iowa Adoptee Sample*, 153 AM J. MED. GENETICS PART B: NEUROPSYCHIATRIC GENETICS 710, 710-11 (2009).

organs in vitro.[88] Isoflavones, compounds found in soy, also have demonstrated the ability to modulate gene expression in ways that counteract cancer cell development.[89] Much of this evidence is preliminary, and further research will be needed to understand the connections between epigenetic regulation and cancer prevention by polyphenols and isoflavones, but the development of increasingly sophisticated technologies for examining epigenetic mechanisms makes this an important and promising field for further exploration.

In addition, animal studies suggest that substances known as methyl donors, including folic acid, betaine, and choline, can promote methylation of genes during gestation and thereby influence various physical traits in offspring. In mice, supplementing maternal diets with methyl donors has allowed researchers to influence genes that code for traits such as coat color[90] and tail type,[91] and it has even allowed researchers to mitigate some of the detrimental epigenetic effects associated with maternal exposure to a chemical called bisphenol A or BPA.[92] Additionally, folate and choline deficiency in mice has been associated with neural changes leading to decreased memory function, and this effect is thought to occur through epigenetic mechanisms.[93] In humans, epidemiological studies suggest that folate intake may be associated with protection against certain cancers,[94] while higher blood concentration of some B-vitamins (cofactors for the enzymes that move methyl groups from methyl donors) has been correlated with decreased methylation of several genes related to disease in former smokers.[95] Although there is still much to understand regarding how and to what extent diet may create epigenetic changes that modulate human health, preliminary results suggest that dietary supplementation of key nutrients that

88. Mingzhu Fang et al., *Dietary Polyphenols May Affect DNA Methylation*, 137 J. NUTRITION 223S (2007).

89. For an in-depth review, *see* Maria Pudenz et al., *Impact of Soy Isoflavones on the Epigenome in Cancer Prevention*, 6 NUTRIENTS 4218 (2014).

90. David M.J. Duhl et al., *Neomorphic* Agouti *Mutations in Obese Yellow Mice*, 8 NATURE GENETICS 59 (1994). For a review of dietary methyl donors, *see* Olivia S. Anderson et al., *Nutrition and Epigenetics: An Interplay of Dietary Methyl Donors, One-Carbon Metabolism, and DNA Methylation*, 23 J. NUTRITIONAL BIOCHEMISTRY 853, 853-55 (2012) [hereinafter Anderson, *Nutrition*].

91. Robert A. Waterland et al., *Maternal Methyl Supplements Increase Offspring DNA Methylation at* Axin Fused, 44 GENESIS 401 (2006).

92. Dana C. Dolinoy et al., *Maternal Nutrient Supplementation Counteracts Bisphenol A-Induced DNA Hypomethylation in Early Development*, 104 PROC. NAT'L ACAD. SCI. 13056 (2007).

93. Anderson, *Nutrition*, *supra* note 90, at 876.

94. *See* Anderson, *Preconceptional*, *supra* note 83, at 330.

95. Paolo Vineis et al., *DNA Methylation Changes Associated with Cancer Risk Factors and Blood Levels of Vitamin Metabolites in a Prospective Study*, 6 EPIGENETICS 195, 197-99 (2011).

work through epigenetic mechanisms may be able to play an important role in disease prevention and therapy.

2. Chemical Exposure

Epigenetic effects have been demonstrated from various forms of stress, diet, and twin studies, but the principal concern of the chemical regulatory regime is whether industrial, agricultural and consumer chemicals have epigenetic effects in humans or animals. To address this, in this Article we provide two examples for which considerable epidemiological and experimental information is available for epigenetic effects on humans, and we identify others for which there is some likelihood of similar effects although the research base is less robust.

The first example from the world of environmental chemicals is diethylstilbesterol (commonly called DES), a known estrogenic substance (a chemical that mimics the action of estrogen).[96] In the 1940s and 1950s DES was prescribed by physicians in the United States, Europe, and Australia for pregnant women who experienced bleeding or spontaneous abortions in the, as we now know, false hope that it would prevent early fetal loss. As the daughters born to DES mothers reached their teenage years, it was noted that an unexpectedly high number of them developed a rare cancer.[97] DES was taken off the market in the late 1970s in the United States, and in accordance with the standard genetic model that dominated thinking at the time, this regulatory action should have taken care of the principal threat of the chemical.[98]

It soon became clear, however, that the cancerous effects of DES might continue in the second generation of exposed women, and perhaps beyond.[99] Similar DES effects were shown to occur in female mice treated with DES during pregnancy, thus providing a useful animal model to allow more detailed studies.[100] One experiment on mice demonstrated increased susceptibility for reproductive tumors in subsequent generations.[101] A more

96. Retha R. Newbold et al., *Adverse Effects of the Model Environmental Estrogen Diethylstilbestrol Are Transmitted to Subsequent Generations*, 147 ENDOCRINOLOGY S11, S11 (2006).

97. *See* Arthur L. Herbst et al., *Adenocarcinoma of the Vagina: Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women*, 284 NEW ENG. J. MED. 878, 880 (1971).

98. CDC, *The History of DES*, https://www.cdc.gov/des/hcp/nurses/history.html (last visited Sept. 16, 2017).

99. Linda Titus-Ernstoff et al., *Offspring of Women Exposed in Utero to Diethylstilbestrol (DES): A Preliminary Report of Benign and Malignant Pathology in the Third Generation*, 19 EPIDEMIOLOGY 251 (2008).

100. Newbold, *supra* note 96.

101. *Id.* at S15.

recent study[102] confirmed the DES effects on female offspring and showed that there were also effects on male reproductive anatomy following neonatal exposure to DES.[103] The effects in both sexes resulted from epigenetic changes to the genome,[104] and the effects of DES found in mice to the third generation, as well as the advances in our understanding of the mechanisms involved, prompted some preliminary research on human effects. One study found no overall increase of cancer risk in the sons and daughters of women exposed prenatally to DES.[105] The researchers did find, however, that the number of ovarian cancer cases in the granddaughters of exposed women was significantly higher than expected. A study of sons born to women known as "DES daughters" (i.e. women exposed in utero when their mothers took DES) found a significant increase in a specific birth defect.[106] These studies on the third generation were preliminary in the sense that this generation of offspring was in the early stages of sufficient reproductive maturity, so it was difficult to demonstrate the full extent of reproductive effects.

A second example of an endocrine disruptor with possible multigenerational effects is BPA, a compound used to make rigid plastic items such as disposable water bottles, the lining of food cans, medical devices, sealants and heat sensitive printing tapes such as the paper used by receipt printers.[107] The use of BPA has been so widespread that it was detected in the urine of over 90 percent of humans from the age of six to sixty tested in the United States.[108] BPA is known to affect reproductive development as well as a variety of behaviors in rats and mice, especially if exposure occurs during fetal development.[109] An assessment of the risks of BPA exposure in

102. Wendy N. Jefferson et al., *Persistently Altered Epigenetic Marks in the Mouse Uterus After Neonatal Estrogen Exposure*, 27 MOLECULAR ENDOCRINOLOGY 1666 (2013).

103. *See also* Rando, *supra* note 14 (discussing potential transgenerational effects of a male's environment on its offspring).

104. *See* Vandenberg, *Hormones*, *supra* note 23 (further clarifying the cellular mechanisms).

105. Titus-Ernstoff et al., *supra* note 99.

106. The birth defect was hypospadias. Nicolas Kalfa et al., *Prevalence of Hypospadias in Grandsons of Women Exposed to Diethylstilbestrol During Pregnancy: A Multigenerational National Cohort Study*, 95 FERTILITY & STERILITY 2574 (2011).

107. Helmut Fiege et al., *Phenol Derivatives*, *in* 26 ULLMANN'S ENCYCLOPEDIA OF INDUSTRIAL CHEMISTRY 521, 562 (2000); INTEGRATIVE ENVIRONMENTAL MEDICINE 31-34 (Aly Cohen & Frederick S. vom Saal eds., 2017).

108. Antonia M. Calafat et al., *Urinary Concentrations of Bisphenol A and 4-Nonylphenol in a Human Reference Population*, 113 ENVIL. HEALTH PERSP. 391, 392 (2005).

109. Heather B. Patisaul & Heather B. Adewale, *Long-Term Effects of Environmental Endocrine Disruptors on Reproductive Physiology and Behavior*, 3 FRONTIERS BEHAV. NEUROSCIENCE, June 2009, at 3-4 (2009); Bryce C. Ryan & John G. Vandenbergh, *Developmental Exposure to Environmental Estrogens Alters Anxiety and Spatial Memory in Female Mice*, 50 HORMONES &

humans was made by a National Toxicology Program review expert panel, and the conclusion relevant here is that the expert panel expressed "some concern" that neonatal exposure to Bisphenol A affects the developing fetus and young children.[110] The FDA did not impose regulatory limitations based on this conclusion, but several corporations responded by removing BPA from their products.[111]

In addition to DES and BPA, several other types of chemicals have been shown to induce epigenetic effects that carry into later generations, including fungicides and metals.[112] We focus here on one example, lead,

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BEHAV. 85 (2006); *see also* Johanna R. Rochester, *Bisphenol A and Human Health: A Review of the Literature*, 42 REPROD. TOXICOLOGY 132 (2013) (summarizing effects on human health).

110. Robert E. Chapin et al., *NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A*, 83 DEVELOPMENTAL & REPROD. TOXICOLOGY 157, 248 (2008); *see also* Frederick S. vom Saal et al., *Chapel Hill Bisphenol A Expert Panel Consensus Statement: Integration of Mechanisms, Effects in Animals and Potential to Impact Human Health at Current Levels of Exposure*, 24 REPROD. TOXICOLOGY 131 (2007).

111. Although private environmental governance initiatives often involve collective, multi-stakeholder processes that include advocacy groups, suppliers, and outside experts, some private toxics regulation occurs through a more unilateral or bilateral process without the collective standard-setting and transparency more common in multi-stakeholder processes. An example arises from the area of chemicals that can leach into food from food containers. The FDA has not restricted the use of BPA, but advocacy groups have raised concerns. In the face of this advocacy group pressure, roughly one third of food companies have entered into agreements not to use BPA or have committed to a timeline for phasing out its use. *See* Liz Szabo, *Companies Graded on Getting Chemical BPA Out of Cans*, USA TODAY, Oct. 22, 2010, 11:09 AM, http://usatoday30.usatoday.com/yourlife/food/safety/2010-10-21-bpa-cans_N.htm (noting that pressure by food advocacy groups induced thirty-two percent of food companies to announce timelines or agreements to remove BPA from can linings without FDA regulatory action). These commitments are unilateral actions by food companies in response to advocacy group pressure, not responses to FDA regulation or collective private standard-setting initiatives. Implementation likely includes imposition of supply chain requirements on can manufacturers with the food companies functioning as private toxics regulators for their suppliers.

112. For a review of epigenetic effects of metals, *see* Paul D. Ray et al., *Incorporating Epigenetic Data into the Risk Assessment Process for the Toxic Metals Arsenic, Cadmium, Chromium, Lead, and Mercury: Strategies and Challenges*, 16 FRONTIERS IN GENETICS, July 2014, at 1. For a review of epigenetic trans-generational actions of several endocrine disruptors, *see* Michael K. Skinner et al., *Epigenetic Transgenerational Actions of Endocrine Disruptors*, 31 REPROD. TOXICOLOGY 337 (2011). Chemicals that may induce epigenetic effects that carry into later generations include flutamide, an antifungal agent widely used as an agricultural fungicide and a known anti-androgen compound that has shown second but not third trans-generational effects on spermatogenesis. For a review of its actions in rats, *see id.* Another chemical is Vinclozolin, a fungicide that has been used in several crops and in turf grasses, and is an anti-androgenic compound that disrupts masculine development in first and second generation male rats. *See* Matthew D. Anway & Michael K. Skinner, *Transgenerational Effects of the Endocrine Disruptor Vincolozolin on the Prostate Transcriptome and Adult Onset Disease*, 68 PROSTATE 517 (2008). A phthalate, DEHP, is used as a plasticizer in the manufacture of polyvinyl compounds, Peter M. Lorz et al., *Phthalic Acid and Derivatives*, *in* 27 ULLMANN'S ENCYCLOPEDIA

given the importance to the regulatory regime of the widespread exposure to lead that has occurred in Flint, Michigan. Although regulatory efforts have focused on those exposed to lead during their lifetimes, a recent report reveals that a woman's exposure to lead during her pregnancy may have epigenetic effects that are passed to her grandchildren.[113] For this study, investigators measured lead concentrations in the blood of 35 mother-infant pairs living in Detroit, MI and examined methylation patterns at 450,000 genetic loci in both the mother and child.[114] They found that high blood lead concentration in mothers who had been exposed to lead during their fetal development correlated with methylation at 564 genetic loci in the blood cells of both mother and child.[115] In other words, the grandchildren of women who were exposed to lead during pregnancy exhibited DNA methylation patterns mirroring those that occur due to direct lead exposure. Although much research remains to be done to understand the effects of this methylation, and although some effects on the expression of the genome will not be known for decades, the initial results suggest that lead exposure of pregnant women may have multigenerational consequences.

In sum, epidemiological data from human studies and evidence from controlled, often replicated studies using animal models reveal that a variety of compounds found in pharmaceuticals, foods, and drinking water have endocrine disrupting effects in the exposed individuals, effects that persist for one or more generations after exposure. These data suggest that current regulatory test protocols might be missing subtle but long-lasting effects of

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OF INDUSTRIAL CHEMISTRY 131, 144 (7th ed. 2007), and another, DBP, is found in adhesives and cosmetics. *See* Jan L. Lyche et al., *Reproductive and Developmental Toxicity of Phthalates*, 12 J. TOXICOLOGY & ENVTL. HEALTH 225, 226 (2009). Both compounds were reported to have reproductive and developmental toxicant effects in rats that carry into the third generation. *See* Mohan Manikkam et al., *Plastics Derived Endocrine Disruptors (BPA, DEHP and DBP) Induce Epigenetic Transgenerational Inheritance of Obesity, Reproductive Disease and Sperm Epimutations*, 8 PLOS ONE, Jan. 2013, at e55387. Exposure was shown to induce DNA methylation regions in gene promoters. Genistein, a phytoestrogen compound, is a common component in animal foods and adult and infant human foods, especially soy products. Herman Aldercreutz et al., *Maternal and Neonatal Phytoestrogens in Japanese Women During Birth*, 180 AM. J. OBSTETRICS & GYNECOLOGY 737, 737 (1999); Patricia L. Whitten et al., *Effects of a Normal, Human-Concentration, Phytoestrogen Diet on Rat Uterine Growth*, 57 STEROIDS 98 (1992). Studies of neonatal exposure to genistein in mice resulted in adult females with multi-oocyte follicles resulting in ovarian dysfunction and reduced fertility of the treated females and their daughters. Wendy N. Jefferson et al., *Disruption of the Female Reproductive System by the Phytoestrogen Genistein*, 23 REPROD. TOXICOLOGY 308 (2007).

113. Arko Sen et al., *Multigenerational Epigenetic Inheritance in Humans: DNA Methylation Changes Associated with Maternal Exposure to Lead Can Be Transmitted to the Grandchildren*, 29 SCI. REP., Sept. 29, 2015, at 1, 1.

114. *Id.*

115. *Id.*

chemical exposure. In addition, the results in experimental animal models suggest that the consequences of chemical exposure are somewhat specific to the chemical and differ in each of the affected tissues.[116] In Part III, we explore the implications of this knowledge for environmental law and policy.

III. Implications for Environmental Law and Policy

The new findings in epigenetics will test the ability of the regulatory regime to evolve. Can it do so? In a simple model of government regulation, a new threat would provoke a timely, proportionate legislative, administrative, and judicial response. Since the emergence of the regulatory state, though, scholars have noted the roles of capture, ossification, ideology, information overload, and other factors that can thwart the regulatory response. They also have noted that misperceptions of risk cause over-and under-reactions by the public, experts, and policymakers.[117] As we mentioned at the outset, confirmation bias poses an additional barrier.[118]

We begin by examining the ability of the public regulatory regime to adapt to the new understanding of epigenetics, focusing on the principal federal regulatory statute, the Toxic Substances Control Act (TSCA). We then relax our assumption that the public regulatory regime will be able to respond to the new problems presented by epigenetic effects of toxics and turn to private governance. We demonstrate that toxics regulation has transitioned in recent years from a public regulatory regime to a public-private regime, and we explain why we are optimistic that this new public-private regime can adapt to the conceptual shift required by the emergence of epigenetics.

A. *Public Governance*

For more than forty years, toxics regulation has—appropriately in our view—been framed principally as a field of public governance, with a complex network of international, national, and subnational government requirements, including statutes, regulations, and guidance documents. The regulatory regime, in turn, rests largely on research funded by agencies such as the National Science Foundation, the National Institutes of Health, and the EPA. The federal regulatory regime interacts with other public regulatory regimes at the international level such as the Registration, Evaluation,

116. Eric E. Nilsson & Michael K. Skinner, *Environmentally Induced Epigenetic Transgenerational Inheritance of Disease Susceptibility*, 165 Translational Res. 12 (2015).

117. Cass R. Sunstein & Timur Kuran, *Availability Cascades and Risk Regulation*, 51 Stan. L. Rev. 683 (1999); Vandenbergh, *Regulation*, *supra* note 34, at 718 n.7, 720–21, 730–40.

118. *See* discussion *supra* note 34.

Authorisation and Restriction of Chemicals (REACH)[119] program of the European Union[120] and state measures such as Prop 65 in California and the Toxics Use Reduction Act in Massachusetts.[121] The emerging understanding of epigenetics will require the public regulatory regime at each of these levels to update widely-used toxicology methods, re-examine a wide range of chemicals that are candidates for epigenetic effects, account for multigenerational effects when making regulatory decisions, re-examine legal standards, and coordinate information flow and regulatory decision-making across agencies.[122]

1. Toxic Substances Control Act (TSCA)

As adopted in 1976, TSCA authorized EPA to regulate new chemical substances, with the general exception of foods, drugs and cosmetics, which the Food and Drug Administration (FDA) regulates under the Federal Food Drug and Cosmetic Act (FFDCA), and pesticides, which EPA regulates under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).[123] FIFRA and the FFDCA play important roles in toxics regulation, but we focus here on TSCA, which has the broadest reach. In its original form, TSCA Section 4 authorized EPA to promulgate rules requiring testing of a chemical by manufacturers, importers, and processors, but only if the agency concluded that the chemical may present an unreasonable risk or be produced in substantial quantities.[124] TSCA Section 5 required notification of plans to manufacture a new chemical substance and authorized EPA to issue "Significant New Use Rules" if exposure to or release of the substance

119. *See* Commission Regulation 1907/2006 of Dec. 18, 2006, Concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), 2006 O.J. (L 396) (EC).

120. *Id.*

121. CAL. HEALTH & SAFETY CODE §§ 25,249.5–25,250.25 (West 2016); Toxics Use Reduction Act, MASS. GEN. LAWS Ch. 21I, § 2 (1989).

122. *See* Rothstein, *The Ghost*, *supra* note 12, at 24–37. It may be difficult to distinguish between innocuous and harmful methylation changes, especially when the methylation may be reversible or may not be associated with increased risk of disease. *Id.* at 22–23.

123. *See* U.S. Envtl. Prot. Agency, *Summary of the Toxic Substances Control Act*, https://www.epa.gov/laws-regulations/summary-toxic-substances-control-act (last visited Sept. 16, 2016).

124. Toxic Substances Control Act, 15 U.S.C. § 2603(a) (2006). It is important to note, though, that EPA's implementation of TSCA has induced companies that introduce chemicals into commerce to bear much of the burden to conduct the testing and produce the information necessary to support assessments of their human and environmental safety. *See id.* § 2601. This aspect of the TSCA regulatory process is thus more of a public-private hybrid than a purely public regulatory regime, with private actors engaging in negotiations with the EPA regarding the implementation of the statute.

would arise from the use of the substance.[125] TSCA Section 6 authorized EPA to impose requirements on a chemical if it determined that the chemical presents or will present an unreasonable risk and included specific requirements for chemicals such as polychlorinated biphenyls (PCBs).[126]

Over time, critics pointed out numerous shortcomings of the TSCA chemical review authorities and the regulatory process, most notably the locus of the burden to demonstrate that a chemical substance poses a threat. Unlike FIFRA, which places the burden on a pesticide registrant, the original TSCA placed the burden on EPA to determine whether a chemical posed an unreasonable risk before it could regulate. TSCA also provided limited authority for EPA to require submission of the information necessary for the EPA to make that determination.[127]

A second criticism of TSCA arose from different views of the process by which EPA should evaluate the risks of toxics. In theory, a rational agency response to any chemical risk would involve an analysis not only of the risks posed by a chemical, but also the risks posed by the alternatives that would be used if the agency banned or reduced the use of the chemical. Responding to this reasoning, in 1991 the Fifth Circuit, in *Corrosion Proof Fittings v. EPA*, read TSCA to require the Agency to evaluate alternative regulatory approaches to determine the least burdensome response and required the assessment of the substitutes that may replace the banned or otherwise regulated chemical.[128] Although eminently rational in the abstract, in practice the complex and costly analysis required by the *Corrosion Proof Fittings* case imposed large data collection and analysis burdens on EPA, slowing the regulatory process.[129]

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125. *Id.* § 2604(a).

126. *Id.* § 2605. EPA rulings under the Act have been held to be reviewable under a "substantial evidence" standard. Corrosion Proof Fittings v. EPA, 947 F.2d 1201, 1213 (5th Cir. 1991) (quoting 15 U.S.C. § 2618(c)(1)(B)(i)).

127. For an early comparison of the burdens under FIFRA and TSCA, *see* Michael P. Vandenbergh, Note, *The Rutabaga That Ate Pittsburgh: Federal Regulation of Free Release Biotechnology*, 72 VA. L. REV. 1529 (1986); *see also* Linda K. Breggin et al., *Addressing the Risks of Nanomaterials Under United States and European Union Regulatory Frameworks for Chemicals*, *in* ASSESSING NANOPARTICLE RISKS TO HUMAN HEALTH 179, 185-94 (Gurumurthy Ramachandran ed., 2016).

128. *Corrosion Proof Fittings*, 947 F.2d at 1214-17, 1229.

129. EPA did not regulate asbestos under TSCA Section 6 following the burdens imposed by the *Corrosion Proof Fittings* decision. *See, e.g.*, Robert V. Percival, *Who's Afraid of the Precautionary Principle?*, 23 PACE ENVTL. L. REV. 21, 71–75 (2006) (discussing implications of the decision).

2. The Lautenberg Act

EPA found it difficult to regulate toxics under the 1991 *Corrosion Proof Fittings* interpretation of TSCA, but public concern about chemical hazards did not disappear.[130] Politicians, regulators, companies, and advocacy groups all had to account for this public concern, as well as for the public chemical regulatory programs that continued to develop at the international and subnational levels. We discuss the interplay of public and private toxics initiatives in more detail below, but for now it is enough to note that some mix of these or other factors enabled Congress in 2016 to overcome legislative gridlock by passing the Frank R. Lautenberg Chemical Safety Act for the 21st Century (the "Lautenberg Act").[131] The Lautenberg Act addresses the first criticism of TSCA by providing EPA with authority to issue test rules in situations in which it lacks the information necessary to make a finding about risk or widespread exposure. It addresses the second criticism by changing the "least burdensome" standard for risk regulation, requiring the EPA only to take steps "to the extent necessary" to prevent "unreasonable risk" from chemical substances.

Courts have yet to interpret these provisions, but they appear to create a health-based standard: reasonableness is based on the magnitude of the health risk, and the Agency's response must be designed to result in a reasonable risk.[132] Although these provisions appear to require EPA to set standards based on health considerations without accounting for costs, the Lautenberg Act also requires EPA to use "reasonably available information" to consider costs and benefits when promulgating a Section 6(a) rule.[133] In short, the Act appears to direct EPA to assess reasonableness of risk based on a health-based standard without accounting for costs, but when promulgating a rule to regulate those risks, EPA must nevertheless consider costs. The Lautenberg Act also appears to limit EPA's information burden to the information that is "reasonably available" and to preserve judicial review of

130. Comprehensive survey data on public concern about toxics during the 1990–2016 period are not available, but levels of environmental concern and support for environmental regulations have rarely fallen below 50% of the U.S. population. *See, e.g.*, David P. Daniels et al., *Public Opinion on Environmental Policy in the United States*, *in* THE OXFORD HANDBOOK OF U.S. ENVIRONMENTAL POLICY 461 (Michael E. Kraft & Sheldon Kamieniecki eds., 2012).

131. *See supra* note 33 and related discussion.

132. Frank R. Lautenberg Chemical Safety for the 21st Century Act, Pub. L. No. 114-82, 130 Stat. 448, § 6(a)(2016).

133. *Id.* § 6(c)(2)(A). *See also id.* § 6(c)(2)(B) (requiring EPA to "factor in" cost benefit analysis in its standard-setting decisions "in accordance with subsection (a) . . . to the extent practicable").

EPA's cost-benefit analysis using a "substantial evidence" standard of review.[134]

Other provisions that are important in light of the new understanding of epigenetics include a requirement for EPA to evaluate 20 chemicals each year.[135] The Lautenberg Act also adopts a complex approach to preemption of state restrictions on use of toxic chemicals and requirements to develop new information. The Act preserves common law rights and state information disclosure laws, such as California's Prop 65, and it does not address private toxic chemical standards.[136] The Act does, however, preempt state laws that restrict chemicals that are regulated or under review by EPA.[137] In addition, the Act requires the Administrator to consider effects on vulnerable sub-populations.[138]

Although the Lautenberg Act is the first major statutory amendment to a federal pollution control statute since 1990,[139] it is not yet clear whether it represents an improvement. The Environmental Defense Fund and the principal chemical industry trade association have argued that it addresses several of the core problems with TSCA.[140] At the same time, several scholars and environmental and health organizations have argued that the amendments do not address a number of the statute's principal weaknesses.[141]

3. Implementation of the Lautenberg Act

The implementation of the Lautenberg Act over the next several years will provide an opportunity to test whether the public toxics regulatory regime can adapt to the new understanding of epigenetics. The new language requires the EPA to begin updating the regulation of toxics, but it remains to be seen whether the EPA will use the most current scientific information and can respond to new threats that, in some cases, may not materialize for decades. For instance, does the EPA's expanded authority to order chemical testing under the amended TSCA Section 4 give it adequate authority to assess the low-dose, latency and intergenerational concerns

134. *Id.* § 19(c)(1)(B)(i)(I).
135. *Id.* § 6(b)(2)(B).
136. *See id.* § 18.
137. *Id.* §§ 6(b)(4)(D), 18(c)(2), 18(c)(3), 18(d)(1)(A)(iii).
138. *Id.* § 6(b)(4)(A), (c)(1).
139. *See* Vandenbergh, *Emergence*, *supra* note 32.
140. *See* discussion *infra* Part III.B.4.
141. *See, e.g.*, letter from 34 law professors, public interest lawyers, and legal scholars opposing the amendments because they "preserve some of the most problematic features of the Toxic Substances Control Act." Letter from John S. Applegate, Professor of Law, Ind. Univ. Maurer School of Law, et al., to Barbara Boxer, Chairman, Comm. on Env't & Pub. Works, and David Vitter, Ranking Member (July 31, 2013).

arising from epigenetics? Do the expanded provisions in the amended TSCA Section 5 and regulatory provisions in the amended TSCA Section 6 provide the necessary authority to address these concerns for new chemicals? In addition to uncertainty about statutory authority, conceptual barriers, budgetary and staffing constraints, and general resistance to regulation all may undermine EPA's ability to account for epigenetics in the implementation of the amended TSCA.[142] As to epigenetics, it remains uncertain whether the EPA and the courts will interpret TSCA, as updated by the Lautenberg Act, to authorize or require EPA to assess chemicals for epigenetic effects and to regulate when epigenetic harms are detected.[143] Furthermore, Congress may block regulations that the Lautenberg Act requires the EPA to promulgate.

If we assume that EPA managers will have the resources, capacity, and desire to respond to epigenetics, we can identify several initial steps that the EPA could take. The first is to ensure that toxicological assessments address the effects of environmental exposures on future generations for chemicals that may have epigenetic effects, even if they do not cause genetic mutations.[144] Similarly, assessments could account for the effects of chemical exposure in utero, given research suggesting that individuals may be most susceptible to epigenetic effects during this period.[145] At this point, it is unclear whether the toxicology practices and guidelines that steer assessment of toxics by EPA, the Agency for Toxic Substances and Disease Registry, and other agencies will be updated to require the assessment of epigenetic effects and provide instructions on how to conduct those assess-

142. *See* Frank R. Lautenberg Chemical Safety for the 21st Century Act, § 6(b)(4)(A) (stating that unreasonable risks include unreasonable risks to a "susceptible population identified as relevant to the risk evaluation"); *see also* Pat Rizzuto, *Chemical Rules Could Be Foiled by Regulatory Oversight Bill*, ENV'T REP. (BNA) (Jan. 24, 2017), https://www.bna.com/chemical-rules-foiled-n73014450209/.

143. Rothstein posed a related question prior to the adoption of the Lautenberg Act. *See* Rothstein, *Epigenetic*, *supra* note 12, at 735. Ultimately, regulators must determine when regulatory action is warranted based on the scientific data. *Id.* at 736 n.21 (citing GENOMICS AND ENVIRONMENTAL REGULATION: SCIENCE, ETHICS, AND LAW (R. R. Sharp et al. eds., 2008)).

144. An important issue that is beyond the scope of this Article is the extent to which epigenetic mechanisms of action can be included to update current standard test protocols for multi-generation reproduction studies or developmental toxicity studies, which extend across generations and include in utero exposures and exposures to newborns. Although they do not explicitly account for epigenetics, it is possible that the current test protocols nevertheless detect adverse effects caused by such mechanisms of action. Further research will be necessary to determine the extent to which gaps in existing protocols justify the allocation of the resources necessary to develop, validate and gain acceptance of new study protocols that explicitly account for epigenetics.

145. *See* Kaiser, *supra* note 29; *see also* Skinner, *New Kind*, *supra* note 16.

ments.[146] In addition, at some point it may be possible to identify categories of chemicals that are more likely to present epigenetic concerns, but in our view there is insufficient information to make these estimates at this point.

Several examples demonstrate the importance of a thoughtful response if the federal regulatory regime is to reflect the new understanding of epigenetics. Studies in mice and rats show that epigenetic alterations in a single generation of adults can persist, reappear, or change in unanticipated ways in subsequent generations. One study that exposed adult rats to vinclozolin, an endocrine disruptor,[147] produced epigenetic effects and associated behavioral changes in females of the third generation.[148] Similarly, stress exposure in adult female mice had epigenetic and behavioral consequences for both offspring and grand-offspring.[149] In this case, the effects on gene expression differed between individuals of the first and second generations. That exposure to chemicals and other environmental stressors can have sex-specific[150] as well as multigenerational effects indicates the need to evaluate and consider both sex-specific and multigenerational evidence of epigenetic harms.

Similarly, studies in mice show that the female brain can be epigenetically modulated at multiple stages of development.[151] One study demonstrated that epigenetic changes can be chemically induced during gestation: BPA exposure to pregnant mice modulated the epigenetic profiles of offspring and reduced maternal behavior when these offspring later gave birth.[152] After birth, and even in adulthood, chemical and environmental

146. *See* Vandenberg, *Hormones*, *supra* note 23, at 378–80, 398, 405–6, 426. Many federal environmental statutes require assessments for human health risks that may have epigenetic effects. *See* Rothstein, *The Ghost*, *supra* note 12, at 24–25.

147. *See* U.S. Envtl. Prot. Agency, Final Report: Endocrine Disruptors and Testis Development (2002), https://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.highlight/abstract/992/report/F; *see also* Memorandum from David G. Anderson to S. Lewis & J. Stone (May 17, 1993) (on file in EPA Archives); L. Earl Gray, Jr. et al., *Developmental Effects of an Environmental Antiandrogen: The Fungicide Vinclozolin Alters Sex Differentiation of the Male Rat*, 129 Toxicology & Applied Pharmacology 46, 46-52 (1994).

148. *See* Michael K. Skinner et al., *Transgenerational Epigenetic Programming of the Brain Transcriptome and Anxiety Behavior*, 3 PLOS One, Nov. 2008, at 1.

149. *See* Hiba Zaidan & Inna Gaisler-Salomon, *Prereproductive Stress in Adolescent Female Rats Affects Behavior and Corticosterone Levels in Second-Generation Offspring*, 58 Psychoneuroendocrinology 120 (2015).

150. *See* Linda Sterrenburg et al., *Chronic Stress Induces Sex-Specific Alterations in Methylation and Expression of Corticotropin-Releasing Factor Gene in the Rat*, 6 PLOS One, Nov. 2011, at 1.

151. *See* Samantha M. Keller & Tania L. Roth, *Environmental Influences on the Female Epigenome and Behavior*, 2 Envtl. Epigenetics, June 2016, at 1.

152. *See* Marija Kundakovic et al., *Sex-Specific Epigenetic Disruption and Behavioral Changes Following Low-Dose in Utero Bisphenol A Exposure*, 110 Proc. Nat'l Acad. Sci. 9956 (2013).

stressors can still change the epigenome in ways that affect behavior.[153] That epigenetic alterations can occur in the womb as well as throughout the lifetime suggests the importance of testing chemicals at multiple stages of development to ensure the safety of exposed individuals at every stage of the life cycle.[154]

As Professor Jamie Grodsky noted in 2005, standard genetic variations can make some individuals more susceptible than others to harm from certain environmental exposures.[155] Thus, she suggested that genetic knowledge could be used to identify the individuals and groups most sensitive to environmental harms due to genetic susceptibility — rather than due to high rates of exposure — and to design responses that protect these groups.[156] As she noted, this presents challenges for determining whether genetic susceptibility justifies the same regulatory response as disproportionate pollutant exposure and whether the threshold concept of unsafe exposure remains relevant given that a continuum of susceptibilities exists.[157] Epigenetics presents a new challenge, signaling the existence of new types of sensitive subpopulations. The Lautenberg Act explicitly requires the EPA to consider sensitive subpopulations,[158] and if epigenetic information indicates differential susceptibilities, this information could enhance the ability to protect individuals and populations particularly at risk. Similarly, as the science progresses, patterns of epigenetic marks or changes could provide biomarkers of exposure or effect.[159]

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153. Paolo L. Palanza et al., *Exposure to a Low Dose of Bisphenol A During Fetal Life or in Adulthood Alters Maternal Behavior in Mice*, 110 ENVTL. HEALTH PERSP. 415, 419-20 (2002); Tania L. Roth et al., *Lasting Epigenetic Influence of Early-Life Adversity on the BDNF Gene*, 65 BIOLOGICAL PSYCHIATRY 760 (2009).

154. *See* Leonardo Trasande et al., *Peer-Reviewed and Unbiased Research, Rather than 'Sound Science', Should be Used to Evaluate Endocrine-Disrupting Chemicals*, 70 J. EPIDEMIOLOGY COMMUNITY HEALTH 1051, 1054 (2016).

155. *See* Grodsky, *Genetics*, *supra* note 13.

156. *See id*. at 196-98.

157. *Id.* at 198-201. An important related issue is the extent to which current risk assessment methods may be inadequate with respect to epigenetic effects. Standard risk assessments for non-cancer endpoints typically include a safety factor of ten to account for human variability, and some agencies also use an additional child safety protection factor of three in some instances. An important question for regulators and ultimately for courts is whether there is a sufficient scientific basis to conclude that that the current methodologies are under-protective with respect to epigenetic effects.

158. *See* Frank R. Lautenberg Chemical Safety for the 21st Century Act, Pub. L. No. 114-82, 130 Stat. 448, § 6(b)(4)(A)(2016) (stating that unreasonable risk includes unreasonable risk to a "susceptible population identified as relevant to the risk evaluation"); *see also* Rothstein, *The Ghost*, *supra* note 12, at 49–50.

159. Rothstein, *The Ghost*, *supra* note 12, at 13, 23, 26, 27, 30–31.

Epigenetics also raises questions about the legal standards for regulatory action and regulatory priorities under TSCA.[160] For instance, toxic chemicals known to create multigenerational epigenetic effects may require more stringent constraints, as these chemicals could prove harmful to a large number of individuals over the long term if effects persist in multiple generations. Conversely, chemicals known to cause epigenetic changes that can be reversed by subsequent pharmacological[161] or dietary[162] intervention may merit lower priority for regulation than those that create effects without known methods of reversal.

Importantly, epigenetics also will challenge the EPA to shift from an approach that focuses on avoiding "bads" to one that also focuses on promoting "goods"—in other words, to account for the fact that opportunities to develop new solutions may arise, such as new ways to treat or mitigate the risks of chemical exposures. This increases the need to understand the biological mechanisms of compounds that act as epigenetic modifiers to combat the negative consequences of the toxins. For instance, although there is still much to understand regarding how and to what extent diet may create epigenetic changes that modulate human health, preliminary results suggest that dietary supplementation of key nutrients that work through epigenetic mechanisms may come to play an important role in disease prevention and therapy.[163]

B. *Private Governance*

Recent developments at the federal level create uncertainty about the appetite of the federal government for environmental regulation. These developments increase the importance of understanding other approaches to reducing the risks posed by toxic chemicals. In this Part III.B, we explore the emerging role of private environmental governance in toxics regulation over the last decade and how the new public-private regulatory regime may respond to epigenetics.[164]

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160. *See* Vandenberg, *Hormones*, *supra* note 23, at 381, 404–6. *See also* Rothstein, *The Ghost*, *supra* note 12, at 32–34 (discussing the adequacy of legal standards).

161. Tania L. Roth et al., *Lasting Epigenetic Influence of Early-Life Adversity on the BDNF Gene*, 65 Biological Psychiatry 760 (2009).

162. Dolinoy et al., *supra* note 92.

163. Emily Ho et al., *Dietary Factors and Epigenetic Regulation for Prostate Cancer Prevention*, 505 Advances in Nutrition 497, 505 (2011).

164. *See* Vandenbergh, *Private Environmental Governance*, *supra* note 36, at 129, 136, 191 n.260; Sarah E. Light & Michael P. Vandenbergh, *Private Environmental Governance*, *in* Decision Making in Environmental Law, Elgar Encyclopedia of Environmental Law 253 (Lee Paddock et al. eds., 2016). Private governance has been called "non-state market driven governance," *see* Benjamin Cashore, *Legitimacy and the Privatization of Environmental Governance: How Non-State Market-Driven (NSMD) Governance Systems Gain Rule-Making Authority*, 15

1. The Emergence of Private Environmental Governance

For those of us who have taught and practiced environmental law over the last several decades, it is easy to assume that private governance is a sideshow and that public environmental law is the only meaningful source of standards for toxic chemicals and the only major driver of corporate environmental behavior regarding those chemicals. Yet over the past two decades, private initiatives have emerged to complement, fill gaps in, compete with, and encourage public environmental regulation. Private actors such as corporations, advocacy groups, nongovernmental organizations, socially responsible investors, lenders, and others have played important roles in monitoring and enforcing environmental standards, including standards that apply to toxic chemicals. Private sustainability standards now apply to 10 percent of all fish caught for human consumption and 15 percent of all temperate forests around the world.[165] In the United States, private initiatives by major electricity buyers such as Google and Facebook are pushing utilities to provide renewable power even in the absence of state or federal requirements to do so.[166]

Private environmental governance initiatives are particularly influential in toxics regulation, and private actors may play a new and important role in enabling the public-private toxics regulatory regime to account for epigenetics. As we mentioned at the outset, an industry trade association official has described private retailers as the de facto regulators of chemicals in the United States. Large-scale, collaborative standard-setting processes by major retailers working with advocacy groups and suppliers have received the most attention, but private governance regarding toxics occurs in many other ways as well. We begin by providing a brief overview of private governance efforts in the U.S. that are directed at toxics. We then explore the role of private initiatives in chemical assessments, standard-setting and enforcement, and examine how private initiatives may affect the ability of

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GOVERNANCE: INT'L J. POL'Y ADMIN. & INSTITUTIONS 503 (2002); "private authority," JESSICA F. GREEN, RETHINKING PRIVATE AUTHORITY: AGENTS AND ENTREPRENEURS IN GLOBAL ENVIRONMENTAL GOVERNANCE (2013); "transnational private governance," Kenneth W. Abbott, *Strengthening the Transnational Regime Complex for Climate Change*, 3 TRANSNAT'L ENVTL. L. 57 (2014); and "private politics," David P. Baron, *Private Politics, Corporate Social Responsibility, and Integrated Strategy*, 10 J. ECON. & MGMT. STRATEGY 7 (2001). The key from our perspective is that private sector action can occur even in the absence of government action. The absence of the requirement for government action is the principal distinction between private governance and collaborative or hybrid governance. *See* Jody Freeman, *The Private Role in Public Governance*, 75 N.Y.U. L. REV. 543, 543-44 (2000).

165. Vandenbergh, *Private Environmental Governance*, *supra* note 36, at 158-60.

166. *See id.* at 136; *see also* Michael P. Vandenbergh & Jonathan M. Gilligan, *Beyond Gridlock*, 40 COLUM. J. ENVTL. L. 217, 218 (2015) [hereinafter Vandenbergh & Gilligan, *Beyond Gridlock*].

the public toxics regime to evolve in the face of the new understanding of epigenetics.

2. Private Toxics Standards and Enforcement

Private governance regarding toxic chemicals occurs when corporations and other private organizations respond to pressure from advocacy groups, consumers, investors, and others much as we might expect government to respond—by compiling lists of toxic chemicals, assessing safety, setting standards, and regulating the use of the chemicals.[167] Since soon after the 1976 enactment of TSCA, chemical manufacturers and processors have played an important role in chemical testing, often in response to or anticipation of EPA requests. Over the last decade, though, an important new form of private activity has become more common: downstream companies that use or sell products have responded to a range of external pressures and internal motivations by becoming private regulators.

The new downstream private toxics initiatives take many forms, but a recent example is the Policy on Sustainable Chemistry in Consumables, which Walmart developed in cooperation with the Environmental Defense Fund and other non-profit groups.[168] Walmart adopted the policy in 2013 to reduce toxics in household and personal care products, and Walmart claims to have achieved a 95 percent reduction, by weight, in the use of high-priority chemicals in the products it buys from its suppliers.[169] Similarly, in 2013 Target launched a "Sustainable Product Standard," which was developed in cooperation with advocacy groups and suppliers.[170] It uses this new private standard to evaluate and score products based in part on the chemicals associated with the products, which in turn motivates suppliers to re-

167. Vandenbergh, *Private Environmental Governance*, *supra* note 36, at 136–38, 147, 156–62.

168. *Policy on Sustainable Chemistry in Consumables*, Walmart, http://az204679.vo.msecnd.net/media/documents/wmt-chemical-policy_130234693942816792.pdf (last visited Feb. 8, 2017). For a discussion of the role of the Environmental Defense Fund, *see Getting Toxics out of Household Products: EDF and Walmart Work Together to Make Retailer's Products Safer*, Envtl. Def. Fund, https://www.edf.org/health/chemicals/getting-toxics-out-what-we-buy (last visited Sept. 16, 2017); Kevin J. Dooley & Jon Johnson, *Product Category-Level Sustainability Measurement: The Sustainability Consortium's Approach to Materiality and Indicators*, 19 J. Indus. Ecology 337 (2015). For an overview of the Sustainability Consortium, *see Our Story*, The Sustainability Consortium, https://www.sustainabilityconsortium.org/about/ (last visited Sept. 19, 2017).

169. *Supporting Transparency and Quality in the Products We Sell*, Walmart, http://corporate.walmart.com/2016grr/enhancing-sustainability/promoting-product-transparency-and-quality (last visited Sept. 16, 2017).

170. Target, *Introducing the Target Sustainable Product Standard*, A Bullseye View (Oct. 7, 2013), https://corporate.target.com/article/2013/10/introducing-the-target-sustainable-product-standar.

duce toxic chemical use.[171] Target initially applied the standard to its suppliers of 7,500 products in three categories (household cleaners, personal care and beauty, and baby care) with plans to extend the initiative to other categories.[172] To collect information from suppliers and make the information transparent to customers, it also developed a customized web-based platform with GoodGuide, a product disclosure firm that is now part of Underwriters Laboratories.[173] Within the retail sector, the prospects are good that private toxics initiatives will extend to other companies in addition to Walmart and Target. For instance, even as the federal government has shifted focus away from public regulation, advocacy groups have begun to increase the pressure on other large retailers, such as Costco.[174]

Private toxics initiatives are not limited to major retailers. For example, private toxics standards have existed for several years in the electronics sector. Advocacy groups have targeted the use of toxics in the electronics industry for years, and trade associations have developed private governance initiatives such as the Electronic Industry Code of Conduct.[175] A 2007 study found that seven of the ten largest firms in the personal computers sector impose environmental requirements on their suppliers.[176] Companies such as Hewlett Packard and Intel have played leading roles in developing toxics requirements for suppliers and have included these requirements in supplier policies and contracts.[177] In the automotive sector, major firms such as Ford and General Motors impose supply chain environmental requirements on their suppliers, including toxics provisions.[178] Many other sectors,

171. *See Target Sustainable Product Index*, TARGET, https://corporate.target.com/_media/TargetCorp/csr/pdf/TARGET-SUSTAINABLE-PRODUCT-INDEX.pdf (last visited Sept. 16, 2017).

172. Target, *Introducing the Target Sustainable Product Standard*, *supra* note 170.

173. *See About GoodGuide*, GOODGUIDE, http://www.goodguide.com/about (last visited Sept. 16, 2017).

174. Gabriel Dunsmith, *Toxics: Advocates Press Costco to Develop Chemicals Policy*, E&E NEWS (Jan. 27, 2017), https://www.eenews.net/eenewspm/stories/1060049137.

175. *See* Vandenbergh, *New Wal-Mart Effect*, *supra* note 42, at 933.

176. *See id.* at 932-33.

177. *See, e.g.*, *Supply Chain Environmental Impact*, HEWLETT-PACKARD, http://www8.hp.com/us/en/hp-information/global-citizenship/environment/supplychainenviromgt.html (last visited Sept. 16, 2017) (describing supply chain standard with toxics requirements). The profusion of standards has led to the creation of a document by several electronics industry organizations that lists regulated chemicals. *See* Electronic Industries Alliance et al., JOINT INDUSTRY GUIDE (JIG): MATERIAL COMPOSITION DECLARATION FOR ELECTROTECHNICAL PRODUCTS (JIG-101 Ed 4.0) (2010). For a discussion, *see New Environmental Guide Offers Electronics Industry Better Data on Regulated Materials*, JEDEC, https://www.jedec.org/news/pressreleases/new-environmental-guide-offers-electronics-industry-better-data-regulated-materia (last visited Sept. 16, 2017).

178. *See, e.g.*, FORD, *Building Shared Commitment and Capability*, SUSTAINABILITY REPORT 2013/14, https://corporate.ford.com/microsites/sustainability-report-2013-14/supply-creating

such as building design and construction, also have regulated the toxic chemicals in the materials delivered by suppliers.[179]

The private toxics standards established by the retailing, electronics, and other industries often become criteria that firms use for selecting suppliers, and in some cases the standards are also included in supply chain contracts. These supply chain contracting standards then influence the vast network of suppliers around the globe.[180] Due to the global nature of commodity chains, supply chain regulations result in a private toxics regulatory regime that affects the behavior of companies operating in countries with lax environmental standards or enforcement, reducing the harmful chemicals in products used around the world even in the absence of an international toxics agreement.[181] For instance, even if Walmart and Target do not explicitly require suppliers to eliminate harmful chemicals from their products in the near-term, these retailers' disclosure requirements and stated preferences for toxics-free products put suppliers on notice that products that include or are made with certain toxics are disfavored. This creates powerful incentives for manufacturers to reduce the use of harmful chemicals and to search for safer alternatives.

In addition to supply chain efforts, other private initiatives also are playing important roles in chemical regulation for consumer products. The

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-commitment.html (last visited Feb. 8, 2017) (discussing automotive supply chain requirements). For early overviews, *see, e.g.*, P.N. Grabosky, *Green Markets: Environmental Regulation by the Private Sector*, 16 L. & POL'Y 419, 429–32 (1994) (discussing requirements in automotive supply chains); Richard N.L. Andrews et al., *Environmental Management Systems: History, Theory, and Implementation Research*, *in* REGULATING FROM THE INSIDE 31, 32 (Cary Coglianese & Jennifer Nash eds., 2001) (discussing automotive requirements for environmental management systems).

179. *See* Vandenbergh, *New Wal-Mart Effect*, *supra* note 42, at 916-17. The United States Green Building Council, a private organization, has developed the widely-used Leadership in Energy and Environmental Design standard, which addresses the sustainability of building materials along with other factors. *See Better Buildings Are Our Legacy*, U.S. GREEN BLDG. COUNCIL, http://www.usgbc.org/leed (last visited Sept. 16, 2017). In addition, three private standards and certification systems, Health Product Declaration Collaborative, Cradle-to-Cradle, and Greenguard, address the toxic chemicals in the materials used in construction, along with other environmental concerns. *See* HEALTH PRODUCT DECLARATION COLLABORATIVE, https://www.hpd-collaborative.org/ (last visited Sept. 16, 2017); CRADLE TO CRADLE, http://www.c2ccertified.org/ (last visited Sept. 16, 2017); GREENGUARD CERTIFICATION, http://greenguard.org/en/CertificationPrograms.aspx (last visited Sept. 16, 2017); *see also* Diana Budds, *Google's Plan to Make Our Buildings Less Poisonous*, CO. DESIGN, Feb. 6, 2017, https://www.fastcodesign.com/3066686/googles-plan-to-make-our-buildings-less-poisonous.

180. *See supra* note 177 and discussion.

181. This may close loopholes regarding reporting of chemicals imported into the US as components of finished articles. *See* U.S. ENVTL. PROT. AGENCY, TSCA CHEMICAL DATA REPORTING FACT SHEET: IMPORTED ARTICLES (2016), www.epa.gov/sites/production/files/2015-12/documents/cdr_fact_sheet_imported_ articles_-_final_dec2015.pdf.

availability of information about the content and provenance of goods is a constraint on private environmental governance, but companies such as GoodGuide have used the proliferation of new technologies to address some of these constraints.[182] GoodGuide, which independently analyzes and rates products according to health and environmental safety measures, facilitates consumer and advocacy group pressure on companies and creates incentives for companies to reveal and modify the ingredients used in their products.[183] By increasing access to product safety information, GoodGuide creates incentives not only for ingredient disclosure, but also for reduced use of toxic chemicals in the retail sector. In a move that will affect the building sector, Google recently collaborated with the Healthy Building Network, an advocacy group, to develop Portico, an analogous tool that enables architects and construction managers to identify the chemicals in building materials.[184] Similarly, private certification companies such as NSF International set standards for chemical safety, certify compliance, and allow certified products to display a label demonstrating this compliance to consumers.[185] Companies such as GoodGuide, Portico, and NSF International are in a position to incorporate the evolving scientific literature on epigenetics into their existing chemical evaluation and certification systems.

3. Private Chemical Assessments

Several existing private environmental governance initiatives could account for epigenetic effects in product safety standards, but chemical assessment remains a barrier to implementation. Thus far, the major retailers that have adopted standards for toxics have drawn primarily on government information to assess and determine which chemicals should be considered harmful. They do not independently conduct assessments or determine criteria of harm on their own, but this is not surprising: funding of basic

182. GoodGuide was acquired in 2011 by UL Environment, which is a business unit of UL (Underwriters Laboratories) and has the purpose of providing information, tools, expertise, and resources to help companies manage the sustainability of their global supply chains. *See About GoodGuide*, GoodGuide, http://www.goodguide.com/about (last visited Sept. 19, 2017). *See also UL Environment Acquires GoodGuide*, UL (Aug. 2, 2012), http://www.ul.com/newsroom/pressreleases/ul-environment-acquires-goodguide/ (clarifying that GoodGuide now operates as an independent subsidiary of UL).

183. *Methodology*, GoodGuide, http://www.goodguide.com/about/methodologies (last visited Sept. 19, 2017).

184. *See Introducing Portico, the Healthy Materials Tool*, Google, https://support.google.com/healthymaterials/answer/6080283?hl=EN&ref_topic=7165276 (last visited Sept. 19, 2017).

185. *What is NSF Certification?*, NSF, http://www.nsf.org/consumer-resources/what-is-nsf-certification (last visited Sept. 19, 2017). Note that NSF International is a private organization not affiliated with the National Science Foundation, a government agency.

research faces classic public goods problems and is often a role assigned to government, and toxicological assessments of chemicals suffer from the same problems.

For instance, Walmart has required its suppliers to disclose the chemicals used to formulate their products and has expressed the goal of reducing use of the chemicals on the retailer's list of "priority chemicals for reduction, restriction, and elimination."[186] This list does not draw from private chemical assessments, but rather relies on various inventories already established by intergovernmental organizations, national governments, and state governments, such as the EPA persistent bioaccumulative toxic (PBT) list, California Proposition 65, and other state lists of priority chemicals.[187] Likewise, Target's Sustainable Product Index, which evaluates and "scores" chemicals, addresses substances considered harmful not by private regulators but by government agencies such as the EPA and the European Chemicals Agency.[188] Thus, under the current approach to private toxics assessment, if the state, national, and intergovernmental inventories from which private regulators create their own lists of harmful chemicals do not assess substances for epigenetic effects, these effects may not be accounted for in private regulatory schemes.

There is an opportunity, however, for private regulators to act more quickly than governments in response to new toxics information. Private organizations could take the lead in supplementing government assessments with independent private assessments that incorporate the most recent scientific information on epigenetics into their determination of chemical toxicity.[189] Although private actors may be reluctant or unable to establish toxicology programs that parallel government programs, they may be in a better position to address specific gaps arising from new scientific understandings. For instance, they may be in a better position to conduct timely, independent assessments of the literature regarding new information about a subset of chemicals, such as chemicals that may have epigenetic effects, and thus may be able to develop new lists of priority chemicals. Such lists could then be incorporated into corporations' private standards for suppli-

186. *Sustainable Chemistry Policy*, WALMART, http://www.walmartsustainabilityhub.com/sustainable-chemistry/sustainable-chemistry-policy (last visited Sept. 19, 2017).

187. *Appendix 1: Walmart Reference List of Priority Chemicals*, WALMART, http://www.walmartsustainabilityhub.com/sustainable-chemistry/appendices (last visited Sept. 19, 2017).

188. *See Target Sustainable Product Index*, *supra* note 171, at n.1.

189. An example of the large private role in environmental assessments is the fact that corporations spend more money each year on private environmental investigations associated with Superfund liability than is spent on EPA enforcement. *See* Vandenbergh, *Private Environmental Governance*, *supra* note 36, at 135–36, 159.

ers, supplementing the lists of substances considered harmful by government agencies. The resulting combination of public and private toxics assessments could provide a more timely and more complete inventory of harmful chemicals, thereby enhancing the ability of private actors to create and enforce effective chemical safety standards for substances with epigenetic effects.

In addition, even if private initiatives are unable to fill gaps in the chemical assessments available to public and private regulators, these initiatives can change what is done in the absence of the data necessary to resolve significant uncertainties and demonstrate safety. For instance, they can increase the pressure on agencies and industry to act in the face of emerging concerns where data gaps exist. They also can increase the pressure on industry to lobby Congress to provide the EPA with the resources and statutory authority necessary to perform adequate chemical assessments. In turn, these assessments should provide a stronger scientific basis for public and private regulatory actions.

In sum, private initiatives may play a gap-filling role in the near term because they may have sufficient flexibility and opportunities to conduct new assessments or assemble existing assessments and to create and enforce standards based on epigenetic effects. Although it may be unrealistic to assume that private actors will fund or conduct major chemical assessments, private initiatives nevertheless may be more able to act based on incomplete information and thus may be better situated in the near term to reflect the implications of epigenetics. They also may be less subject to political and ideological capture and other forms of pressure that can delay or prevent the updating of the public regulatory response in the face of new scientific information.[190]

4. Effects of Private Governance on Public Governance

Private governance initiatives can not only serve as a complementary regulatory regime that fills gaps in the public toxics regime, but also can increase—or decrease—the likelihood that the public regime will be able to adapt to new scientific conceptual frameworks such as the new understanding of epigenetics. For instance, although private toxics initiatives may re-

190. The emergence of private governance regarding toxics (e.g., the divergence between the FDA and corporate responses to BPA in cans discussed in *supra* note 111) raises important questions about whether the public or private regulatory regimes are more accountable to the public. For overviews of the accountability of the regulatory state, *see* Edward Rubin, *The Myth of Accountability and the Anti-Administrative Impulse*, 103 MICH. L. REV. 2073, 2073-2074 (2005); Lisa Schultz Bressman, *Beyond Accountability: Arbitrariness and Legitimacy in the Administrative State*, 78 N.Y.U. L. REV. 461 (2003).

duce the public's appetite for new toxics legislation or regulations, they also may play a proof-of-concept role, which in turn may facilitate the adoption of public legislative and regulatory programs.[191] In the long term, private efforts to include epigenetic knowledge in assessments and to restrict the use of chemicals with epigenetic effects also may drive re-evaluation of chemicals by public regulatory agencies.

The recent history of the public toxics regime demonstrates how the development of private governance can create momentum for the adoption and implementation of statutory reforms. The challenges of an uneven corporate playing field and public concern about toxics were not sufficient to induce Congress to amend TSCA in the three decades after its enactment in 1976, but by 2016 the motivations of policymakers, industry, and advocacy groups had shifted sufficiently to enable the legislative gridlock to be broken.[192] Numerous factors may have contributed to this shift, but the timing of the 2016 Lautenberg Act suggests that private toxics initiatives played an important role.[193] The international (e.g., REACH) and subnational (e.g., California Prop 65, Massachusetts Toxic Use Reduction Act) toxics regulatory programs created an uneven playing field for industry, but this uneven playing field existed for many years prior to 2016 without inducing industry to support TSCA legislative reforms.[194] In the last decade, however, these public toxics regimes were joined by influential new private governance initiatives, including the Walmart and Target initiatives discussed above.[195] These private initiatives not only affected domestic markets for toxics, but also regulated the toxics in large quantities of goods in global supply

191. *See* Vandenbergh & Gilligan, *Beyond Gridlock*, *supra* note 166, at 224-25, 270 (noting that EDF and other non-profits have worked with private corporations to reduce carbon emissions even in the absence of government regulations). Of course, private governance systems also suffer from the lack of traditional public accountability that arises with governance systems through standard democratic processes. *See, e.g.*, Terry Macdonald & Kate Macdonald, *Non-Electoral Accountability in Global Politics: Strengthening Democratic Control within the Global Garment Industry*, 17 EUR. J. INT'L L. 89, 90 (2006). For an assessment of private accountability measures, *see* Vandenbergh, *New Wal-Mart Effect*, *supra* note 42, at 963–67. The accountability of the public-private toxics regulatory regime is beyond the scope of this Article.

192. *Supra* notes 132-40 and related discussion.

193. Frank R. Lautenberg Chemical Safety for the 21st Century Act, Pub. L. No. 114-82, 130 Stat. 448 (2016).

194. *See, e.g.*, Steffen Foss Hansen et al., *Chemicals Regulation and Precaution: Does REACH Really Incorporate the Precautionary Principle*, 10 ENVTL. SCI. & POL'Y 395, (2007); Christine Russell, *California is Getting Tough on Toxics*, WASH. POST, May 23, 1989, https://www.washingtonpost.com/archive/lifestyle/wellness/1989/05/23/california-is-getting-tough-on-toxics/11343574-c570-4644-99b2-525959586b13/?utm_term=.C4233078e07e.

195. *Supra* notes 182-90 and related discussion.

chains.[196] For instance, Walmart has over $315 billion in annual sales worldwide and 60,000 suppliers.[197] As a result, even if chemical manufacturers were comfortable with the inaction by Congress in the first three decades after 1976, in the last decade they found themselves increasingly subject not only to international and subnational toxics requirements, but also to new private standards from their customers.[198] In short, although it is not possible to establish why Congress adopted the Lautenberg Act while rejecting other major amendments to pollution control statutes, there is good reason to believe that the growth of private toxics initiatives over the last decade created new motivations by industry to support TSCA legislative reforms.

Comments made by leading advocacy group and industry officials reinforce the conclusion that private initiatives helped motivate industry to come to the table, facilitating the adoption of the Lautenberg Act. Diane Regas, a top manager of the Environmental Defense Fund, a leading advocacy group, stated in 2016 that "[c]itizen activism, retailers drove change" and that "[t]his reform is part of a process that began with citizen activism and greater consumer awareness. . . For many years, consumer product companies and major retailers have been responding to these rising consumer demands by removing hazardous ingredients and calling for safer alternatives."[199] Although advocacy groups can be expected to claim that private initiatives, which they often have sponsored or managed, create motivations for new legislation, more revealing are industry comments on the topic. An example is the comment of American Chemistry Council official Sarah Brozena at a public forum in Washington, D.C., just weeks after the Lautenberg Act was enacted:

> "[as] even retailers, big retailers, started demanding that their suppliers look at the chemicals in products they were selling and ask whether those in fact should be deselected . . . so [there were] pressures from around the world, from retailers, from states, and our board of directors looked at this whole question of our position on TSCA, given all of these activities at a voluntary level and

196. *Supra* notes 177-90 and related discussion; *see* Vandenbergh, *New Wal-Mart Effect*, *supra* note 42, at 916-17.

197. Vandenbergh, *New Wal-Mart Effect*, *supra* note 42, at 927.

198. *See* Pat Rizzuto, *EPA Lacks Capacity for Chemical Risk Assessments*, DAILY ENV'T REP. (BNA) (Feb. 24, 2017) (noting that "[i]ndustry objections to a more than 10-year trend of increased state chemical laws and regulations coupled with retail purchasing policies that became defacto chemical-regulations were critical drivers leading to last year's overhaul of the Toxic Substances Control Act").

199. Diane Regas, *We Just Got the Biggest Environmental Law in a Generation*, EDF VOICES: PEOPLE ON THE PLANET (June 22, 2016), https://www.edf.org/blog/2016/06/22/we-just-got-biggest-environmental-law-generation.

> global level and state level and retailer level, and asked, 'Do we need to change our position on the status quo relative to TSCA?' And in 2008 . . . the board of directors adopted a change which said we support modernizing this old law."[200]

The private toxics regime thus not only can fill regulatory gaps, but also can shift the motivations of some interest groups that might otherwise favor legislative inaction.

Private initiatives also may affect the implementation of the TSCA legislative reforms over the next several years. Even if skepticism about environmental regulation affects EPA implementation of the Lautenberg Act reforms, the forces that induced Congress to amend TSCA in 2016 have not disappeared. States and foreign countries will continue to regulate, creating a complex and uneven regulatory playing field for industry, particularly for firms that operate in many regions around the world.[201] In addition, widespread concerns in the general public about toxic chemicals will continue to hover in the background, creating diffuse pressure on corporate managers, investors, lenders, and policymakers. These diffuse concerns may be reflected in private toxics initiatives even if they are not reflected in the views of federal legislators or agency managers. As a former manager of the EPA toxics program observed in 2017, if the EPA does not create confidence in its ability to regulate toxics, retailers are likely to continue their "chemical deselection policies."[202]

IV. Beyond the Public-Private Toxics Regulatory Regime

The emergence of epigenetics has important implications not only for toxic chemical regulation, but also for efforts to facilitate rational risk regulation across many fields and to address specific topics ranging from the safety of foods and drugs, to hunger and the food supply, to child abuse and other forms of trauma during life.[203] Over the long term, we suggest a joint

200. Envtl. Law Inst., *The Story of TSCA Reform*, YouTube 58:52 (July 15, 2016), https://www.youtube.com/watch?v=0riZtGD-Q4Q (comments of American Chemistry Council official Sarah Brozena).

201. *See* Rizzuto, *EPA Lacks Capacity*, *supra* note 198 (noting that former EPA toxics program manager Mark Greenwood stated at an American Bar Association meeting that "states will step up their chemical regulatory activity if the EPA proves unable to act").

202. *Id.* (noting that according to former EPA assistant administrator Jim Jones, "[r]etailers also are likely to continue their chemical deselection policies if confidence in the federal agency's authority isn't established").

203. As we noted at the outset, we use the term "rational risk regulation" in a broad sense. *See* Michael P. Vandenbergh & Jonathan A. Gilligan, *Macro-Risks: The Challenge for Rational Risk Regulation*, 21 Duke Envtl. L. & Pol'y F. 401 (2011). For differing perspectives on rational risk regulation, *compare* Sunstein, *supra* note 5, *and* Stephen Breyer, Breaking the

science and policy research effort to study the evolution of governance institutions in the face of new scientific conceptual frameworks. The parallel development of epigenetics and private environmental governance can serve as an important case study. For now, we focus principally on two issues that are important to the public-private toxics regulatory regime: the analytical tools designed to improve the regulatory process (the precautionary principle, risk-risk analysis, and cost-benefit analysis) and toxic torts.

A. *Analytical Tools for Rational Risk Regulation*

The implications of epigenetics, such as the latent effects within one generation, intergenerational effects, and ability to create and ameliorate harms, raise important questions for several of the core analytical tools that have been used to assess regulatory threats and government responses to them.

The Precautionary Principle and Risk-Risk Analysis. For decades, scholars have debated the merits of the precautionary principle—the idea that the burden of demonstrating safety should be on those seeking to distribute chemicals, not on agencies to show that they are unsafe. Should the precautionary principle be a fundamental principle of environmental law, or is it flawed because it does not account for the risks of the chemicals that will substitute for a chemical that is awaiting government approval? The precautionary approach has strong supporters in Europe and the US, but it has been criticized for failing to account for the economic and human costs of requiring proof of safety before a product can be marketed.[204]

Advocates of risk-risk analysis emphasize the importance of evaluating the risks of the alternatives that will be on the market if a chemical is banned or not approved.[205] In many ways, the precautionary principle reflects an intuitive risk-risk analysis, one that concludes that the risks of new products are likely to be greater than those of the existing products that they would displace, and that agencies need precautionary authority given their limited resources and the large number of new chemicals being produced every year. Critics of the precautionary principle start with the intui-

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VICIOUS CIRCLE: TOWARD EFFECTIVE RISK REGULATION 21–29 (1993), *with* FRANK ACKERMAN & LISA HEINZERLING, PRICELESS: ON KNOWING THE PRICE OF EVERYTHING AND THE VALUE OF NOTHING (2008).

204. *Compare* Christian Gollier et al., *Scientific Progress and Irreversibility: An Economic Interpretation of the 'Precautionary Principle'*, 75 J. PUB. ECON. 229, 229 (2000) (identifying "the class of quite restrictive but plausible conditions such that scientific uncertainties justify an immediate reduction of the consumption of a potentially toxic substance") *with* SUNSTEIN, *supra* note 5, at 129 (identifying shortcomings in the precautionary principle).

205. *See* RISK VS. RISK: TRADEOFFS IN PROTECTING HEALTH AND THE ENVIRONMENT, *supra* note 5.

tion that there is no *ex ante* difference in the risks of new versus existing products, or, even if the risks of some new products are greater, that the delay and regulatory costs of precaution are likely to outweigh the benefits.[206] This Article is not the place to resolve these differences, but it provides an opportunity to examine the implications of epigenetics for the precautionary principle and risk-risk analysis.

In our view, the new understanding of epigenetics does not change the core analysis of the advantages and disadvantages of the precautionary principle, but it points out the importance and the difficulty of analyzing alternatives. For instance, epigenetics may exacerbate the informational burdens on agencies. The epigenetics findings suggest that some chemical exposures in utero will not manifest themselves for decades, or will only do so in later generations, and in some cases, will only do so in later generations of males or females.[207] Detecting these effects at the level of certainty necessary to support regulatory action can be difficult, and failure to use a precautionary approach might allow toxics on the market that will cause harmful effects that will not be apparent for generations. Likewise, given that the timing of exposure to substances with epigenetic effects often is relevant to the likelihood or degree of harm, it may be necessary to expand test periods for evaluation of toxicity to include all sensitive periods. The inability of the EPA to overcome the informational burdens of the extensive analysis required by *Corrosion Proof Fittings* is a reminder of the need to strike a balance between the value of assessing alternatives and the transaction costs and delay associated with the assessment process.

Similarly, the ability of chemicals, drugs, foods and experiences to have epigenetic effects that are positive and negative—with some potentially causing diseases and others inhibiting or treating them—complicates the analysis. The existence of positive effects demonstrates the value of risk-risk analysis, which might lead regulators to examine the full range of implications of a chemical under review along with its substitutes. Epigenetics provides insights into the possibility for dietary or other interventions that may mitigate or reverse the harmful effects of epigenetic changes (i.e., taking folic acid might counteract the epigenetic changes induced by BPA), which may enable the regulatory regime to promote interventions that mitigate the harmful effects of some toxic chemicals.[208] Since chemicals with epigenetic effects can have positive as well as negative outcomes, it will be important for the analysis to account for both. Environmental law tends to focus

206. *See id.*

207. Rothstein, *The Ghost*, *supra* note 12, at 14.

208. *Id.* at 28–29; Gerda Egger et al., *Epigenetics in Human Disease and Prospects for Epigenetic Therapy*, 429 NATURE 457, 460 (2004).

on preventing or compensating for harms, but the new understanding of epigenetics suggests the importance of enabling the regulatory system to provide not only a shield against health risks, but a sword to achieve health benefits as well.

Furthermore, the emergence of the public-private toxics regulatory regime suggests that the relationship between precaution and risk-risk analysis now should be evaluated in light of the interactions among the private and public actors that are involved in regulating toxics. Do the private actors in the toxics regulatory regime serve a more precautionary function than the public actors? Is that a preferable role, or will that lead to over- or under-regulation by the public-private regime as a whole? Does the expense of risk assessment make it unlikely that private actors will be able to take a more precautionary role? These questions suggest the importance of accounting for private action when examining precaution and risk-risk analysis.

Cost-Benefit Analysis. Epigenetics also complicates cost-benefit analysis.[209] The Lautenberg Act created a statutory obligation for EPA to account for costs and benefits in its chemical regulatory decisions.[210] The role of cost-benefit analysis in the Trump Administration is not yet clear, but it is clear that cost will be a focus of the regulatory review process.[211] As discussed above, a promising aspect of epigenetics is that it can reveal new ways to prevent and treat diseases, but if only the costs of regulation can be considered, these benefits will not be accounted for in regulatory analysis. If a regulation is needed for a chemical to get to market, and if the regulation imposes some costs, will the new federal regulatory review process block the regulatory action because only the costs and not the benefits could be considered? That seems unlikely, but the response to new chemicals with epigenetic effects may test this issue.

Another challenge to cost-benefit analysis presented by epigenetics arises from the hotly contested area of discounting. Experts differ sharply on how discounting should be applied to harms that will not occur for a generation or more. Events that occur thirty, forty, or eighty years in the future are valued at almost nothing when standard annual discount rates are used to assess future costs and benefits. In theory, the interests of future generations are accounted for in discount rates, yet intergenerational dis-

209. For general information about the complexities of cost-benefit analysis *see* Matthew D. Adler & Eric A. Posner, *Rethinking Cost-Benefit Analysis*, 109 YALE L.J. 165, 175 (1999).

210. *See* Frank R. Lautenberg Chemical Safety for the 21st Century Act, Pub. L. No. 114-82, 130 Stat. 448, §6(c)(2)(A)(2016).

211. *See* Reducing Regulation and Controlling Regulatory Cost, 82 Fed. Reg. 9339 (Feb. 30, 2017).

counting presents several problems.[212] The cost to an individual exposed to a chemical in utero who knows throughout her life that she has a high risk of developing a disease late in life and that she may pass the trait along to her offspring may be difficult to quantify. In addition, intergenerational governance problems may arise, since the harms to her children and grandchildren will be given little weight at the time the chemical is considered for approval, and those individuals will not be able to participate in the regulatory process when the decision is made to approve the chemical.

B. *Toxic Tort Law*

In addition to complicating the analytical tools used in the public aspects of the toxics regulatory regime, the new understanding of epigenetics has important implications for common law toxic tort litigation. As professor Grodsky noted about standard genetics before the concept of epigenetics gained wide exposure, emerging methods and understandings in genomic science have important implications for toxic tort law.[213] Grodsky predicted that the developments in these areas would continue to put pressure on litigants and judges in tort actions, and she pointed to the diminishing distinction between "risk" and "injury" as an example.[214] Epigenetics may accelerate these challenges by increasing the ability to detect and characterize intermediate mechanisms and subclinical effects that occur between toxic exposure and disease.[215] For instance, if I have been exposed to a chemical that has methylated key genes that epigenetics research suggests will not affect me for several decades, but will cause a serious disease late in life, have I been harmed today? If I will not suffer the effects but they may affect half of my children and a quarter of my grandchildren, have I been harmed? When must I sue? Can my grandchildren sue? How can the damages be calculated?

Similarly, epigenetic information could provide evidence that specific environmental exposures are responsible for specific cases of disease, since unique molecular signatures in some cases can be detected on the genome to indicate toxic exposure in an affected individual.[216] Will courts rely on or

212. Even strong CBA supporters such as Judge Richard Posner have noted the problems that arise when standard discount rates are applied to intergenerational problems. Richard A. Posner, Catastrophe: Risk and Response 246 (2004); Richard L. Revesz & Matthew R. Shahabian, *Climate Change and Future Generations*, 84 S. Cal. L. Rev. 1097 (2011).

213. Grodsky, *Genomics*, *supra* note 13.

214. *Id.*

215. *Id.* at 1673-74.

216. *Id.* at 1703, 1707, 1708-09. For instance, recent data suggest strong correlations between methylation patterns at specific loci and chronological age. *See* Steve Horvath, *DNA Methylation Age of Human Tissues and Cell Types*, 14 Genome Biol. R115 (2013), 16 Genome

even require this evidence as proof of causation in such cases? The specific answers will take years to develop, but it is clear that the emerging importance of epigenetics will continue to put pressure on the ability of the toxic tort system to adapt, and the response of the common law system is likely to affect the public-private toxics regulatory regime as well.

C. *Other Fields*

Epigenetics also has implications for laws, policies, and programs regarding the regulation of pesticides, drugs, workplace chemical exposure, workplace discrimination, malnutrition, child abuse, human rights, and other areas.[217] We now know that dietary and other forms of stress may affect not only an individual today, but also that individual later in life, and future generations as well. As a result, researchers and policymakers will need to ask new questions if they want to understand the effects of events such as malnutrition and child abuse as to individuals and the population as a whole. Laws, policies, and programs in these areas all may need to be reshaped and the priority given to them may need to be reevaluated in light of the fact that epigenetic-related harms may become apparent later in life and may extend to future generations.

Conclusion

A central understanding of biology for generations has been that biological characteristics could only be passed on to subsequent generations through mutations in the building blocks of DNA in the germline. Yet a growing body of scientific evidence demonstrates that chemical alteration of a gene's expression may have ramifications not only for the individual exposed to a chemical, but for future generations as well. Subtle chemical changes to DNA occur in response to both the physical environment (e.g., chemicals and even some foods) and the behavioral environment (e.g., traumatic experiences). The modified DNA results in altered patterns of gene expression, which can prevent proper biological function. This interaction between DNA and the environment, known as epigenetics, has revolutionized the understanding of expression of genes within an individual. Even more strikingly, the science of epigenetics has demonstrated that these modifications affect offspring, in some cases for multiple generations. We now know that an individual who is exposed to chemicals today may pass along effects to children and grandchildren even though no mutation has

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Biology 96 (2015)(erratum); Gregory Hannum et al., *Genome-wide Methylation Profiles Reveal Quantitative Views of Human Aging Rates*, 49 Molecular Cell 359 (2013).

217. For instance, endocrine disruptor pesticides may have epigenetic effects and new assays may be needed to evaluate these effects. Rothstein, *The Ghost*, *supra* note 12, at 25.

occurred. These effects result in altered physiology and behavior, and can lead to an increased risk for disease. The new understanding of epigenetics also suggests that some foods and chemicals may be able to treat or reduce the risk of disease. The new understanding of epigenetics also has broader implications across a wide spectrum of laws, policies, and programs regarding problems such as malnutrition and child abuse. The public and private responses to these problems may need to be reassessed in light of the risk that harms may not appear in the individual for decades and may affect not only the immediate victim but offspring as well.

The emerging understanding of epigenetics is sufficiently persuasive that it is time not only for further scientific research, but also for the legal system to account for the new understanding about inheritance of acquired traits. Scholars over the last several decades have identified numerous factors that have generated the remarkably complex, slow-moving public regulatory regime for toxics, and adapting to epigenetics will be difficult. The emergence of epigenetics has occurred in parallel with the emergence of private environmental governance, though, and this new form of environmental governance provides room for optimism. Toxics regulation now includes not only governments at the international, national, and subnational levels, but also private actors, including advocacy groups, corporations, private standards organizations, and others, with the result that the institution responding to toxics is now a public-private toxics regulatory regime.

Just as epigenetics requires a conceptual shift among scientists who must now recognize and study epigenetic phenomena, lawyers and policymakers should now recognize, study, and shape the new public-private toxics regulatory regime. Simply examining the statutes, regulations, guidance, and budgets of regulatory agencies, or the decisions of courts will miss important toxics initiatives by private actors. The new public-private toxics regulatory regime, however, may be surprisingly adaptable in the face of epigenetics and other new scientific developments. The interplay of public and private institutional responses to toxics may be able to keep pace with the new science of epigenetics even if the federal government does not lead the way.