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Preserving Human Potential as Freedom: A Framework for Regulating Epigenetic Harms

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PRESERVING HUMAN POTENTIAL AS FREEDOM: A FRAMEWORK FOR REGULATING EPIGENETIC HARMS

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ABSTRACT

Epigenetics is a rapidly evolving scientific field of inquiry examining how a wide range of environmental, social, and nutritional exposures can dramatically control how genes are expressed without changing the underlying DNA. Research has demonstrated that epigenetics plays a large role in human development and in disease causation. In a sense, epigenetics blurs the distinction between "nature" and "nurture" as experiences (nurture) become a part of intrinsic biology (nature). Remarkably, some epigenetic modifications are durable across generations, meaning that exposures from our grandparents' generation might affect our health now, even if we have not experienced the same exposures. In the same vein, current exposures could affect the health of not only individuals currently living but also future generations. Given the relative novelty of epigenetics research and the multifactorial nature of human development and disease causation, it is unlikely that conclusive proof can be established showing that particular exposures lead to epigenetic risks that manifest into specific conditions. Using the Capabilities Approach ("CA") developed by Amartya Sen and Martha Nussbaum, this article

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argues that epigenetic risk is not merely a medical issue, but that it more generally implicates the underlying fairness and justice of our social contract. For instance, how we develop mentally or physically has a tremendous impact upon our inherent capabilities and our set of life options. The CA prompts us to ask questions such as: (1) what impact do particular epigenetic risks have on our ability to exercise free choices; (2) are these risks avoidable; and (3) how are these risks distributed across society? Due to the complex nature of epigenetic risk, tort law is predictably incapable of addressing this harm. Further, while regulatory agencies possess the statutory authority to begin addressing epigenetic harms, currently these agencies are not attuned to measure or to respond to this type of harm. This article argues that it is imperative to initiate a regulatory framework to address epigenetic risk from specific substances even if conclusive proof of disease causation cannot be established. Shifting the burden of generating epigenetic risk data to producers of suspected harmful substances serves as a start. As information concerning epigenetic risks accrues, the regulatory response should evolve concurrently. As part of a dynamic policy-making approach our goals need to encompass the following: (i) promotion of knowledge in the scientific, legal, and public domains; (ii) assessment and modification of current regulations to address preventable risk; and (iii) an overarching commitment to protect human capabilities in an equitable manner.

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INTRODUCTION

Do our ancestors' experiences from several generations ago play a role in our current health? Could a famine or a period of food abundance experienced by our grandfathers influence whether some of us are currently obese or likely to develop diabetes? Can being the grandchildren of those who suffered through the threat of genocide or intense racial discrimination affect levels of certain chemicals in our brains even if we are not exposed to the same social stresses? In other words, are we biologically fettered to the "memories" of past generations independent of changes to our ancestors' DNA – that is, our human genome?

Surprisingly, according to rapidly growing research in the area of epigenetics, the answer to all of the questions above is converging on

yes.[1] Therefore, an individual's diet, environmental exposures, and social interactions could influence the health and behavior of that individual's offspring. The implications of epigenetics are far-ranging and can alter the way we think about policies as widely divergent as product safety, environmental regulation, and even affirmative action. In a profound way, epigenetics challenges the notion that genetics predominantly determine a person's fate and will make many of us reconsider what we think we know about human capabilities and predispositions.[2]

As explained below, although epigenetics may predict baffling hereditary effects, the science behind epigenetics is not incomprehensible. Ultimately the greater challenge to policymakers will be to decide whether regulations designed to avoid such harms *should even be attempted*? In the face of any potential health risks, harms may arise from inaction as well as from regulatory inaction.[3]

Given that our understanding of the science behind epigenetics is still relatively new, the conservative approach might be to advocate a "hands-off" regulatory attitude until scientific data conclusively demonstrates disease causation through this process. However, in the face of initial compelling evidence that the repercussions of serious

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[1] *See* Matthew W. Gillman, *Developmental Origins of Health and Disease*, 353 NEW ENG. J. MED. 1848, 1848 (2005) ("At first glance, it may seem implausible that your mother's exposure to stress or toxins while she was pregnant with you, how she fed you when you were an infant, or how fast you grew during childhood can determine your risk for chronic disease as an adult. Mounting evidence, however, indicates that events occurring in the earliest stages of human development – even before birth – may influence the occurrence of diabetes, cardiovascular disease, asthma, cancers, osteoporosis, and neuropsychiatric disorders.").

[2] For instance, see RICHARD J. HERRNSTEIN & CHARLES MURRAY, THE BELL CURVE: INTELLIGENCE AND CLASS STRUCTURE IN AMERICAN LIFE (1994), which argues that intelligence is predetermined by genetics and in turn is the major cause of socioeconomic success. Accordingly, Herrnstein and Murray conclude that disparities in socioeconomic measures such as income, crime rates, and academic success between classes and races are genetic in origin rather than environmental. Under such logic, social welfare policies such as affirmative action are exercises in futility because poverty in genetic endowment are to blame for group disparities, not structural inequities or discrimination.

[3] For example, mandating that everyone over the age of thirty has a full-body scan might be seen as a protective health policy that would increase the early detection of cancer. However, in addition to the direct cost of such a mandate, such a rule might generate many false positives and needlessly expose many people to invasive tests and procedures that carry serious health risks. Doctors call tumors discovered in the absence of clinical symptoms or suspicion "incidentalomas." *See* Claudia D. Furtado et al., *Whole-Body CT Screening: Spectrum of Findings and Recommendations in 1192 Patients*, 237 RADIOLOGY 385, 392 (2005) (estimating that thirty-seven percent of people who receive a full body CT scan may have abnormal findings that need further work up).

harm to human health could span several generations, we cannot afford to take a laissez-faire approach. Further complicating our calculus is the likelihood, supported by recent research, that some epigenetic modifications may be *reversible*.[4] So how do we proceed in the face of uncertain, but grave, harms that may or may not be reversible?[5]

Currently, the two dominant paradigms for shaping governmental response to public safety threats are cost-benefit analysis and the precautionary principle.[6] Cost-benefit analysis requires that the quantified benefits of a proposed regulation exceed or "justify" the quantified costs.[7] However, if the risk of a threat is uncertain and therefore unquantifiable, cost-benefit analysis provides little guidance, except perhaps to do nothing in the absence of quantifiable justification. In contrast, the precautionary principle holds that when an activity raises threats to human health, precautionary steps should be taken even if cause and effect has not been fully established. These two paradigms are often pitted against one another and perceived in cultural and political terms.[8] Cost-benefit analysis is often seen as more libertarian

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[4] *See* Moshe Szyf et al., *The Social Environment and the Epigenome*, 49 ENVTL. & MOLECULAR MUTAGENESIS 46, 46 (2008) ("Epigenetic programming of gene expression is stable and long-term but yet reversible and responsive.").

[5] We have to keep in mind that while some epigenetic marks may be reversible, their effects may be irreversible depending on when they occur during an individual's life-cycle. For instance, if a certain epigenetic mark affects early childhood physical or mental development, reversing that epigenetic mark later in adult life will not undo the developmental changes that have already occurred. In contrast, if a certain epigenetic mark conveys an increased risk of late-onset disease, reversing that mark in early adulthood could dramatically alter that individual's disease risk. *See, e.g.*, Geneviève P. Delcuve et al., *Epigenetic Control*, 214 J. CELLULAR PHYSIOLOGY 243, 243-50 (2009).

[6] *See, e.g.*, United Nations Conference on Environment and Development, Rio de Janeiro, Braz., June 3-14, 1992, *Rio Declaration on Environment and Development*, ¶15, U.N. Doc A/CONF.151/26 (Aug. 12, 1992) (stating the best known formulation of the "Precautionary Principle": "In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.").

[7] *See* John D. Graham, *Saving Lives Through Administrative Law and Economics*, 157 U. PA. L. REV. 395, 432-34 (2008) (describing "hard" and "soft" cost-benefit analysis).

[8] Cass Sunstein has recognized that:

> It has become standard to say that, with respect to risks, Europe and the United States can be distinguished along a single axis: Europe accepts the Precautionary Principle, and the United States does not. On this view, Europeans attempt to build a "margin of safety" into public decisions, taking care to protect citizens against risks that cannot be established with certain-

and as representing an "American way" of thinking about risk, while the precautionary principle is cast as more paternalistic and "European."[9] Of course, these are general characterizations of the decision-making models, and they are not mutually exclusive, as many models in actual use combine elements of both cost-benefit analysis and the precautionary approach.[10]

Regarding the causation of human diseases from substance exposures in particular, our knowledge of epigenetics is likely to be very fluid over the next several decades. Further, in speaking with researchers in the field and reviewing the scientific literature, it is evident that the medical and scientific community generally believes that epigenetic theory is valid and that research in this area will likely shed much light on disease causation.[11] However, the status quo of current legal rules and regulatory policies do not seem to provide adequate protection to the public from epigenetic harms. The tort system in theory can regulate harmful substances in the stream of commerce by imposing liability on products that cause too much harm. However, for a variety of reasons explained below, tort law appears incapable of limiting epigenetic risk. In addition, while the Food and Drug Administration and Environmental Protection Agency possess adequate statutory authority, their historical and current regulatory postures are not attuned to regulating epigenetic harms.

> ty. By contrast, Americans are reluctant to take precautions, requiring clear evidence of harm in order to justify regulation. These claims seem plausible in light of the fact that the United States appears comparatively unconcerned about the risks associated with global warming and the genetic modification of food; in those contexts, Europeans favor precautions, whereas Americans seem to require something akin to proof of danger.

Cass R. Sunstein, *Precautions Against What? The Availability Heuristic and Cross-Cultural Risk Perception*, 57 ALA. L. REV. 75, 76 (2005).

[9] *See id.*

[10] *See generally* Graham, *supra* note 7, at 432-34 (discussing a cost-benefit approach); Holly Doremus, *Precaution, Science, and Learning While Doing in Natural Resource Management*, 82 WASH. L. REV. 547, 550 (2007). The hybridization of both cost-benefit analysis and the precautionary approach is especially prevalent in the area of climate change and environmental regulations where the costs of regulation are typically more defined than the putative benefits, not allowing for a strict balancing of costs and benefits. Doremus, *supra*, at 551.

[11] For this proposition, the author acknowledges the expert opinions of Dr. Mark Farmer, Chair of Cell Biology Department at the University of Georgia (UGA), Dr. Richard Meagher, Professor of Genetics at UGA, and Dr. John McDonald, Professor of Genetics at the Georgia Institute of Technology. Further, a search of the National Institutes of Health's PubMed database using the keywords "epigenetics" and "cancer" during the last five years returns nearly seven thousand hits. *See* Nat'l Inst. of Health, PubMed, http://www.ncbi.nlm.nih.gov/pubmed (last visited May 3, 2010).

This article proposes a dynamic regulatory framework allowing for decisive actions against epigenetic threats without conclusive proof of harm, but requiring continual adaptation as new learning becomes available. My initial claim is that available evidence regarding epigenetic pathways of disease is sufficient to justify significant government funding of basic scientific research in this area. However, implementing societal protections from epigenetic harms cannot wait until research provides "conclusive" findings. The rationale for such action comes from applying the Capabilities Approach ("CA") normative framework, as developed by Amartya Sen and Martha Nussbaum. Namely, it is government's responsibility to address preventable harms that potentially limit a person's innate capabilities and life options.[12] Therefore, I assert that for certain suspect classes of substances, regulation should shift the burden to producers to force acknowledgement of the epigenetic effects of their products and activities. Going forward, in response to new learning about general epigenetics and specific substances, an epigenetic regulatory agency can modulate the intensity of regulations accordingly.[13] The different levels of regulation include: (a) information disclosure, (b) labeling requirements, (c) epigenetic taxes, and (d) restricted uses and bans on certain substances.

Section I describes the science of epigenetics and how it profoundly changes the scientific community's previous understanding of heredity, environmental exposures, and disease causation. Section II discusses how the tort system is generally incapable of addressing epigenetic claims. Section III addresses how the American regulatory system for harmful exposures has the potential to address epigenetic harms but cannot perform this function effectively under its current

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[12] The "Capabilities Approach" (CA) developed by Amartya Sen and Martha Nussbaum, is a normative framework that focuses on what people are actually able to do and become from a holistic perspective, encompassing the material, political, and social. *See* Martha C. Nussbaum, *Forward: Constitutions and Capabilities: "Perception" Against Lofty Formalism*, 121 HARV. L. REV. 4, 25 (2007).

[13] As discussed below, initially this organization may just be a working group that coordinates between EPA (Environmental Protection Agency), FDA (Food and Drug Administration), and OfIRA (Office of Information and Regulatory Affairs) to implement epigenetic regulations, as opposed to an entirely new agency. Justice Stephen Breyer has famously proposed an agency comprised of interdisciplinary, neutral experts who would generate risk-assessments and policy recommendations insulated from public hysteria and special-interest groups. *See* Graham, *supra* note 7 (noting that the Institute of Medicine of the National Academy of Sciences, has used such an organizational framework to provide expert assistance for many controversial science and health issues such as Agent-Orange, breast implant, and vaccine injury litigation). However, the IOM works outside the framework of government and does not have the type of agency authority envisioned by Breyer or my proposal.

scheme of knowledge generation and its assessment of "unproven" risks. Section IV discusses the normative framework of the Capabilities Approach and how focusing on protecting human capabilities can provide guidance to regulatory agencies on what interventions should be taken with respect to epigenetic harm. Section V examines the challenge of regulating epigenetic risks in the face of uncertainty. Finally, Section VI outlines an adaptive regulatory framework to protect human capabilities that can modulate the intensity of regulations as we learn more about particular epigenetic harms.

I. SCIENCE OF EPIGENETICS: OUT WITH THE NEW, IN WITH THE OLD?

The hereditary theory of adaptation, as elucidated by Aristotle[14] and most famously by French biologist Jean-Baptiste Lamarck,[15] held that the physiological changes acquired over the life of an organism (such as a giraffe stretching its neck to reach the top of a tree or a watchmaker developing fine motor skills) are transmitted to that organism's offspring. The scientific community firmly rejected the concept of inheriting acquired characteristics after the acceptance of Charles Darwin's theory of evolution and Gregor Mendel's work on gene-based inheritance. The conclusive rejection was apparently provided by Watson and Crick's discovery of DNA, which provided physical evidence of gene-based inheritance.[16]

Classic genetic theory holds that one's DNA sequence contains genes that code for proteins which in turn determine a person's biological fate. Therefore, under this concept, a future generation's biological fate is determined largely by its ancestors' DNA sequences and not at all by their ancestors' experiences. The only exception, of course, is if an organism's exposure, to say radiation or a mutagenic chemical, changes the underlying DNA sequence, and that altered sequence then gets passed on to offspring.[17] However, as the Human

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[14] 1 ARISTOTLE, HISTORIA ANIMALIUM (A.L. Peck trans., Harvard Univ. Press 1965) (350 B.C.); ARISTOTLE, GENERATION OF ANIMALS (A. L. Peck trans., Harvard Univ. Press 1963).

[15] JEAN-BAPTISTE LAMARCK, PHILOSOPHIE ZOOLOGIQUE (1984); JEAN-BAPTISTE LAMARCK, HISTOIRE NATURELLES DES ANIMAUX SANS VERTEBRES (G.P. DeShayes & H. Milne Edwards eds., 2d ed. 1835).

[16] Four nucleotides, adenine, cytosine, guanine, and thymine (symbolized as "A, C, G, T") comprise the DNA (deoxyribonucleic acid) code. The specific order of these four nucleotides (e.g., A-A-T-G-C-A) code for different gene products which in turn produce different traits such as hair texture, body types, and inherited diseases.

[17] *See* WASH. STATE DEP'T OF HEALTH, GENETIC EFFECTS AND BIRTH DEFECTS FROM RADIATION EXPOSURE, http://www.doh.wa.gov/Hanford/publications/

Genome Project came to fruition, scientists realized that this massive effort of mapping out all of the human genes would provide less answers than they hoped. The total number of genes this project discovered was less than one-third of what geneticists expected given diversity of observable traits (phenotypes).[18] Mapping human DNA did not turn out to be a Rosetta Stone unlocking the mysteries of heredity and disease; it was evident that a tremendous amount of biological code existed outside of the human genome. Further, if it is supposed that DNA primarily accounts for the diversity among different biological species, then how can genetics explain that modern humans have ninety-nine percent of their genes in common with puffer fish and Tyrannosaurus rex?[19] Also, given that all of the cells in the human body contain the exact same DNA, where does "additional" information originate that instructs one cell to develop into brain tissue and another cell to become liver tissue?[20] Finally, perhaps the most gaping hole in classic genetic theory is that despite identical DNA sequences, how can "monozygotic twins or cloned animals [. . .] have different phenotypes and different susceptibilities to a disease?"[21] Gradually, scientists reconsidered the previously discarded notion that the biological code individuals inherit involves more than just reshuffled genes from our ancestors – thus the advent of epigenetics.

Epigenetics literally means "outside of genetics" and can be defined as "heritable changes in gene expression that are not due to any alteration in the DNA sequence."[22] In other words, epigenetic changes do not mutate or change the genetic code nor do they alter

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overview/genetic.html (last visited May 3, 2010).

[18] At the outset of the Human Genome Project, researchers expected to discover at least 100,000 genes in the human body. However, they found a fraction of this number – less than 30,000. Elizabeth Pennisi, *A Low Number Wins the Gene Sweep Pool*, 300 SCIENCE 1484, 1484 (2003).

[19] *See* Margaret G. Kidwell & Damon Lisch, *Transposable Elements as Sources of Variation in Animals and Plants*, 94 PROC. NAT'L ACAD. SCI. U.S. 7704, 7704 (1997) (explaining that differential epigenetic programming of extremely similar genomes seems to account for most of the physical differences among plants and animals).

[20] Differential epigenetic programming of the exact same DNA within an organism explains organ differentiation. In other words, the precursor of a brain cell has certain parts of its DNA turned on and other parts turned off so that eventually it may form a neuron. Likewise, a precursor of a fat cell would have different parts of its DNA activated ultimately to form a fat cell.

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

[22] *Id.*

gene products.[23] Dramatic variation in cell morphology (e.g., brain v. fat cell) and species (e.g., human v. T. rex) can be explained by highly variable gene expression in terms of quantity of protein products manufactured and the timing of such expression during physical development.[24]

Several different types of epigenetic markers have been identified.[25] The best known marker is DNA methylation, which involves the binding of a methyl group to the DNA base cytosine to form methyl-cytosine.[26] This modification has the effect of muting the expression of the surrounding DNA code. If enough cytosine bases are methylated in a key area of a gene called the promoter region, the gene can effectively be shut off. Epigenetic modifications can also occur at the chromosomal level. A chromosome is an organized structure of DNA and histone proteins – collectively, the DNA and these binding proteins are called chromatin. Binding of methyl or acetyl molecules to histone proteins can either "loosen up" a chromosome to form euchromatin, which will have active areas of DNA transcription, or such binding can make parts of the chromosome more tightly wound to form heterochromatin, which becomes inactive. Imagine a chromosome as a long magnetic tape of information that is tightly

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[23] Here is a quick primer on human gene expression: (1) double stranded DNA in the nucleus has to be separated; (2) transcription occurs when the separated DNA strand is converted into mRNA; (3) mRNA leaves the nucleus and goes to ribosomes in the cytoplasm; (4) ribosomes translate the mRNA into a series of amino acids; and (5) the string of amino acids folds into a protein. Thus, most genes contain information to make functional protein molecules (a few genes code for molecules that aid the cell in assembling proteins).

[24] *See* Wolf Reik, *Stability and Flexibility of Epigenetic Gene Regulation in Mammalian Development*, 447 NATURE 425 (2007) ("Development is, by definition, epigenetic. Differences in the programmes of gene expression that result in the development of different organs and tissues occur without changes to the sequence of our DNA (with one or two exceptions). There is nothing mysterious in this concept; subsets of the ~30,000 genes in our genome are active in different tissues and organs, depending on their regulation by different sets or combinations of transcription factors. This implies that if we were to take all of the transcription factors that activate genes in a liver cell and transfer them to a brain cell (while inactivating all brain-specific transcription factors), then the brain cell would turn into a liver cell.").

[25] *See id.* ("During the early stages of development, genes that are required later in development are transiently held in a repressed state by histone modifications, which are highly flexible and easily reversed when expression of these genes is needed. During differentiation, genes that are crucial for pluripotency are silenced by histone modifications, as well as by DNA methylation. Some of these genes are also silent in mature germ cells, meaning that epigenetic marks probably need to be reversed rapidly after fertilization to allow re-expression of pluripotency-associated genes in the next generation.").

[26] Methyl, CH3, is a small molecule. It forms methyl-cytosine after binding to cytosine nucleotide bases.

coiled around many tiny beads (histones). If the tape is tightly wound, it cannot be read or transcribed. However, if a loop of tape is unwound, the information can be accessed and transcribed. Several other epigenetic controls have been identified, and they all act in a similar fashion, subtly affecting or altogether blocking the transcription of DNA.[27]

The collection of these epigenetic chemical marks on the DNA and histone proteins forms what is called the epigenome. Some have analogized that our DNA is like computer hardware, and epigenetic marks act as software instructing the DNA how and when to operate. For example, if you merely possess a gene that codes for disease X, it is not certain that you will develop disease X, as an epigenetic marker on top of this deleterious gene can switch the gene off. Conversely, an epigenetic marker can switch off a helpful tumor-suppressing gene (i.e., a cancer-fighting gene) in an individual's body and thus increase that individual's susceptibility to cancer. In terms of persistence across generations, the genome has been characterized as "ink" and the epigenome as "pencil":

> The sequence of the four nucleotides of the genetic code is like an indelible ink that, with rare exceptions, is faithfully transcribed from cell to cell and from generation to generation. But on top of this code lies another one, literally "epigenetic," which is represented by methyl groups added to the DNA base cytosine, as well as covalent changes in histone proteins around which DNA is coiled. This epigenetic information is more like a code written in pencil in the margins around the DNA. Although the genome largely distinguishes one person from another, the epigenome, or epigenetic information, distinguishes one cell type from another, changing rapidly in early embryogenesis as cells differentiate. Mistakes that may arise during this process are thought to be erased in the same germ line . . . [however] this eraser may leave smudges, potentially allowing disease to be transmitted epigenetically as well as genetically.[28]

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[27] These other epigenetic controls include: (1) remodeling of other chromatin-associated proteins; (2) transposition or "jumping" of stretches of the DNA sequence itself; and (3) RNA interference, where RNA molecules produced from the DNA code bind back to the DNA.

[28] Roger G. Gosden & Andrew P. Feinburg, *Genetics and Epigenetics – Nature's Pen-and-Pencil Set*, 356 NEW ENG. J. MED. 731, 731 (2007).

Therefore, the mechanism of epigenetic traits being passed on to subsequent generations appears to be dependent upon epigenetic marks being incompletely "erased" or else being erased but then added again during critical periods of germ cell (i.e., sperm and ova) development:

> On rare occasions, however, epigenetic marks are carried over from a previous generation . . . [and] the inherited characteristic has evidently been caused by incompletely erased epigenetic marks . . . . Reprogramming occurs at different times in testes and ovaries, and there may be corresponding differences in the vulnerability of targets of epigenetic modifications . . . . The female germ cell may be more vulnerable to environmental damage because . . . [t]he chromatin of growing oocytes has a more open configuration than that of male germ cells.[29]

Is there a plausible evolutionary rationale for what appears to be a highly variable phenomenon? Given that an individual is most susceptible to epigenetic modifications during early stages of fetal and childhood development, one credible hypothesis is that this process allows an organism to "take a sample" of its environmental conditions while still developing and then to adjust the expression of its genetic code accordingly. Since DNA is highly conservative across many generations, epigenetic variability allows for more adaptability on a shorter time scale. Imagine if an embryo is genetically predisposed to be physically large, but the mother is suffering through a famine during fetal development. The DNA code cannot adjust to this reality, but the epigenome can – thus, the epigenome can alter gene expression to make the individual smaller and more capable of surviving in a low-resource environment. This response appears to be a useful adaptation for survival of a species. However, given that epigenetic marks can last for several generations, a rapid increase in the quantity and

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[29] *See id.* at 731-32 ("The epigenome is not permanent but undergoes dramatic changes at specific stages during development until it achieves more stability in differentiated cells. Since the epigenome affects gene activity, errors can lead to abortive development, birth defects, and cancer. A critical period for epigenetic modification extends from the time when migrating primordial germ cells arrive in the embryonic gonad until post-fertilization stages . . . . Most methylation marks are erased from imprinted genes in primordial germ cells of both sexes, but they are replaced at different stages of development in a sex-specific pattern. In men, the marks reappear in prospermatogonia, before the cells have reentered mitosis. By contrast, epigenetic changes in women are delayed until after meiosis has been initiated and the oocytes have started growing in follicles, which occurs mainly after birth.").

energy-profile (high fat and calorie) of the food supply, as we have seen in nearly all countries, can lead to a population with an epigenome maladapted to current conditions.[30]

The following section briefly covers animal and human findings that demonstrate the existence and effect of epigenetic marks. However, before discussing those studies, as a matter of scientific history, it is important to note a resurgence of Lamarckism that ended in ignominy. Trofim Lysenko (1898-1976) was a poorly trained agronomist who improbably became the Soviet's top biologist under Stalin.[31] Lysenko's "peasant-intuition" and rejection of orthodox genetics dove-tailed with Stalinist ideology that human nature and biology are not predetermined, but extremely malleable.[32] This notion supported the Stalinist theory that the state could fashion "new men" if it applied the right conditions.[33] With the staunch support of Stalin, Lysenko purged Soviet scientists (sometimes fatally) who advocated Mendelian views. Specifically, Lysenko claimed that treating seeds to cold temperatures ("vernalism") could improve seed and crop yields in cold climates for several generations of plantings.[34] However, his claims of increased agricultural production could not be replicated, and after many years of disastrous crop yields, Soviet scientists rejected Lysenko as a fraud during Kruschev's tenure.[35] Do recent studies mean that Lysenko, one of the great villains in science history, has now been vindicated by the acceptance of epigenetic inheritance? Not really. Modern epigenetics does not reject the existence of gene-based inheritance, but posits that there is another layer of acquired information that contributes to and modifies heredity. In essence, Lysenko's theory of acquired inheritance was far from complete.

A. Proof of Concept: Evidence of Epigenetic Mechanisms

A search within the online medical journal database PubMed using the search terms "genetics and cancer" would return 40,704 hits for the period of 1980-1990. In contrast, a search for "epigenetics and cancer" during this same time period would reveal forty-three hits.[36] Although epigenetics was a known factor in some diseases involving "parental imprinting," there was almost no understanding of epigenet-

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[30] *See* Christian Nordqvist, *Obesity Is a Global Epidemic*, MED. NEWS TODAY, Sept. 3, 2006, http://www.medicalnewstoday.com/articles/51123.php.

[31] *See* DAVID JORAVSKY, THE LYSENKO AFFAIR (1970).

[32] *See id.*

[33] *See id.*

[34] *See id.*

[35] *See id.*

[36] *See* Nat'l Inst. of Health, *supra* note 11.

ic markings capable of turning genes on and off in a general fashion. The generally accepted cancer causation model is that organisms possess different genetic predispositions and that certain triggers, such as viral or chemical exposures, activate these underlying susceptibilities. With a few rare exceptions, the notion that non-genetic factors could be inherited and could lead to disease causation was simply not on the research community's radar.[37] With the growth of new research discoveries, this prevailing belief has changed. A search on "epigenetics and cancer" on PubMed now would return over 6,300 hits for the past five years.[38] In other words, epigenetics is no longer a fringe area of research in the medical-scientific community.

The formulation of groundbreaking theoretical and empirical work in this area should be credited to Dr. Randy Jirtle, a cancer researcher at Duke University.[39] He developed an elegant research model demonstrating the operation of epigenetic mechanisms. He began with *agouti* mice, so named because they contain a mutation for the *agouti* gene.[40] Expression of this deleterious gene in agouti mice causes obesity, yellow fur, increased susceptibility to cancer and diabetes, and a dramatically shortened lifespan.[41] Because the *agouti* gene is dominant, breeding two of these mice together invariably results in offspring having the noticeable *agouti* physical characteristics of being sickly, yellow, and obese.[42] However, Jirtle was able to breed two *agouti* mice together whose offspring were healthy, thin, and mousy brown.[43] More importantly, these offspring did not possess their parents' propensity to develop cancer and diabetes or to have a decreased lifespan.[44] Jirtle successfully silenced the effect of the *agouti* gene.

Did Jirtle engage in genetic engineering and change the underlying DNA code? No. The offspring's DNA still contained the *agouti*

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[37] Courts have recognized that DES (diethylstilbestrol) ingestion by pregnant mothers led to vaginal adenocarcinoma and other deformities in female offspring. Because the ingestion occurred during pregnancy, the cases were explained as a case of fetal toxicity. However, in most cases, courts have barred third generation DES claims (granddaughters of women who ingested DES). It will be interesting to see if these claims are brought again under an epigenetic theory.

[38] *See* Nat'l Inst. of Health, *supra* note 11.

[39] Robert A. Waterland & Randy L. Jirtle, *Transposable Elements: Targets for Early Nutritional Effects of Epigenetic Gene Regulation*, 23 MOLECULAR & CELLULAR BIOLOGY 5293, 5293 (2003).

[40] *Id.*

[41] *Id.*

[42] *Id.*

[43] *Id.* at 5294-96.

[44] *Id.* at 5296.

gene of their parents with the harmful DNA sequence intact.[45] Jirtle's intervention was surprisingly much simpler than genetic engineering – he merely changed the mothers' diets.[46] Right before conception, the test group of maternal mice was fed a folate rich diet filled with methyl-donors[47] which are molecules that are common in foods such as onion, garlic, and beets. As the pregnant mothers followed this diet, the methyl-donor molecules passed into the developing embryos' DNA code and specifically onto the *agouti* gene.[48] The harmful gene was passed onto the offspring unchanged, except that the gene now contained a chemical dimmer switch that blocked its expression.[49] Incredibly, these beneficial epigenetic changes were passed on to subsequent generations of offspring, even in the absence of a folate rich diet.[50]

As expected, additional studies have demonstrated harmful epigenetic markings enduring multiple generations. For instance, another rodent study found that harmful epigenetic changes related to toxic fungicide or pesticide exposure can persist in rat offspring for at least four generations, even though subsequent generations were not exposed to these harmful chemicals.[51] In a series of infant rat studies examining cortisol release and coping responses, researchers demonstrated that epigenetic markings could change in response to parental care.[52] Rat pups who were licked by their mother displayed more assertive social behaviors and, when startled, were able to calm down more quickly than pups who were not so soothed by their mother.[53] The neglected pups, on the other hand, developed into passive adults who reacted nervously when startled or placed in unfamiliar settings.[54] These "licked rats" developed epigenetic markers that removed "dimmer switches" located on a gene that regulates cortisol release. In a sense, the licked rats had a better developed "stress thermostat," which translated into the rats being less anxious and more capable of

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[45] *Id.* at 5294.

[46] *Id.*

[47] *Id.*

[48] *Id.* at 5298.

[49] *Id.* at 5296-97.

[50] *Id.* at 5299-300.

[51] Matthew D. Anway & Michael K. Skinner, *Epigenetic Transgenerational Actions of Endocrine Disruptors*, 147 ENDOCRINOLOGY S43 (2006).

[52] Randy L. Jirtle & Michael K. Skinner, *Environmental Epigenomics and Disease Susceptibility*, 8 NATURE REV. GENETICS 253, 258 (2007); Craig A. Cooney, *Epigenetics – DNA-Based Mirror of Our Environment?*, 23 DISEASE MARKERS 121, 128 (2007).

[53] Cooney, *supra* note 52, at 127-28.

[54] *Id.*

coping in stressful situations.[55] The neglected rats did not develop this regulatory gene to the same extent, thus these rats suffered from an overproduction of cortisol in response to stress, thereby amplifying their anxiety.[56] These changes were stable throughout adulthood in the rats.[57] Thus, the mother's nurturing behavior did not simply affect her offspring's behavior; it physiologically altered the functioning of the stress regulation gene inside the brain.[58] But mice are not men – is the same mechanism seen in humans?

B. Evidence of Epigenetic Mechanisms in Human Studies

Although human studies showing cause and effect for diseases through epigenetic mechanisms are much more difficult to design and ethically perform (humans cannot be isolated from confounding exposures in labs over a lifetime or several generations like mice), epidemiological studies focused on epigenetics are uncovering intriguing findings. In 2005, European researchers presented a study examining two centuries of crop yields and food prices for a geographically isolated town in Northern Sweden.[59] The researchers discovered that fluctuations in the locality's food supply influenced health outcomes spanning at least two generations. Specifically, grandfathers who lived their pre-adolescent years during times of bountiful food supply were more likely to have grandsons with diabetes – *doubling* these grandsons' risk of early death. In other words, abundant availability of food was demonstrated to be bad for future generations. Further, grandsons of grandfathers who experienced plenitude during the prepubescent "slow-growth" period of sperm development were the most affected.[60] Therefore, the timing of when an exposure occurs relative to an ancestor's stage of development is crucially important for future generations' physical development.

Compelling evidence suggests that epigenetics plays a significant role in human mental development. Combining epigenetics with neuropsychology, Canadian researchers examined the brains of men who committed suicide after suffering physical, sexual, mental, or a combination of all three types of abuse as children.[61] The researchers

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[55] *See id.* at 127.

[56] *Id.*

[57] *Id.*

[58] *Id.*

[59] Marcus E. Pembrey et al., *Sex-Specific, Male-Line Transgenerational Responses in Human*, 14 EUR. J. HUM. GENETICS 159 (2006).

[60] *Id.*

[61] Patrick O. McGowan et al., *Epigenetic Regulation of the Glucocorticoid Receptor in Human Brain Associates with Childhood Abuse*, 12 NATURE

found that childhood abuse alters the typical chemical marking of DNA in the brain.[62] Compared with men who also suffered abuse but died of natural causes, the suicidal men possessed decreased functioning in the gene that regulates the release of the stress hormone cortisol.[63] These findings are analogous to the previously mentioned study of the neglected rat pups that were also not able to regulate their cortisol release effectively. The researchers speculated that the men's brains were hardwired to insufficiently cope with stress as adults, which thereby contributed to their suicides.[64] Based on growing research, scientists are concluding that childhood abuse instigates an epigenetic response that alters the molecular structure of the developing brain.[65]

Moreover, maternal exposures have been the focus of many recent epigenetic studies. For example, in the urban, low-income, minority communities of New York City, the asthma rate is twenty-five percent greater than the national average.[66] A recent study has found a potential epigenetic explanation for this anomaly.[67] Polycyclic aromatic hydrocarbons (PAHs) are released from the burning of fossil fuels and reach higher ambient concentrations in heavy-traffic, inner-city areas. This study found that prenatal exposure to PAHs is associated with a higher risk of childhood asthma.[68] As the researchers explained:

> Developmental plasticity allows the fetus to make anticipatory responses to the external environment . . . . However, a pronounced mismatch between "anticipatory adaptations" made during early life and demands in later life could be a cause of disease. More importantly, environmental insults could "mislead" early organogenesis resulting in serious ailments in later life . . . . This body of research suggests that transplacental exposure to high levels of airborne PAHs could

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NEUROSCIENCE 342 (2009).

[62] *Id.* at 345.

[63] *Id.* at 342.

[64] *Id.* at 345-46.

[65] *Id.* at 346.

[66] Frederica Perera et al., *Relation of DNA Methylation of 5'-CpG Island of ACSL3 to Transplacental Exposure to Airborne Polycyclic Aromatic Hydrocarbons and Childhood Asthma*, 4 PLOS ONE e4488, e4488 (2009).

[67] *Id.* ("Finally, the current finding of a putative epigenetic marker that is associated with PAH exposure and asthma adds to other evidence from the CCCEH cohort that PAHs increase risk of respiratory symptoms and probable asthma.").

[68] *Id.*

> cause aberrant DNA methylation changes, leading to dysregulation of gene expression and perhaps childhood asthma.[69]

A study examining maternal intake of fish (with low mercury content) found that increased intake is correlated with higher cognitive test scores for her children.[70] Another study found the higher the mother's calcium intake, the lower her child's blood pressure.[71] Paradoxically, although maternal smoking during pregnancy is associated with reduced fetal growth, it also associated with an increased risk of obesity for offspring.[72] While the associations found in these studies are not conclusive proof of cause and effect, their implications are very significant. As one researcher noted, "[i]f you have a generation of poor people who suffer from bad nutrition, it may take two or three generations for that population to recover from that hardship and reach its full potential."[73] Although it is outside the scope of this article, going forward it seems inevitable that governmental policies intended to reduce socio-economic gaps, such as Affirmative Action, will have to address the possibility that structural discrimination may cause multigenerational harms that persist long after visible signifiers of discrimination have been overcome (e.g., an African-American being elected president).[74]

II. TORT LAW'S INABILITY TO ADDRESS EPIGENETIC HARM

How should epigenetic risk be regulated in society? Some sources of epigenetic risk (violence, discrimination, etc.) are so diffuse and complex that these risks are obviously not amenable to regulation by the tort system. [75] However, if an epigenetic risk factor can

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[69] *Id.*

[70] Pennisi, *supra* note 18, at 1484.

[71] Matthew W. Gillman et al., *Maternal Calcium Intake and Offspring Blood Pressure*, 110 CIRCULATION 1990 (2004).

[72] A. M. Toschke et al., *Early Intrauterine Exposure to Tobacco-Inhaled Products and Obesity*, 158 AM. J. EPIDEMIOLOGY 1068, 1069-70 (2003).

[73] Ethan Watters, *DNA is Not Destiny*, DISCOVER, Nov. 11, 2006, at 32 (quoting Dr. Lawrence Harper of University of California at Davis).

[74] The debate regarding Affirmative Action has heated up again following the election of President Barack Obama. Some question whether this policy is needed after an African-American has been elected president. Joseph Williams & Matt Negrin, *Affirmative Action Foes Point to Obama: Say Candidate is Proof Effort No Longer Needed*, BOSTON GLOBE, Mar. 18, 2008, at A1. The implication of epigenetic research is that the harms of structural racism might persist long after official sources of discrimination have largely been dismantled.

[75] As discussed in the Introduction, preliminary epigenetic research impli-

be traced back to a particular consumer good or manufacturing activity, assigning liability through the tort system appears feasible. Thus, private actors could use the courts to regulate epigenetic risk in the same way the legal system utilizes products liability and environmental toxic torts to deter harmful products and activities. A hypothetical epigenetic tort claim asserted against water bottle manufacturers that sold bottles containing bisphenol A (BPA) can demonstrate how the tort system might address a typical claim alleging epigenetic harm.

During the past decade or so, people frequently consumed beverages from BPA-containing bottles. However, because of well-publicized health concerns, consumers shied away from these bottles, and manufacturers like Nalgene voluntarily came out with a BPA-free line of bottles. BPA has been shown to cause harmful epigenetic effects in many animal studies, especially to mice that were exposed *in utero* to BPA-tainted food.[76] BPA mimics the female hormone estrogen, and studies have demonstrated BPA's ability to remove methylation marks, resulting in genes being turned on at the wrong time or in the wrong tissue during crucial periods of development. In animal studies, BPA exposure has been implicated in breast cancer,[77] prostate cancer,[78] diabetes type II,[79] abnormal brain structure and behavior,[80]

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cates various exposures, from environmental, nutritional, to societal, that can cause epigenetic markings. *See, e.g.*, Rachel Yehuda et al., *Transgenerational Effects of Posttraumatic Stress Disorder in Babies of Mothers Exposed to the World Trade Center Attacks During Pregnancy*, 90 J. CLINICAL ENDOCRINOLOGY & METABOLISM 4115 (2005) (discussing the relationship between PTSD symptoms in mothers and infants of mothers directly exposed to the World Trade Center collapse on September 11 during pregnancy). For example, stress associated with discrimination or social strife (e.g., being a refugee, living in a warzone) can cause epigenetic modification of stress hormone genes. This article, however, will limit its particular focus to epigenetic harm caused by external substances (whether natural or synthetic) and manufacturing activities, as these exposures are most amenable to direct regulation. I plan to address other sources of epigenetic harm in future articles.

[76] Janet Roloff, *More Troubling News About BPA: Animal Studies Link Bisphenol A with New Adverse Health Effects*, SCIENCENEWS, June 12, 2009, http://www.sciencenews.org/view/generic/id/44577/title/Science_%2B_the_Public_More_troubling_news_about_BPA.

[77] T.J. Murray et al., *Induction of Mammary Gland Ductal Hyperplasias and Carcinoma* in situ *Following Fetal Bisphenol a Exposure*, 23 REPROD. TOXICOLOGY 383 (2007).

[78] Shuk-Mei Ho et al., *Developmental Exposure to Estradiol and Bisphenol A Increases Susceptibility to Prostate Carcinogenesis and Epigenetically Regulates Phosphodiesterase Type 4 Variant 4*, 66 CANCER RES. 5624, 5624 (2006).

[79] Paloma Alonso-Magdalena et al., *The Estrogenic Effect of Bisphenol A Disrupts Pancreatic B-Cell Function In Vivo and Induces Insulin Resistance*, 114 ENVTL. HEALTH PERSP. 106, 106 (2006).

[80] Kazuhiko Kubo et al., *Low Dose Effects of Bisphenol A on Sexual Differentiation of the Brain and Behavior in Rats*, 45 NEUROSCIENCE RES. 345, 354 (2003).

accelerating puberty,[81] and obesity.[82] Could these studies form the foundation for a successful tort claim against BPA manufacturers by someone who is able to demonstrate exposure to BPA in their bloodstream and one of the harms listed above? For multiple reasons, including difficulties with rules of evidence, statutes of limitations, statutes of repose, and common law issues of fairness and justice, the tort system would not be capable of addressing epigenetic risks and harms emanating from BPA and other similar substances.

A. Latency Problem

By definition, with latent diseases there is a passage of time between the harmful exposure and the manifestation of disease. The longer the latency period, the more difficult it becomes to accurately identify to which product one was exposed many years ago. The problem of latency arises in other toxic torts such as asbestos, but with epigenetic claims, the biological model posits that latent harm can persist several generations, so qualitatively speaking, latency is a different beast than even traditional long-tail tort problems such as asbestos exposure. BPA has been used in commercial products for over fifty years, so if the plaintiff is constructing an epigenetic claim, how can she be sure that the harmful exposure occurred during her lifetime and not her mother or grandmother's lifetime? One might counter that "marketplace liability," as in asbsestos and diethelstilbestrol (DES) cases, can rescue claims from the problem of uncertainty in product identification.[83] However, as discussed below, in an era of globalization and exponential growth in consumer goods, capturing all of the manufacturers of BPA in a lawsuit would be nearly impossible.

1. Statutes of Limitations / Repose

When dealing with latent diseases, statutes of limitations and repose also erect a difficult barrier for potential epigenetic tort claims. Statutes of limitations for tort claims are statements by legislatures that the time period for bringing certain kinds of claims is limited.

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[81] Kembra L. Howdeshell et al., *Exposure to Bisphenol A Advances Puberty*, 401 NATURE 763, 763 (1999).

[82] *Id.*

[83] In these cases, courts have imposed liability on a particular industry in total, and the various manufacturers within this industry then have to compensate victims in proportion to their market share of the offending product. For instance, if defendant Acme Corp. produced twenty-five percent of the asbestos on the market and a plaintiff X won a $100,000 lawsuit for asbestos-related injuries, then Acme Corp. would have to pay plaintiff X $25,000 of the lawsuit award based on its market share. *See* Sindell v. Abbott Labs., 607 P.2d 924, 938 (Cal. 1980).

Underlying these laws is the idea of repose: a potential defendant should not be chained down with the threat of indefinite liability.[84] Typically, the statute of limitations for a tort claim starts to run at the time of the defendant's alleged wrongful act. When act and injury coincide (e.g. hunting accident), the policy of repose can be enforced without causing injustice by extinguishing valid claims that may remain hidden. However, the problem with epigenetic claims, as with many toxic tort claims, is that the injury underlying the claim will very rarely manifest or be apparent within the statutory time limit. First, the epigenetic harm might not manifest itself for many years, if not generations, after the harmful exposure occurs. Second, many of the diseases thought to be related to epigenetic harms, such as cancer, have long latency periods and do not become clinically apparent until after many years or decades. Thus, the time lag between the tortious action and the harm makes it difficult to understand how a potential victim of epigenetic harm could sue within the statute of limitations.

One might counter that the "discovery rule," which allows for the tolling of the limitations period for equitable reasons until the plaintiff reasonably should have realized or discovered the cause of her injury, can salvage these claims. However, many jurisdictions have a statute of repose in addition to a statute of limitations. A statute of repose bars legal claims after a set period of time has run from the occurrence of some event apart from the injury which gave rise to the legal action. For instance, in the products liability context, many statutes of repose run from the time of delivery or sale of a product. Thus, in the case where an epigenetic insult does not cause injury until many years or several generations later, a statute of repose could bar an epigenetic claim before it even accrues.

2. Product Identification

Suppose a mother intends to bring a claim on behalf of a child suffering from developmental defects linked to BPA exposure. Additionally, assume that the mother can prove that she only used one particular brand of plastic water bottle for the last twenty years at the gym and at the workplace and is now bringing a claim on behalf of a child who is suffering from developmental defects allegedly linked to BPA exposure. Does this plaintiff have a viable claim? Even with these hypothetical facts, product identification would still be a major hurdle for this plaintiff.

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[84] Palma J. Strand, *The Inapplicability of Traditional Tort Analysis to Environmental Risks: The Example of Toxic Waste Pollution Victim Compensation*, 35 STAN. L. REV. 575, 580 (1983).

The Centers for Disease Control and Prevention estimates that over ninety percent of Americans have measurable levels of BPA in their urine.[85] However, the market penetration of BPA-containing water bottles is not ninety percent, so how is that possible? It has to do with the ubiquity of BPA in many household products and the myriad pathways of exposure.[86] Most people do not realize that BPA is embedded in many consumer goods including the lining of metal food cans, baby bottles and toys, cavity-fillings in dentistry, microwave ovenware, eating utensils, flooring, enamels, varnishes, water main filters, and many other products.[87] Further, would product identification require tracking down what BPA-containing products her parents and grandparents used?[88] What one might initially consider a straightforward issue of product identification (i.e., BPA from one manufacturer's gym bottle) becomes very complicated once one factors in all potential sources of exposures across multiple generations.

B. Multifactorial Nature of Disease Causation

A major problem with assessing tort liability for epigenetic harms is proving causation. Plaintiffs in most tort cases have the burden to prove their case by a preponderance of the evidence, which means showing a greater than fifty percent probability that a particular agent caused a harm. Given the multi-factorial genesis of most diseases that can be ascribed to epigenetic harm, conceptually it is difficult to imagine more than fifty percent of the blame being assigned to a single agent. Further, with epigenetic claims, the causal chain can be very attenuated and indirect compared to typical toxic tort claims. For instance, if the harmful exposure occurred to your grandfather and not you, most likely there would be too many intervening variables for a trier of fact to attribute more than fifty percent blame to any given agent. Further, if a lab analyzed any random individual's fat tissue, it would discover measurable levels of numerous chemicals that studies have linked to various diseases, including the same diseases linked to BPA. The problem is that on a global scale, human populations are exposed to a giant stew of chemicals that are inevitably absorbed

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[85] CTRS. FOR DISEASE CONTROL & PREVENTION, U.S. DEP'T OF HEALTH & HUM. SERVS., SPOTLIGHT ON BISPHENOL A (2009), http://www.cd c.gov/exposure report/pdf/factsheet_bisphenol.pdf [hereinafter BISPHENOL FACTSHEET].

[86] *Id.*

[87] Sheldon Krimsky, *Plastics in Our Diet: The Need for BPA Regulation When Scientists Find Chemicals that Disrupt Human Systems, Regulators Must Ban Them*, SCI. AM., Oct. 3, 2008, *available at* http://www.scientificamerican.com/article .cfm?id=plastics-in-our-diet.

[88] *See* latency discussion *supra* Section II(A).

within their bodies. Given these considerations, any competent defense attorney likely would be able to nullify any epigenetics-based tort claims.

C. Tort Claims for Increased Risk

Could the tort system be adjusted to take account of epigenetic claims? As research continues, we will likely learn more about epigenetic profiles (epigenomes) associated with increased risk of disease. This development raises the issue of whether risk can be considered an "injury." A basic element of personal injury torts is that the plaintiff must show evidence of harm in the form of a "physical injury." In textbook personal injury cases, a harm-inducing event, whether from a botched surgery or industrial accident, results in a readily apparent injury. Absent a showing of injury, there is no basis for recovery. However, considering advances in diagnostic laboratory tests which can predict disease conditions prior to the development of clinical symptoms, some legal commentators argue that the traditional risk-injury dichotomy may no longer be tenable.[89] This debate is especially relevant for potential epigenetic claims as scientists predict the eventual ability to generate individual epigenetic fingerprints which can demonstrate a causal relationship between certain exposures and epigenetically modified diseases. The question then becomes, how would tort law treat epigenetic marks linked to certain diseases? Are these marks merely indicators of future risk, or do they represent actual harm compensable under the law?

While the risk-injury debate in tort policy is not new, innovative research in the area of "biomarkers" has reinvigorated this discussion. A biomarker is a biochemical substance or feature that can be objectively measured and analyzed to indicate the presence of a normal or pathologic biological mechanism at the molecular levels of cells. Focusing at this level of detail has enabled researchers to identify previously undetectable "intermediate events between chemical exposure and clinically recognizable disease."[90] Thus, epigenetic markings can be understood as a particular type of biomarker which, in certain cases, indicates a heightened risk of disease.

Under the traditional tort model, subcellular damage, or damage that occurs at the level of DNA or genetic repair mechanisms but has

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[89] *See* Jamie A. Grodsky, *Genomics and Toxic Torts: Dismantling the Risk-Injury Divide*, 59 STAN. L. REV. 1671, 1671 (2007); Albert C. Lin, *Beyond Tort: Compensating Victims of Environmental Toxic Injury*, 78 S. CAL. L. REV. 1439 (2005).

[90] Lin, *supra* note 89.

not manifested as structural damage at the cellular level or above, is deemed to be benign and hence legally irrelevant.[91] Alternatively, the "diseased state" model holds that although disease might be undetectable using traditional techniques, it may be present and ongoing. Therefore, the "true" latency period is shorter than what classical medical symptoms would suggest. In other words, what medicine once characterized as "enhanced risk" stemming from toxic exposures can now be understood as actual "injuries" at the subclinical level.[92] If this argument is accepted, then tort law would transform to regard subcellular insults as actual physical harm instead of potential harm. A legal implication of this change would be that the traditional tort element of harm could now be demonstrated before the clinical manifestation of the disease.

One can argue that courts have already shown an increasing awareness of biological risk and latent disease processes by recognizing nontraditional claims such as "enhanced risk" and "medical monitoring." The basic elements of a medical monitoring claim are:

> A plaintiff can recover the costs of medical monitoring if (1) he establishes that he was significantly exposed to a proven hazardous substance through the negligent actions of the defendant; (2) as a proximate result of the exposure, the plaintiff suffers a significantly increased risk of contracting a serious latent disease; (3) by reason of the exposure a reasonable physician would prescribe a monitoring regime different from the one that would have been prescribed in the absence of the exposure; and (4) monitoring and testing procedures exist that make the early detection and treatment of the disease possible and beneficial.[93]

Not surprisingly, industry and the defense bar have vehemently argued that liability should only be assessed for actual injuries, not latent risks. They contend that latent risk claims would fling open the proverbial floodgates of litigation. The Supreme Court's rejection of a medical monitoring claim under the Federal Employers Liability Act I in *Metro-North Commuter Railroad Co. v. Buckley* is highly relevant to the risk versus injury tort debate.[94] The plaintiff was exposed to asbestos as a pipe-fitter but did not have evidence of any present injury. These specific facts are relevant because it is well-established

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[91] Grodsky, *supra* note 89, at 1676.

[92] *See* Lin, *supra* note 89.

[93] Metro-North Commuter R.R. Co. v. Buckley, 521 U.S. 424, 450 (1997).

[94] *See id.* at 455.

that this type of occupational exposure is associated with future development of mesothelioma (cancer of tissue lining the lungs).[95] As a matter of epidemiology, this relationship is not speculative or in the "twilight zone" of medical acceptance. While the Court did not reject the validity of medical monitoring claims as a general matter, its decision in the context of these particular facts sent a clear signal that the Court disfavored imposing liability without evidence of harm.[96] Indeed, since the *Metro-North* decision, five state supreme courts have considered whether to recognize medical monitoring claims without evidence of present injury, and all five courts have declined to recognize such claims.[97]

It seems inconsistent that courts accept the validity of claims for latent harms, but only if the offending exposure causes an additional harm that has already manifested. If epidemiological evidence has demonstrated a substantial risk between exposure and latent harm, and evidence of sufficient harmful exposure is present, the requirement of "present injury" should not be needed if the judiciary accepts compensation for latent risks. The reality seems to be that courts are uncomfortable addressing issues of biological risk and require that plaintiff's suffer demonstrable physical injury to legitimate an assignment of liability. From a biological perspective, the concept of disease as a spectrum rather than a binary on/off event is logical. Indeed, this concept informs many medical protocols that focus on well-being as opposed to just disease prevention and treatment.[98] However, abstracting a legal rule from this spectral disease paradigm is problematic. Logically, many people are suffering from early stages of disease even if outwardly they feel healthy. For instance, researchers have detected coronary atherosclerosis in many teenagers and young adults who do not present any outward symptoms of heart disease.[99] While

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[95] Occupational Safety & Health Admin., U.S. Dep't of Labor, Asbestos Hazards, http://www.osha.gov/SLTC/asbestos/hazards.html (last visited May 3, 2010).

[96] 521 U.S. at 440-41.

[97] SHAWN D. BRYANT, WASHINGTON LEGAL FOUND., FEDERAL COURT FINDS MEDICAL MONITORING TORT UNAVAILABLE IN TEXAS (2006), http://www.wlf.org/publishing/publication_detail.asp?id=1761.

[98] The World Health Organization's (WHO) definition of health captures this concept: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." Preamble to the Constitution of the World Health Organization, opened for signature July 22, 1946, 62 Stat. 2679, 14 U.N.T.S. 185.

[99] E. Murat Tuzcu et al., *High Prevalence of Coronary Atherosclerosis in Asymptomatic Teenagers and Young Adults: Evidence from Intravascular Ultrasound*, 103 CIRCULATION 2705, 2706-08 (2001).

early atherosclerosis likely portends future heart problems, this condition is difficult to classify as an injury if it is presently causing no symptoms or functional decline.[100] This conundrum raises the difficulty of establishing thresholds for when epigenetic markers of risk can be considered injuries in the tort sense. It seems that one would first need to establish what a "normal" risk profile is, which may not be possible. Thus, one is brought back full circle to the logic that a clinically diagnosed injury must be the predicate for a medical tort claim.[101]

D. Weak Deterrent Signal from Torts

As discussed above, the tort system is not capable of addressing epigenetic harms for a variety of reasons. So what are the consequences of this legal failure? In many ways, the barriers epigenetic claims putatively face in the tort system mirror those barriers present in environmental and toxic torts although, as discussed above, the expected barriers for epigenetic claims would be even higher. In the context of environmental and toxic harms, one of the primary roles the tort system is considered to fill is a regulatory public health role.[102] In other words, the tort system sends deterrent signals to environmental harm producers via those who are injured and legally pursue claims against these producers.[103] However, "[e]mpirical evidence suggests that environmental tort suits" send "a weak deterrent signal."[104] In theory, a person harmed by toxic waste seeping from an industrial factory can bring a tort claim, receive compensation for his or her injuries, and deter future exposures. In practice, studies have shown that such individuals are unlikely to receive tort compensation. Legally toxic waste disposal injuries are intrinsically different from the particularized, immediate harms around which tort law developed. The lapsed time between the disposal and injury, and the inherently diffuse nature of causation, generally act to discourage these claims.[105] In addition, potential plaintiffs for these claims face stiff practical barriers to accessing the judicial system, such as high financial costs and

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[100] *See id.* at 2708-09.

[101] Allan L. Schwartz, Annotation, *Recovery of Damages for Expense of Medical Monitoring to Detect or Prevent Future Disease or Condition*, 17 A.L.R. 5th 327 (1994).

[102] This primary role is in addition to compensating individuals who suffer harm.

[103] Troyer A. Brennan, *Environmental Torts*, 46 VAND. L. REV. 1, 2 (1993).

[104] *Id.*

[105] Strand, *supra* note 84, at 575.

the ability to find willing counsel.[106] If the deterrent signal for traditional toxic torts is weak, then we can expect the tort deterrent signal for epigenetic harms to be minimal to non-existent.

E. Minimal Tort Incentive for Long-Term Safety Precautions

Lack of toxicological or material safety data is a problem that undermines many potential toxic tort claims. However, private actors have very little incentive to generate this data. Such defendants will likely not invest to protect against expected harms that seem minimal in nature and not lucrative enough for plaintiffs to pursue in litigation. Conversely, harm producers will only invest enough research resources to avoid liability from activities or products that can be *foreseen* to cause extreme injuries or harm a large number of people. Of course, the problem with this foreseeability standard is that the general public is often not aware of what is not known.[107] Additionally, even if a corporation can foresee a fairly high risk (say forty percent) of financially damaging tort liability emerging thirty years into the future, it is not clear that most corporate managers would take action to avoid such liability. Avoiding such liability would require corporate managers to incur a present cost to receive an indeterminate benefit (liability avoided) that will be recognized in the future, perhaps long after they leave the corporation. Furthermore, rewards for short-term performance (higher share value and bonuses) mean that incentives to minimize present costs greatly outweigh any incentive to avoid future tort liability.

Lastly, the tort system places the burden on plaintiffs to establish the causal link between a substance and an injury, but plaintiffs rarely have the resources necessary to analyze existing data or to generate new scientific results. Corporate defendants have better access to relevant information about their products and manufacturing activities, but if these defendants are not required to generate safety data by

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[106] Mary L. Lyndon, *Tort Law and Technology*, 12 YALE J. ON REG. 137, 168 (1995).

[107] Secretary of Defense Donald Rumsfeld famously uttered this gem on the subject of foreseeability, "Reports that say that something hasn't happened are always interesting to me, because as we know, there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns – the ones we don't know we don't know." Donald H. Rumsfeld, U.S. Sec'y of Defense, Dep't of Defense, DoD News Briefing – Secretary Rumsfeld and Gen. Myers (Feb. 12, 2002), http://www.defenselink.mil/transcripts/transcript.aspx?transcriptid=2636.

some regulatory body, they have little incentive to disclose or develop risk data that can lead to liability.[108]

F. The Justice Problem: Being Punished for Wrongs Committed by Others

Assuming *arguendo* that one could somehow reformulate tort rules to accommodate epigenetic claims stemming from many years or generations past, it is not clear that one should welcome this end based on considerations of justice and efficiency. As discussed above, one of the major rationales for the tort system is to deter and regulate harm in society. The other major rationale is to achieve corrective justice between the harmed victim and the tortfeasor. This notion stems from a conception of justice based on individual liberty. For instance, if a corporation negligently causes injury, imposing liability on the corporation furthers corrective justice if the group of people represented by the corporation does not change significantly between the time the tortious act occurred and the time the liability is imposed.[109] However, if there is a substantial change in the individuals representing the company, the imposition of corporate liability would not further this notion of individual-based corrective justice.[110]

The concern therefore is that imputing liability for epigenetic harms on present-day individuals for harms caused by past actors seems like an unfair debt to inherit. One might be tempted to retort that the truly unfair debt to inherit is the epigenetic harm, not the tort liability. However, this latter view would entail holding defendants to contemporary standards of scientific knowledge, rather than what was known at the time of their actions. If actors are unaware of harms they cause due to lacunae in general scientific knowledge, as opposed to willfully remaining ignorant of knowable risks, it is not fair to impose judgment of wrongdoing *ex post*.

Efficiency considerations also argue against imposing tort liability for long-past actions. At the margins, endeavors that reasonably appear to be beneficial and safe might be avoided due to fear of unknown future liability.[111] Further, if a manufacturer stopped producing the offending product many years ago, relaxing statute of repose laws to account for epigenetic causation would not satisfy any deterrent role. Instead, such action may only serve to punish a party that might produce entirely unrelated and highly beneficial products.

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[108] Strand, *supra* note 84.
[109] *Id.* at 605.
[110] *Id.*
[111] *Id.* at 601.

In summary, the tort system does not seem the proper framework to address epigenetic harms. As some have suggested in the realm of toxic tort injuries, the only way to accommodate epigenetic legal claims would require stretching tort standards regarding causation, evidence, presence of physical injury, and limitations periods. However, we have to ask whether such Procrustean measures are justified and likely to be effective. It appears that the answer to both of these questions is negative; in using the tort system to hear epigenetic claims, it seems that there is a trade-off between justice and effective outcomes.

III. INADEQUACY OF CURRENT REGULATORY REGIME TO ADDRESS EPIGENETIC HARM

As presently conceived, U.S. regulatory agencies cannot adequately address epigenetic harm. For example, skin is the largest organ in the human body. While our skin can protect our internal organs from many environmental exposures, it is not an impermeable barrier and many substances can pass through our skin. Hence the efficacy of nicotine or birth control patches. Given this fact, it would be fair for most American consumers to assume that products that come in contact with our skin, such as cosmetics, shampoos, and other personal care products are tested for safety by the Food and Drug Administration (FDA). However, this assumption would be wrong. The FDA only focuses on the safety of hair dyes and does not have the explicit authority to regulate cosmetics.[112] The issue of expanding FDA authority to regulate cosmetics has been raised many times in the Senate over the past five decades, but each time lobbyists from the cosmetics industry have defeated such efforts.[113] For instance, a recent study conducted by a consumer protection group found that many popular brands of lipstick sold in the United States contain measurable amounts of lead, a known neurotoxin that is especially damaging for the developing brain.[114] But since the FDA does not regulate lipstick directly, no federal guidelines govern lead content in cosmetics.[115]

A. Legal Authority for Public Safety Regulation

The lack of current regulation does not mean that the FDA and Environmental Protection Agency (EPA) do not possess the legal au-

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[112] *Don't Pucker Up: Lead In Lipstick*, ABC NEWS, Oct. 12, 2007, http://abcnews.go.com/GMA/story?id=3722013.

[113] *Id.*

[114] *Id.*

[115] *Id.*

thority, under their existing statutory grants, to more closely protect human health and the environment from unsafe foods, drugs, cosmetics, consumer products, pesticides, and manufactured chemicals. Under the Food, Drug, and Cosmetic Act (FDCA), the FDA places the burden on pharmaceutical and medical device manufacturers to demonstrate that their products are (i) safe and (ii) effective through a rigorous multi-phase testing process. Similarly, under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the EPA requires pesticide manufacturers to prove that their products are reasonably safe.[116] In both cases, there is no presumption of safety, and the manufacturers bear the burden of showing that a product is safe.[117] In the abstract, the FDA and EPA have the power to shift the burden onto manufacturers to demonstrate that their products do not cause undue epigenetic harm. However, the reality is that the FDA does not use this burden-shifting power for the vast majority of commercial substances absorbed through human skin. As a consequence, if the regulatory status quo is maintained, the FDA and EPA will do very little to bridge the huge gaps in knowledge regarding the epigenetic safety of most consumer products and chemicals. An examination of these agencies' current efforts to regulate known or suspected toxins bears out this dim assessment.[118]

The Administrative Procedure Act (APA) governs the legality of actions taken by federal agencies. In *Chevron*, the Court constructed a two-part test for reviewing agency decisions pursuant to a statute.[119] The first part is to ascertain whether Congress has already decided the issue in question, or in other words, whether it has precluded what the agency proposes to do. The second part is to determine whether the agency interpretation is reasonable and not arbitrary or capricious.

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[116] The EPA administers the Federal Insecticide Fungicide and Rodenticide Act (FIFRA) which is aimed at protecting people and the environment from "unreasonable adverse effects." FIFRA shifts the burden onto manufacturers to prove that their products are safe for their intended use before obtaining federal approval for sale. Prior to marketing a new pesticide the manufacturer must provide to the EPA health information such as "data on its acute toxicity, neurotoxicity, and potential carcinogenicity." Nathaniel Garrett, *"Life is the Risk We Cannot Refuse:" A Precautionary Approach to the Toxic Risks We Can*, 17 GEO. INT'L ENVTL. L. REV. 517, 545 (2005).

[117] Based upon safety data pesticide manufacturers submit, the EPA then sets what levels of human exposures are allowable. Under this burden-shifting scheme, the presumption is that the chemical is not safe for use until the manufacturer proves otherwise. In other words, the burden of showing that a pesticide is safe "remain[s] at all times on the applicant and registrant." *Id.*

[118] *Id.*

[119] Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837 (1984).

Therefore, generally speaking, federal agencies have broad discretion to interpret the scope of regulatory statutes, and the courts are reluctant to second-guess agency rulemaking. However, courts have not extended this general rule to the EPA's application of the Toxic Substances Control Act (TSCA).[120]

Among other things, TSCA grants the EPA the authority to restrict the use of and mandate safety testing of suspected toxins produced by chemical companies. Thus, after its passage, TSCA was considered a potentially powerful tool to protect against harmful exposures. In 1989, after conducting a ten-year study costing millions of dollars and amassing a 100,000 page administrative record, the EPA announced it would phase out and ban all uses of asbestos.[121] The EPA's stated rationale was that "asbestos is a human carcinogen and is one of the most hazardous substances to which humans are exposed in both occupational and non-occupational settings."[122] The United States Court of Appeals for the Fifth Circuit overturned this ban in *Corrosion Proof Fittings v. EPA*, holding that the EPA failed to present "substantial evidence" under which to justify the ban.[123] The court found that:

> [c]ontrary to the EPA's assertions, the arbitrary and capricious standard found in the APA and the substantial evidence standard found in TSCA are different standards, even in the context of an informal rulemaking . . . . Congress specifically went out of its way to provide that "the standard of review prescribed by paragraph (2)(E) of section 706 [of the APA] shall not apply and the court shall hold unlawful and set aside such rule if the court finds that the rule is not supported by substantial evidence in the rulemaking record . . . taken as a whole." 15 U.S.C. § 2618(c)(1)(B)(i) . . . . The substantial evidence standard mandated by [TSCA] is generally considered to be more rigorous than the arbitrary and capricious standard normally applied [ ].[124]

The court further reasoned that the EPA had failed to show that a ban was the "least burdensome alternative" for dealing with the risk posed

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[120] Corrosion Proof Fittings v. EPA, 947 F.2d 1201, 1213-14 (5th Cir. 1991).

[121] Asbestos; Manufacture, Importation, Processing, and Distribution in Commerce Prohibitions, 54 Fed. Reg. 29,460, 29,461 (July 12, 1989) (to be codified at 40 C.F.R. pt. 763).

[122] *Id.* at 29,468.

[123] 947 F.2d 1201 (5th Cir. 1991).

[124] *Id.* at 1213-14.

by asbestos, failed to consider the cost of there not being adequate substitute products, and improperly considered "unquantifiable benefits" in its cost/benefit analysis.[125] The EPA did not appeal this decision.

Given the significant legal and knowledge burdens the Fifth Circuit construed TSCA as requiring, this decision effectively eviscerated the utility of this Act as a regulatory tool. Regarding safety data for commercially produced toxins, since the passage of TSCA over three decades ago, the EPA has promulgated testing protocols for less than one percent of the 75,000 manufactured chemicals on its own Toxic Substances Inventory list.[126] Further, by focusing on the absence of currently available substitutes for asbestos, the court ignored the incentives that "technology-forcing" regulations can place upon industry to create such alternatives. It is a common American perception that government regulation necessarily hurts innovation and economic growth.[127] Returning to the differences between European and American regulatory attitudes, the Europeans are more comfortable in mandating standards on industry even if such standards require the development of technology that does not currently exist. For instance, European regulators are far more aggressive in mandating fuel efficiency standards for automakers and technology standards for cell phone manufacturers.[128] In the United States, automakers and cell phone manufacturers resisted such regulations, arguing that the regulations were not technically feasible and were likely to cause economic injury to the industry.[129] However, these technology-forcing regulations did not harm the European auto or cell phone industry;

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[125] *Id.* at 1219.

[126] Noah Sachs, *Blocked Pathways: Potential Legal Responses to Endocrine Disrupting Chemicals*, 24 COLUM. J. ENVTL. L. 289, 313-14 (1999).

[127] *See* Kimberly S. Johnson, *Ford CEO Says Regulation Often Hurts Innovation*, ABC NEWS, June 17, 2009, http://abcnews.go.com/Business/wireStory?id=7862126 ("Ford Motor Co. CEO Alan Mulally said government regulation in many ways has hurt innovation among businesses and manufacturers in the United States. 'We've become so stymied with regulation,' said Mulally Wednesday during a panel discussion on innovation in manufacturing at The National Summit in Detroit. 'We have to say enough is enough and get back to freeing people up.'").

[128] Reilly Brennan, *New, Stricter Fuel Standards for Cars*, AOL AUTOS, May 20, 2009 (announcing President Obama's new mileage and emission standards that will require cars and trucks to meet a comprehensive 35.5-mpg standard by 2016, and explaining that the U.S. will still lag behind Japan and Europe despite these new standards); *Telecom Firms Back Standard Phone Charger in Europe*, REUTERS, June 29, 2009 ("Top mobile telephone suppliers have agreed to back an EU-wide harmonization of phone chargers, the European Commission said on Monday, hailing the pact as good news for consumers and the environment.").

[129] BRYANT, *supra* note 97.

instead, by being forced to produce more efficient cars and to focus industry efforts on one cell phone standard (GSM), European automobile and cell phone makers are in better economic positions than their American counterparts.[130]

B. Phthalates: A Case Study of Regulatory Inaction

As discussed in the previous section, BPA belongs to a class of chemicals known as endocrine disruptors and has been implicated in causing epigenetic harm. Phthalates are another class of chemicals that have been identified as endocrine disruptors and might cause similar epigenetic harm as BPA.[131] Phthalates are used in the manufacture of a variety of products, including plastic films used in food packaging, infant toys (they make plastics soft and pliable), and paint.[132] Alarmingly, phthalates have been detected in many processed foods such as margarine, cheese, and baby formula.[133] Studies have shown that if children suck on plastic toys that contain phthalates, then they may experience elevated levels of this chemical. Responding to these findings, the European Union (EU) removed phthalates from children's toys starting almost a decade ago. In contrast, the United States Congress did not take action to ban phthalates in products for children until August 2008, when it banned phthalates in products designed for children under twelve years old.[134] Further, this law allows retailers and manufacturers to sell off their existing inventory of toys, plastic sip cups, and other products that contain this chemical. Currently, there is no legal requirement to label products containing phthalates.[135]

From an epigenetic perspective, this regulation safeguarding children under age twelve is woefully under-protective. Theoretically, children who currently use phthalate products may pass along harmful developmental defects to their future offspring mediated by epigenetic

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[130] While all automakers have been hurt by the economic downturn, it is clear that American manufacturers have been particularly hard hit in the global marketplace by lagging behind in making more fuel-efficient cars.

[131] *See generally*, Liz Szabo, *Toy with Phthlates Can Be Sold After U.S. Ban Takes Effect*, USA TODAY, Nov. 19, 2008, *available at* http://www.usatoday.com/news/health/2008-11-19-phthalate-federalban_N.htm (reporting on dangers that phthalates in children's products pose to the hormone system); Env't & Human Health, Inc., *Plastics that May Be Harmful to Children and Reproductive Health*, http://www.ehhi.org/reports/plastics/phthalates_exposures.shtml (last visited May 3, 2010).

[132] Env't & Human Health, Inc., *supra* note 131.

[133] *Id.*

[134] *See* Szabo, *supra* note 131.

[135] *See id.*

mechanisms. The bottom line is that without a coherent and comprehensive regulatory policy to quantify and control such epigenetic harm, we cannot construct rules rationally tailored to avoid such harms. Instead we may be saddled with policies that are reactionary, quasi-arbitrary, and ultimately ineffectual in achieving their intended goals.

Going forward, the question to ask is whether agencies such as the EPA and FDA have the ability to regulate epigenetic harm emanating from industry. Put another way, can these agencies impose practical steps on industry such as mandatory testing, information disclosure, or product restrictions based upon epigenetic rationales? This question can be answered by assessing whether epigenenetic risks fall within the bounds of risks these agencies are currently authorized to regulate. Analogizing to examples involving asbestos and cosmetics, most likely affected industries could successfully challenge the enforceability of epigenetic-based regulations under current regulatory guidelines, arguing that such actions are based upon unquantifiable costs and benefits or that available data is not "substantial" enough.

Given the qualitative nature of epigenetic risks (diffuse, multi-generational, multi-factorial, etc.), it is predictable that even as researchers learn more about epigenetic risks from everyday exposures, such risks cannot be calculated with any certainty. The consequence is that epigenetic risks will continue to reside within a regulatory lacuna, and preventable harms will go unchecked as a result. The necessary response, then, is for Congress to recognize that epigenetic harms are unique and to specifically grant authority to either a new or existing agency (which can create a new epigenetic division) (i) to address epigenetic harms even if they cannot be quantified under traditional regulatory formulas and (ii) to expand the scope of goods and activities that fall under such regulation (e.g., cosmetics). The new epigenetic regulatory agency, supported by this general statutory grant to address epigenetic harm, can legally implement the adaptive regulatory framework I propose in Section VI. However, before discussing the practical regulatory steps, the normative case for Congress changing the current administrative and regulatory rules has to be made. Therefore, in Section IV below, I detail how the Capabilities Approach provides a compelling normative justification for addressing epigenetic harm in particular.

IV. THE CAPABILITIES APPROACH: THE NORMATIVE CASE TO ADDRESS EPIGENETIC HARM

The descriptive claim that I am making is that epigenetic harm is qualitatively different from other toxic risks that regulatory agencies

have historically perceived and addressed. An expected critique of my view is that epigenetic harm is the same as other garden-variety toxic risks, with the exception that it has a much longer tail, meaning that the manifestation of harm occurs long after the causative exposure. In other words, epigenetic harm is akin to the plight of a pipe fitter who develops mesotheliomia decades after being exposed to asbestos. I would argue that epigenetic harms are qualitatively different than long-tail harms tort law has dealt with and thus requires a novel way of addressing these *particular* harms. First, epigenetic harm can limit *ex ante* an individual's human potential before that individual is even born or conceived. This affliction can be distinguished from having a harmful genetic predisposition because, as discussed earlier, the relative immutability of the genetic code is a fact of biology shared by everyone. In contrast, epigenomes are far more mutable and susceptible to modifications caused by environmental exposures. Second, the person taking on the risk of exposure is often not the individual herself but an ancestor. Third, researchers have demonstrated that epigenetic marks can have a profound impact on an individual's mental and physical development. Thus, such developmental changes will most probably exert a greater impact on an individual's lifelong capabilities compared with a harm like mesothelioma (a typically late-onset cancer) which would not greatly impact an individual's capabilities or freedom of life choices prior to the manifestation of the disease. However, merely proving the case that epigenetic harm is different than other biologically mediated harms does not provide the policy justification for rethinking and adapting how to regulate harmful exposures.

Compared with the two regulatory frameworks that currently predominate – cost-benefit analysis and the precautionary approach – the "Capabilities Approach" (CA) developed by Amartya Sen and Martha Nussbaum, provides an evaluative framework that is better adapted to map the specific policy challenges posed by epigenetic risk. Further, if policymakers apply the CA, it illuminates a clear normative justification for aggressively addressing epigenetic risk – the imperative to protect an individual's autonomy and agency. In other words, an individual's freedom to choose among alternative lives that she could possibly lead if not fettered by preventable epigenetic burdens. The following subsection will first describe what the CA is and the policy directives that it generally commands. Then this section will examine how application of the CA can articulate the need for regulatory policies specifically focused on epigenetic risk.

A. Rawls and the Capabilities Approach

Sen and Nussbaum's development of the CA can be seen as a response and critique, but not a repudiation, of John Rawls' famous *A Theory of Justice*. Indeed, both Sen and Nussbaum acknowledge their debt to Rawls' work, and the CA is similar to Rawlsian theory in that both are social contractarian and explicitly deontological rather than consequentialist.[136] However, Sen and Nussbaum express concern that Rawlsian theory fails to account for the innate diversity within human populations and will still lead to significant injustice in society.[137]

In *A Theory of Justice*, the "original position" plays a central role in Rawls' social contract conception of justice. The original position uses the heuristic of the "veil of ignorance" to ensure unbiased judgment when thinking about fundamental principles of justice. All individuals are veiled or blinded to knowledge of their personal, social, and historical characteristics. Thus, one is unable to select self-serving principles because one's actual status in society is unknowable. Rawls argues that individuals conceived of in this original position possess two moral qualities: (i) they have a sense of fairness and equality which compels them to look for cooperation; and (ii) they possess the ability to form a conception of what it means to have a good life.[138] Rawls concludes that rules derived from his procedural theory of justice will lead to an equal distribution of basic liberties he terms "primary goods."[139] Sen and Nussbaum argue that Rawlsian and other concepts of justice ignore an important element – an individual's capacity to transform whatever is distributed to him or her equally into something that enables that individual to live a meaningful life.

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[136] For this reason the CA has also been described as "Kantian" in that outcomes are irrelevant for judging whether an action or policy is "good." Utilitarianism by contrast is explicitly consequentialist and outcome-focused.

[137] Sen and Nussbaum both point out that individual's born with developmental disabilities would fare poorly under a Rawlsian distribution of primary goods as they might require more resources to ensure the same capability set. Nussbaum, *supra* note 12.

[138] John Rawls, *The Priority of Right and Ideas of the Good,* 17 PHIL. & PUB. AFF. 251, 258 (1988).

[139] Rawls conceives of the primary goods as "a scheme of equal basic liberties and fair opportunities, which, when guaranteed by the basic structure, ensures for all citizens the adequate development and full exercise of their two moral powers and a fair share of the all-purpose means essentials for the advancement of their conceptions of the good." *Id.*

B. Basic Elements of the Capabilities Approach

The CA focuses on ensuring individual autonomy and free choice.[140] This translates into the CA asking what people are actually capable of doing and becoming when viewed from a holistic perspective. As Nussbaum puts it, the CA's concept of capability encompasses the material, political, and social spheres of existence.[141] Thus, the CA goes beyond asking whether people have "freedom" in the legal sense; the CA inquires "to what extent people are really in a position to avail themselves of these freedoms and it directs attention to other areas of choice and opportunity, such as education and healthcare."[142] Thus, the central CA directive is that society must provide its members with the preconditions of a dignified human life – a core group of "capabilities" without which a person could not choose a worthy life.[143]

The CA parses these capabilities from a quasi-biological perspective.[144] For instance, "innate abilities" are the elementary abilities people are born with that give them the potential to live a worthy life characterized by being able to exercise autonomy and make free choices. Viewing them akin to a vulnerable seedling, the CA is concerned that these innate abilities might wither away and not grow into something stronger if society does not provide adequate support to develop these innate abilities into effective capabilities. Nussbaum terms the *developed form* of innate abilities "internal capabilities."[145] The CA argues that equitable distribution of government assistance in areas such as education, healthcare, and safety is a desideratum for citizens to acquire "internal capabilities."[146] However, while internal capabilities are necessary to live a dignified life, they are not sufficient if individuals lack the liberty to freely express their capabilities

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[140] First, it is important to note that Nussbaum diverges from Sen in her development of this theory, and henceforth, when referring to the CA, I am referring to Nussbaum's particular version.

[141] Nussbaum, *supra* note 12.

[142] *Id. See also* AMARTY SEN, DEVELOPMENT AS FREEDOM (1999). However, as Nussbaum points out, while both her version of CA and Sen's focus on an individual's ability to lead a dignified life and argue for the importance of government investing in areas such as education and healthcare, their versions are not the same. When the "CA" is referred to in this paper, it is referring to the particular version articulated by Nussbaum.

[143] Nussbaum, *supra* note 12, at 7.

[144] *Id.* at 11.

[145] MARTHA NUSSBAUM, WOMEN AND HUMAN DEVELOPMENT: THE CAPABILITIES APPROACH 84-86 (2000).

[146] *Id.*

in a functional manner.[147] Thus, the CA articulates that government must produce "combined capabilities" in its citizens, that is, "internal capabilities combined with suitable external circumstances" that protect an individual's opportunity to pursue functions within his or her developed capabilities set.[148] To reiterate, the CA is explicitly not consequentialist – its goal is not to have individuals achieve some meaningful endpoint, but rather to ensure that people have the capability to choose meaningful ends.[149]

The CA posits that government needs to ensure a minimum threshold of capabilities, distributed across its citizens, to achieve a basic minimum of justice. The CA pragmatically recognizes that is it not possible to ensure equal capabilities above a certain minimum threshold and is silent on these inequalities. For instance, a society should provide for universal education and healthcare, but it cannot possibly guarantee that everyone will pursue a university degree or be in good physical shape. Thus, it is acceptable that people possess adequate capabilities without possessing fully equal levels of

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[147] Illustrating from real-world examples how internal capabilities are not sufficient to lead a dignified life, Nussbaum states:

> People may be well educated, well fed, and healthy, however, and yet lack meaningful opportunities to use their powers in action. Many people who are capable of speaking freely, in the sense that they have been educated and cultivated, lack the meaningful opportunity to speak freely in public, because their nation has not protected their freedom of speech, or has not protected it equally for all. For women in many parts of the world, it has been a common experience to find oneself full of internal capabilities that one never gets a chance to use, because many nations have not given women political rights, property rights, rights over their own bodies, and so forth, or have not given these rights to women and men on a basis of equality.

NUSSBAUM, *supra* note 145, at 11-12.

[148] Under this formulation of "combined capabilities," we can see that epigenetic risk can be associated with both innate abilities like cognitive or physical developments and external circumstances such as gender or race discrimination or living in a war zone.

[149] Sen points out that substantive freedom has to be judged not only by the amount of options available to an individual, but also the attractiveness of those options. *See* SEN, *supra* note 142, at 117-18. Further, Nussbaum illustrates the difference between focusing on outcomes versus the freedom to pursue certain outcomes:

> [H]aving meaningful political rights (and *really* having them, not just as words on paper) does not require one to participate in politics. Members of the Old Order Amish have the right to vote, and they choose not to use it. That is just fine. To compel them to vote would be insufficiently respectful of their freedom. Similarly, people who have adequate nutrition available may always choose to fast–for example, for religious reasons. There is, however, a large difference between fasting and starving, and it is that difference that the CA wishes to capture.

Nussbaum, *supra* note 12, at 12.

functioning. However, the CA is not silent on inequities that are the products of discriminatory practices rather than innate abilities. For instance, singling out minority neighborhoods for toxic waste dump sites or neglecting to provide access to good schools in these neighborhoods would violate CA tenets.[150] Therefore, while equality of capabilities is not the goal, equality in terms of nondiscrimination in the cultivation of capabilities is central to the CA.

The CA differs from a utilitarian, or traditional cost-benefit, framework in several fundamental ways. First, the CA considers each person to be an end. This would make it impermissible for the government to promote the overall good in a fashion that infringes upon the rights of individuals to lead a dignified life.[151] For example, the construction of the Three Gorges Dam in China might prove to have a dramatic net benefit when considering its utility for the collective entity of over a billion Chinese citizens and thus would satisfy a traditional cost-benefit analysis.[152] But given that this project severely upended the lives of millions of rural Chinese (without restoring the life options available to them before the project commenced), the CA would evaluate this project as unjust. Instead of summing the individual benefits and costs to individuals, the CA would instead focus on the individuals most adversely affected by this project and ask if they still possessed the basic minimums required for a dignified life. Another key component of the CA is that opportunities are plural and non-commensurable. This means that vital capabilities are distinct and cannot be converted to a generic utility value that can be summed with other distinct capabilities to form a single net utility.[153] For instance, this means that a government cannot compensate for a paucity of political rights by providing extremely generous housing and healthcare entitlements.[154] Lastly, the CA elevates the role of educa-

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[150] *See generally* Dorothy E. Roberts, *Privatization and Punishment in the New Age of Reprogenetics*, 54 EMORY L.J. 1343 (2005).

[151] Nussbaum, *supra* note 12, at 14.

[152] The Three Gorges Dam on the Yangtze River is estimated to provide at least one-nineth of China's energy needs and open the rural interior of the country to further economic development. While these net benefits might accrue to over a billion Chinese, it is estimated that at least 5.3 million Chinese will have to be resettled as their homes become uninhabitable. Antoaneta Bezlova, *China: Three Gorges Dam May Displace Millions More*, IPS NEWS, Oct. 12, 2007, *available at* http://www.ipsnews.net/news.asp?idnews=39621.

[153] *Id.*

[154] Nussbaum clarifies:

> The plurality and distinctness of the ends does not mean, however, that they do not often support one another. For example, education supports political activity, the freedom of speech, *and* the ability to protect one's bodily integrity from abuse (because education gives employment options and thus exit options from

tion and cognitive abilities because the framework considers these capabilities as essential to fulfilling its central political goal of having "a nation of free choosers."[155] For instance, a government policy to provide citizens with solely vocational and scientific training to the exclusion of the humanities might produce more productive workers who can increase societal wealth and GDP (thereby increasing net utility), but this would not satisfy the CA.[156] Meaningful choice and options in life are not possible without an individual's ability to perceive, to think, and to select among varied options and cannot be measured by gross aggregate calculations such as GDP.[157] As discussed below in Section V, the CA's focus on innate abilities and equality of opportunity support a stronger government response to epigenetic risk than would a typical utilitarian, cost-benefit analysis.

Examining epigenetic risk under the CA lens, two major concerns rise to prominence. One is the role of epigenetic harm in impairing mental development. This matter flows from the CA focus on education and cognitive development. Without fully developed mental faculties, individuals cannot exercise meaningful life choices. The other major concern is the potentially unequal distribution of epigenetic harm. This type of disparity would intrinsically disadvantage certain groups from reaching a full capabilities set. Given the CA's insistence on equality of opportunity, the proscription to ensure a basic threshold of capabilities for all citizens would be violated. Thus, viewed from the CA framework, the problems associated with unchecked epigenetic risk go far beyond biological and medical concerns – the CA implicates much deeper questions of justice. The virtue of a framework incorporating both the CA and epigenetics is that such a framework more robustly tests the fairness of any social contract, as compared with a pure Rawlsian approach.

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an abusive marriage).
Nussbaum, *supra* note 12, at 14.

[155] *Id.* at 15.

[156] *See* ALDOUS HUXLEY, BRAVE NEW WORLD (1946) (Aldous Huxley's critique of a modern, technocratic society based on utilitarian principles in his dystopian classic Brave New World parallels my argument. Huxley imagined individuals being manufactured in birthing centers, in assembly-line fashion, to become producers and consumers with varying utilitarian skills, but not free thinkers capable of making free choices.).

[157] Nussbaum, *supra* note 12, at 14.

V. REGULATING EPIGENETIC RISK IN THE FACE OF UNCERTAINTY

Given that researchers are still learning a great deal about epigenetics and are far from proving causation of diseases from particular exposures through this mechanism, how should society approach the problem of epigenetic risk? Put in more practical terms, how do policymakers go about allocating resources or regulating the behavior of individuals or industry regarding potential epigenetic harms? In many ways, the problem of epigenetic risk mirrors the debate over how to manage global climate change. First, the targeted harm is multigenerational since current actions putatively can have dramatic effects on third parties who have not been born. Second, while compelling evidence is emerging that preventable human activities are contributing to or causing both kinds of harm, the scientific community has not established conclusive proof of these relationships. Third, the effects of regulations to protect against these harms remain uncertain. So how should decision-makers proceed? In this regard, a rigorous evaluation of several different decision-making models is needed to come up with a legitimate basis for crafting epigenetic policies. To this end, I will briefly examine the efficacy and fairness of three different decision-making models from a CA perspective: cost-benefit analysis; the precautionary approach; and the optimal-search method. Each model's potential strengths and weaknesses can be seen as I apply these models to a contemporary policy debate with profound epigenetic implications – the decision to mandate fortification of flour with folic acid.

A. Cost-Benefit Analysis

Cost-benefit analysis is utilitarian in nature in that a policy decision or action is acceptable only when the calculated benefits are greater than the costs.[158] It is consequentialist in that it focuses on quantifiable outcomes rather than fairness of process. There are many different iterations of this model, from a simple unweighted approach that treats each individual's utility equally to a weighted approach that gives more weight to the utility of those starting at a lower baseline.[159] However, regardless of the version, net utility has to be positive to justify an action.

In addressing epigenetic harm in particular, the cost-benefit analysis approach has two major weaknesses. First, a regulator cannot

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[158] *See generally* Graham, *supra* note 7.

[159] *Id.*

make an accurate or meaningful calculation of costs and benefits cannot if gaps are present in the data or no proof of causation exists. Without the ability to calculate epigenetic risk, on its own terms this model will not guide a determination of whether a particular policy choice is beneficial. Given the relatively new focus on the field of epigenetics and the countless number of exposures that can cause epigenetic markings, it is unlikely that one will see "conclusive scientific proof" that specific exposures definitively cause particular diseases.[160] Second, it is difficult to conceive of an interpersonal utility measure that adequately signifies the same degree of utility for disparate individuals. Assuming variable trade-offs and outcomes that could occur with epigenetic interventions, finding a way to assign utilities to all of these different outcomes that have universal and objective meaning would be a Sisyphean task. For instance, how does one measure the trade-off between the risk of slightly lower cognitive development versus a slightly higher risk of colon cancer: by cost of treatment, or by summing individual preferences between the two? Ultimately, the cost-benefit approach places the "burden of explanation" on the regulatory agency to justify its policy.[161] Therefore, if scientific proof is lacking or calculating utilities for disparate outcomes is not feasible, this model will not provide an answer. The result is that even if *qualitatively* there is evidence of grave and irreversible harm that could justify regulation, without the quantitative data backing up regulation, inaction is the likely result.

B. Precautionary Principle

The "precautionary principle" has emerged as the predominant guiding principle in almost every major international environmental and natural resource proposal or agreement.[162] The United Nations Rio Declaration on Environment and Development demonstrates how the precautionary principle is applied in practice – "[w]here there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."[163] Some have reduced this

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[160] Besides the complexity of exposures that can cause epigenetic modifications, another level of complexity is variation in genetic predispositions. That is, certain epigenetic markings or exposures almost certainly would not affect all populations equally.

[161] Graham, *supra* note 7.

[162] Garrett, *supra* note 116, at 519.

[163] United Nations Conference on Environment and Development, Rio de Janeiro, Braz., June 3-14, 1992, *Rio Declaration on Environment and Development*, ¶15, U.N. Doc A/CONF.151/26 (Aug. 12, 1992).

principle to the motto "better safe than sorry" or have described it as implementing a "'margin of safety' into public decisions, taking care to protect citizens against risks that cannot be established with certainty."[164] The antecedent of the precautionary principle is the German *vorsorgeprinzip* or "forecaring" principle. While the Germans' love of cars and beer is legendary, so is their passion for their beloved forests which were in danger of disappearing from "acid rain." Thus, in the 1970s, West Germany moved first to take decisive regulatory steps to combat acid rain even though its relation to deforestation was not empirically proven, only suspected. While varying definitions of the precautionary principle exist, its common understanding is that as the interactions between man-made activities and the natural world become more complex, any decision-making model that prevents action until conclusive scientific causation is established leaves society vulnerable to harm. However, despite its preeminence in international accords and its inclusion as "one of the most important ideas of 2001" in the *New York Times Magazine*, the precautionary principle has been largely rejected by Americans.[165] As Cass Sunstein states, "It has become standard to say that, with respect to risks, Europe and the United States can be distinguished along a single axis: Europe accepts the Precautionary Principle, and the United States does not."[166]

Sunstein in particular is associated with a vigorous critique of the precautionary principle. He contends that what people tend to take precautions against is very arbitrary and subject to certain cognitive biases.[167] But perhaps more importantly, Sunstein contends that if applied consistently as a norm, this principle is "paralyzing" and "stands as an obstacle to regulation, and nonregulation, and to everything in between."[168] Sunstein argues that if one truly takes precau-

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[164] Sunstein, *supra* note 8.

[165] *Id.*

[166] *Id.*

[167] Cass R. Sunstein, *Beyond the Precautionary Principle*, 151 U. PA. L. REV. 1003 (2003). According to Sunstein, the precautionary principle is particularly susceptible to the following cognitive biases: (1) availability heuristic; (2) probability neglect; (3) loss aversion; (4) benevolence of nature; and (5) system neglect.

[168] According to Cass Sunstein:

> This point makes the Precautionary Principle hard to implement, not merely where the regulation removes "opportunity benefits" or introduces or increases substitute risks, but in any case in which the regulation costs a significant amount. If this is so, the Precautionary Principle raises doubts about many regulations. If the principle argues against any action that carries a small risk of imposing significant harm, we should be reluctant to spend a lot of money to reduce risks, simply because those expenditures themselves carry risks. In this sense, the Precautionary Principle, taken for

tions against all risks, one should also be equally fearful of risks associated with regulation.[169] So how can the view that the precautionary principle is inherently paralyzing be reconciled with the fact that is has been used to justify substantial environmental and public safety regulations in the EU? The response would be that the EU's more intensive regulatory approach in these areas is based on the peculiar cognitive biases of what Europeans fear, not on a principled application of the precautionary approach.[170] However, even Sunstein acknowledges that experts analyze problems differently than lay people so presumably regulatory agencies, which are data-driven and reliant on experts, would not fall into the same trap of biased thinking as a layperson.[171] Further, it is not as if traditional cost-benefit data is ignored under the precautionary approach; presumably, as new data emerges, this information can be incorporated into the policies initiated under the precautionary approach.

C. Optimal Search

While the cost-benefit approach advocates for choosing the policy with the highest average utility, and the precautionary principle argues for a "better safe than sorry" approach, the optimal search method, under certain conditions, advocates selecting high-risk policies with the potential for the best outcomes even if the average utility is lower

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> all that it is worth, is paralyzing: It stands as an obstacle to regulation, and nonregulation, and to everything in between.

Sunstein, *supra* note 8, at 86.

[169] *See id.*

[170] For instance, Sunstein claims that the Europeans are much more concerned about genetically modified organisms (GMO's) and hormones in meat because they suffered through a mad-cow disease scare which was very prominent in their media and public debate (implicating the availability heuristic), but the U.S. is not as fearful as these products because we did not have a mad-cow scare. *See id.*

[171] In the words of Sunstein:

> Sometimes the precautionary principle has the appearance of being workable only because a subset of the relevant effects are "on-screen"–and, as a result, there seems to be no need to take precautions against other possible adverse effects, also involving health and safety, that do not register. An important aspect of system neglect is *tradeoff neglect*, one source of the conflict between experts and ordinary people in thinking about risks. When experts disagree with ordinary people about risks, it is sometimes because experts look at both the benefits and harms associated with the relevant practice, whereas ordinary people are paying attention to the harms but the not the benefits. I suggest that the precautionary principle seems appealing, to ordinary people, in large part for the same reason.

Sunstein, *supra* note 167, at 1010.

than less risky policies.[172] The primary drawbacks of this particular recommendation are the possibility of discovering flaws after a policy is implemented and the inability to reverse its effects. However, if a high-risk policy fails and its effects are reversible, it can be quickly abandoned for a policy with the highest average outcomes (i.e., less risky) and one would not suffer any long-term consequences. But if the high-risk policy is a success, then its benefits can be adopted and no search is needed for an alternative plan. If policymakers choose the low-risk policy with higher average outcomes in the first instance, then the possibility of achieving more optimal outcomes is precluded. After all, if the low-risk plan confers some net benefit, political inertia would make it less likely that this plan would be abandoned for a more risky option. To the extent a policy is irreversible, uncertainty becomes a liability as a potentially a low-benefit outcome might be cemented in place. In other words, the less one is able to undo the effects of a policy, the more costly the risk becomes in one's policy calculus. Thus, a major limitation of the optimal search framework is that it is highly dependent on choices that are reversible and hence is not universally applicable.

D. Applying the Three Decision Making Models to Ireland's Folic Acid Debate

A national controversy with profound legal and ethical implications is currently raging in Ireland. Most policymakers, however, are unaware of the epigenetic implications of this debate. Explicitly, the policy debate focuses on whether the Irish government should mandate the fortification of flour with folic acid. Giving folic acid to pregnant women is a highly effective means of preventing neural tube defects (NTDs) such as spina bifida and anencephaly in children.[173] However, the folic acid must be consumed four weeks prior to conception and for twelve weeks after conception to achieve this protec-

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[172] *See generally* Yair Listokin, *Learning Through Policy Variation*, 118 YALE L.J. 480 (2008) (arguing the utility of policy variance depends upon the reversibility of the policy).

[173] Spina bifida is a condition where the vertebrae do not fully form a ring around the spinal cord, so that some of the spinal cord or its surrounding membrane sticks out through this opening. *See* Nat'l Inst. of Neurological Disorders & Stroke, Nat'l Inst. of Health, *NINDS Spina Bifida Information Page* (2007), http://www.ninds.nih.gov/disorders/spina_bifida/spina_bifida.htm. Anencephaly is a condition where the higher brain is not formed and only a brain stem. Most of these fetuses are stillborn or spontaneously aborted. In the case of live birth, anencephalic infants have a very short life span typically of a few hours or days. *See* Nat'l Inst. of Neurological Disorders & Stroke, Nat'l Inst. of Health, *NINDS Anencephaly Information Page* (2009), http://www.ninds.nih.gov/disorders/anencephaly/anencephaly.htm.

tive effect.[174] In other words, giving women folic acid only after they discover their pregnancy is akin to closing the barn door after the horse has escaped. As it stands, Ireland has one of the highest rates of NTDs in the developed world for several reasons. First, unlike the United States and Canada, Ireland does not mandate that its flour supply be fortified with folic acid. Second, a very high percentage of pregnancies in Ireland are unplanned (fifty-five percent). And third, elective abortions are illegal in Ireland.

In 2004, Ireland established the National Committee on Folic Acid Fortification (NCFAF). The group was tasked with analyzing three policy choices.[175] The first option presented was structured voluntary fortification. In this case, flour millers and bakers would be legally permitted to voluntarily add specified amounts of folic acid and then carry a special logo and health claim on their product. The second option was mandatory fortification imposed upon bakers and flour millers. The third option was to continue with the current practice of not fortifying flour, but to engage in public health education campaigns to urge women to take folic acid supplements and eat a folate-rich diet.

A policy of mandating folic acid fortification demonstrably reduces NTDs. For instance, Newfoundland reduced its NTD rate by seventy-eight percent after Canada (and the United States) mandated flour fortification in 1996.[176] The NCFAF also considered that, in Ireland, formal campaigns since 1993 advising women to take folic acid have been met with little success. In 2006, the NCFAF recommended the implementation of the second option, mandatory fortification. However, this policy recommendation has yet to be enacted by the Food Safety Authority of Ireland (FSAI), so *de facto*, the third option of maintaining the status quo is in force. Why has the FSAI failed to act on a policy that is recommended by an expert panel and has strong empirical evidence supporting its intended goal? Unfortunately, recent studies have raised the specter that folic acid can increase the risk of human cancers of the colon, breast, and prostate. As a result, the FSAI has received considerable pushback against mandatory fortification from both the Irish food industry, which is concerned

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[174] FOOD SAFETY AUTH. OF IR., PUBLIC'S VIEWS SOUGHT ON FOLIC ACID FORTIFICATION – FOLIC ACID TODAY AND EVERYDAY – POLICY OPTIONS BEING CONSIDERED (Mar. 21, 2005), http://www.folicacid.ie/press/press_20050321.html.

[175] FOOD SAFETY AUTH. OF IR., NATIONAL COMMITTEE ON FOLIC ACID FOOD FORTIFICATION, http://www.folicacid.ed/nat_comm.html (last visited May 3, 2010).

[176] PUB. HEALTH AGENCY OF CAN., EVALUATION OF FOOD FORTIFICATION WITH FOLIC ACID FOR THE PRIMARY PREVENTION OF NEURAL TUB DEFECTS, http://www.phac-aspc.gc.ca/publicat/faaf/chap5-eng.php (last visited May 3, 2010).

about liability, and consumers who are wary of the reported cancer risk.[177]

In general, the studies showing a link between folic acid and cancer are not conclusive and indeed some studies show that folic acid may protect against cancer.[178] As discussed above in Section I, folic acid has significant epigenetic effects because it is a methyl-donor, leading to the hypermethylation of DNA. Recalling Jirtle's mice experiment, it was the mother's folate-rich diet that was responsible for shutting off the harmful *agouti* gene and that shut-off then resulted in a dramatic improvement for these mice "predestined" to die an early death. However, does folic acid "know" only to turn off harmful genes and to not turn off beneficial genes? Of course, there is no intentionality behind this process, meaning that one can logically expect that hypermethylation caused by folic acid might turn off beneficial genes as well. One also has to consider that the impact of shutting down a particular gene varies temporally within the life-cycle of an individual.[179] For example, the p53 gene is important in preventing cancer and suppressing the growth of tumors, which it accomplishes by activating DNA repair proteins.[180] This process of DNA repair is more important as one ages, as DNA errors from repeated replication or sustained environmental damage add up over a lifetime. Thus, for preventing cancers associated with increased age, like colon, breast, or prostate cancer, any deactivation of the p53 gene would be a serious problem. This effect may partially account for the correlation between folic acid consumption and cancers developed later in life.

So how should Ireland resolve this epigenetic debate? Applying the cost-benefit model does not seem to provide an answer because while researchers good data regarding the benefits of folic acid fortification (reduced NTDs), the costs (i.e., increased cancer risk) are

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[177] *See generally* Claire O'Connell, *Folic Acid Delay "Unreasonable"*, IRISH TIMES, July 8, 2008, at Health 2 (reporting on researchers' in Ireland calling for mandatory fortification of flour with folic acid, and the Food Safety Authority of Ireland's position on the matter).

[178] For instance, one study reported the chance of developing colorectal cancer was lowered by forty percent in women with the highest folate intake compared to those with the lowest intake. *See* Paul Terry et al., *Dietary Intake of Folic Acid and Colorectal Cancer Risk in a Cohort of Women*, 97 INT'L J. CANCER 864, 866 (2002).

[179] *See* SCIENCEDAILY, *Health Benefits, Consequences of Folic Acid Dependent On Circumstances,* Apr. 5, 2009, http://www.sciencedaily.com/releases/2009/04/090401134421.htm ("Thus, folate appears to assume different guises depending on the circumstances. The level of intake of this micronutrient that is safe for one person may be potentially harmful to another.").

[180] Yuangang Liu & Molly Kulesz-Martin, *P53 Protein at the Hub of Cellular DNA Damage Response Pathways Through Sequence-Specific and Non-Sequence-Specific DNA Binding,* 22 CARCINOGENESIS 851, 851-60 (2001).

uncertain and unquantifiable at the moment. Therefore, without the ability to conduct this balancing, this model does not provide an answer. Assuming hypothetically that the cancer risk from folic acid supplementation can be quantified, policymakers would still face the challenge of generating an interpersonally comparable utility value to compare the risk of NTDs with the risk of cancer.[181] Does one compare the financial costs of treating a child with spina bifida versus an adult with colon cancer? Some children with spina bifida die very young, so the overall financial cost of treatment might be lower than someone undergoing multiple cancer treatments. Does one compare lost productivity? If a fifty year old employed person develops colon cancer, the loss in productivity can be great. Most children with spina bifida have below average I.Q.'s and require special education – does one measure their lost productivity assuming they would have average I.Q. and be gainfully employed? Maybe the conundrum of establishing interpersonally comparable value can be avoided by asking how much money people would be willing to pay to avoid NTD or different cancers.[182] These individual subjective preferences can then be summed up, and the policy choice with highest net benefits would be chosen. For Irish citizens, this calculus would obviously be different depending on whether a person is expecting to have a child. However, the majority of pregnancies in Ireland are unplanned, and generally speaking, an individual's desire to have children might vary greatly during their span of reproductive years. Thus, even assuming reliable cancer data, this model may not provide a satisfactory policy choice.

Does the precautionary approach provide better guidance for Ireland? In this particular instance, Sunstein's critique of the precautionary approach as paralyzing has some validity. If one wants to focus on taking precautions against NTDs, then one would choose the mandatory folic acid fortification option. But if one is more concerned about taking precautions against cancer risk, then one would

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[181] One of the persisting critiques of utilitarian analysis is that individual preferences are highly subjective and creating utility values that have the same meaning or value to disparate individuals is impossible to accomplish.

[182] *See* Graham, *supra* note 7, 410-11 (Willingness to pay (WTP) and willingness to accept (WTA) are used in the Kaldor-Hicks model of cost-benefit analysis: "[Kaldor-Hicks] is implemented through the use of [WTP] money as the measure of social benefit (B) and [WTA] money as the measure of social cost (C). If an individual expects a regulation to be beneficial to her, WTP is positive. If another individual expects to be harmed by regulation, her WTA will be positive. Citizens who are indifferent (or who perceive that gains equal losses) do not influence the benefit-cost calculation. When multiple regulatory alternatives are compared, the preferred alternative is the one that maximizes net benefits, defined as the sum of B minus the sum of C across all citizens in society.").

reject this option and instead choose the voluntary fortification or the status quo. Being generally precautious would lead to fear of both types of harms which in turn would lead to a policy stalemate. This scenario is what seems to be happening in Ireland, where strong opposing opinions have led to a non-policy for the time being.[183]

As discussed above, the optimal search method argues for choosing policies with a high degree of variability *if* the effects of the policy can be reversed. Compelling scientific data suggests that epigenetic markings associated with blood and solid tumor cancers can be reversed – this evidence has already led to FDA approval of the first anti-cancer epigenetic drug, azacitidine.[184] As one ages, cancer rates stemming from epigenetic risk increases because of a possible excess accumulation of folic acid in our diet, nutritional or pharmaceutical interventions like azacitidine may reverse this risk. However, once an individual is born with spina bifida or some other condition that impairs early mental and physical development, these impairments are mostly irreversible through epigenetics or other means.

Without any pretense of empirical precision or units, *Figure 1* conceptually represents the choices Ireland faces in graphical form. On the y-axis, welfare or benefit is formed by the sum of the risks of NTDs and cancer stemming from a particular folic acid fortification policy. The x-axis is time. The middle solid line represents the baseline or the status quo policy. Given the *a priori* uncertainty regarding cancer risk, the dotted lines around the solid line represent the potential range of welfare values that can occur from either the lower-risk

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[183] As the Irish Times reported:

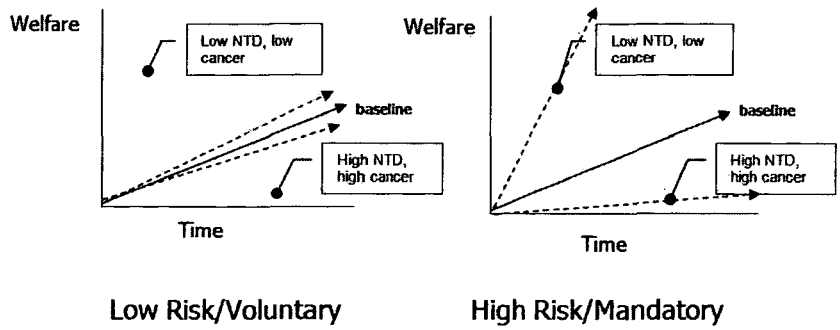
> Director of the Boyne Research Institute (BRI), Dr. Julianne Byrne, has said that she finds the apparent delay in the introduction of mandatory folic acid fortification "unreasonable," because the weight of scientific evidence shows that it protects against most cases of neural tube defects (NTD) . . . . She also questioned the validity of reported links between folic acid supplementation and colorectal cancer. Alan Reilly, deputy chief executive of the FSAI, said decisions about how to proceed with the fortification here would be made on "rock-solid ground."

O'Connell, *supra* note 177.

[184] *See* Medical News Today, *Pharmion Corporation Announces FDA Approval of Vidaza NDA Supplement for IV Administration*, http://www.medicalnews today.com/articles/61849.php ("Azacitidine is the first of a new class of anti-cancer compounds called epigenetic therapies . . . . Epigenetics refers to changes in the regulation of gene expression. Epigenetic changes can silence gene expression and, unlike DNA mutations, may be reversed by targeting the enzymes involved . . . . The epigenetic approach to cancer therapy is that rather than using molecules that kill both normal and tumor cells, the silenced genes are reactivated through targeted epigenetic therapy, re-establishing the cancer cell's natural mechanisms to control abnormal growth.") (last visited May 3, 2010).

voluntary fortification policy or the higher-risk mandatory fortification policy. The voluntary fortification policy is characterized as a lower-risk policy because it represents a smaller deviation from the baseline. Given this, one would expect that both the upside benefit (area between baseline and upper dotted line) and the downside risk (area between the baseline and lower dotted line) for this policy to be smaller than the mandatory fortification policy. Looking at the problem this way, how should a policymaker choose? If our bias is to be risk-averse and avoid large downside risk, the voluntary fortification option seems wise. However, the optimal search method would argue for choosing the mandatory fortification option with its inherently more variable outcomes. If one picks the voluntary option, one is forgoing the opportunity of reaching the higher welfare points available in the mandatory option; namely, very low NTD with no increase in cancer. The avoidance of NTD will then be locked in for an individual's lifetime. If one later learns more information to support that the mandatory folic acid fortification policy causes an unacceptable cancer risk and puts society way below the baseline, one can simply reverse the policy and possibly reverse the cancer risk while still retaining the NTD prevention. Therefore, unlike the cost-benefit and precautionary approach, the optimal search method provides a way through this impasse and a clear policy choice.

Figure 1. Voluntary vs. Mandatory Folate Fortification vs. Human Capabilities



While the optimal search method might provide a compelling choice in the abstract, advocating a policy that admittedly might increase the cancer risk for many citizens is not a politically satisfying narrative. In other words, the optimal search method is a useful heuristic under the conditions described above (reversibility, learning), but it is less helpful when reversibility is not likely, and by itself, it

provides a normatively shallow justification for distributing epigenetic benefits on some and harms on others.

On the other hand, incorporating the CA into this discussion leads one to a consistent and compelling normative framework for epigenetic policymaking. Considering the cost-benefit and optimal search methods, for reasons discussed above, one has to be wary about solely relying on utilitarian calculations to guide one's regulatory choices. Additionally, given the types of questions the CA asks policymakers to address, paralysis may not ensue in the face of tough choices as with the precautionary approach. Under the CA, not all epigenetic risks are qualitatively equal as they raise very disparate normative concerns. For instance, epigenetic risks associated with the development of cognitive disabilities would trigger more concern under the CA than epigenetic risks associated with the development of prostate cancer. The priority would remain the same even if societal cost and number of afflicted people was greater for prostate cancer compared to cognitive disabilities.

The critical difference between the two is that the impact of cognitive disabilities can severely limit the ability to make free choices about one's life's direction. Thus, despite educational efforts or some other remediation, a ceiling already has been placed on one's potential opportunities. In contrast, prostate cancer represents qualitatively different concerns.[185] It is estimated that 37,000 men in the United States die annually from prostate cancer and that treatment costs exceed $5 billion per year.[186] The costs associated with this disease are clearly substantial. However, incidence of prostate cancer is rare before the age of fifty-five, and most men who have prostate cancer die with it, not from it.[187] In fact, the National Cancer Institute estimates that over half of all men in the United States will have some cancer in their prostate glands by the age of eighty.[188] Viewed another way, while prostate cancer is definitely a serious and costly disease on a societal and individual level, it is not the type of impairment that deprives a person of most life opportunities or free choice, which are

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[185] The intent of this example is not to minimize the pain and suffering of prostate cancer victims and their families. Rather, the intent is to show that even for such a serious disease, the CA prompts us to ask different questions than a utilitarian approach.

[186] This places prostate cancer among the top three most costly cancers to treat, along with lung and breast cancer.

[187] NAT'L CANCER INST., U.S. DEP'T OF HEALTH & HUMAN SERVS., UNDERSTANDING PROSTATE CHANGES: A HEALTH GUIDE FOR MEN 17 (2009), http://www.cancer.gov/PDF/4dba13db-81fb-4d8d-9c2d-d0c00a048f57/prostate_booklet.pdf.

[188] *Id.*

prime concerns of the CA. Returning to the Ireland folic acid debate, combining the optimal search method approach with the CA provides policymakers with both a persuasive technocratic (optimal search) and principled normative (CA) argument to push forward with mandatory fortification of flour with folic acid.

Justice concerns are paramount to the CA, especially considerations of equitable distribution of harms and benefits. The CA incorporates the Kantian principle of treating every person as an end in herself. Thus, one might argue that a mandatory fortification policy violates the CA because putative infants seemingly gain a benefit at the expense of the elderly (if the harmful effects of surplus folic acid are not reversible for the elderly). However, viewed from a holistic life-cycle perspective, infants will eventually become old so they are sharing in the burdens of this policy as well. Therefore, if nobody is selected for differential epigenetic risk during a lifetime, equitable concerns are mitigated as the risk would be diffuse and spread nearly evenly across society. One's concern would then turn to whether having this particular consumer good, with its attendant epigenetic risk, either enhanced or limited our capabilities. If a particular epigenetic risk, however, was non-randomly distributed among the population, then the CA would be violated. For example, if an epigenetic pollutant was spread locally from a certain type of industrial plant located near lower-income or minority neighborhoods (a situation which is exceedingly common), the CA would be concerned that society was imposing such costs in a discriminatory manner – even if this activity provided a tremendous amount of benefit to most members of society. Returning to the Irish folic acid debate, the mandatory fortification option satisfies the justice concerns of the CA because even if this policy leads to increased cancer risk, no individuals or groups are being singled out to shoulder this burden disproportionately.

VI. ADAPTIVE KNOWLEDGE FORCING REGULATORY FRAMEWORK

There is a clear logic to Judge Posner's dictum that "law lags science; it does not lead it," in the context of courtroom proceedings.[189] Society would probably not benefit from generalist jurists *de facto* creating scientific policies from the bench and in essence arbitrarily determining the legitimacy of competing scientific theories. However, does it follow that policymakers must also lag behind until

[189] Rosen v. Ciba-Geigy Corp., 78 F.3d 316, 319 (7th Cir. 1996) ("But the courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it.").

scientific research develops definitive answers? This appears to be the conclusion of those who favor a "rationalist" approach based on quantifiable costs and benefits. Their implicit view is that science will tell society the correct course in due time. However, science is not an anthropomorphic being; it does not "tell" anything. Scientific data has no meaning until one interprets it, and such interpretations are inevitably packed with qualitative judgments. For instance, "relative risk" is an epidemiological ratio that represents probability of an event (e.g., disease) occurring to a group exposed to an agent versus a non-exposed control group. A relative risk of 1.0 means there is no difference in observed risk between the exposed and control group.[190] A relative risk of 2.0 indicates a doubling of observed risk in the exposed group, meaning that "the [exposure] agent is responsible for an equal number of cases of disease as all other background causes."[191] By legal and medical convention, a relative risk of at least 2.0 is considered the threshold where science tells us there is "proof" of causation.[192] But what if the relative risk is 1.9? Does this mean that science is telling us we do not have to worry about this particular substance? Considering the myriad of chemical agents one is exposed to on a daily basis along with the increasing recognition of the multifactorial nature of disease causation, the less likely any medical expert is able to demonstrate the "magic" relative risk of 2.0 for contracting a disease based upon any one particular chemical exposure.

Of course, in the realm of policymaking for public health and safety, scientific research should guide our decisions. However, one cannot lose sight of the fact that many of the scientific norms that have developed regarding causation (e.g., relative risk of 2.0 at a ninety-five percent confidence interval) are somewhat arbitrary, and failing to meet these thresholds should not be taken as "rational barriers" to policies or interventions. Further, if one takes a laissez-faire attitude towards manufacturers developing scientific data about the

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[190] FED. JUDICIAL CTR., REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 384 (2d. ed. 2000).

[191] *Id.* (discussing the relative risk: "The threshold for concluding that an agent was more likely than not the cause of an individual's disease is a relative risk greater than 2.0. Recall that a relative risk of 1.0 means that the agent has no effect on the incidence of disease. When the relative risk reaches 2.0, the agent is responsible for an equal number of cases of disease as all other background causes. Thus, a relative risk of 2.0 (with certain qualifications noted below) implies a 50 percent likelihood that an exposed individual's disease was caused by the agent. A relative risk greater than 2.0 would permit an inference that an individual plaintiff's disease was more likely than not caused by the implicated agent. A substantial number of courts in a variety of toxic substances cases have accepted this reasoning.").

[192] *Id.*

safety of their products, does this not mean regulations are held hostage to one's willful ignorance? Instead of having policies that either lag behind science or try to lead it, why not have a policy that actively pushes scientific knowledge forward? In other words, regulators should advocate a policy that forces knowledge generation from manufacturers.

A major barrier for enacting a regulatory system to control epigenetic harm is lack of specific epigenetic risk profiles for almost all manufactured products and activities. So how can we overcome this ignorance? As discussed above, with a few exceptions like regulations stemming from the FDCA, FIFRA, and clean air and water bills,[193] corporations are usually not required to provide information on the impacts of their products or activities. The predominant regulatory scheme of cost-benefit analysis in the United States has *de facto* placed the cost of uncertainty on the public and has granted firms the right to externalize harm when the public is unable to demonstrate that the alleged harm outweighs the benefit. This allocation of burden related to the knowledge of harms does not make sense when one knows that producers possess superior information and ability to generate such information.[194]

Politically it is not viable, nor does it seem appropriate, to place the burden of *general* epigenetic safety research on manufacturers. Much the same way the government subsidized general knowledge involving computers, the Internet, and the Human Genome Project, it seems that the United States and other developed nations have an imperative to finance research in the area of epigenetics. To help prioritize which general classes of substances should be focused on, a new epigenetics agency or division, similar to the Agency for Toxic Substances and Disease Registry (ATSDR), can be established. The federal government established the ATSDR under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA) and tasked it with assessing public health and safety issues stemming from hazardous substances and toxic waste sites.[195]

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[193] For example, under California's Safe Drinking Water and Toxic Enforcement Act (1986), where there is evidence that certain toxins can cause cancer or harmful reproductive effects, the burden is not on the state regulatory agency to prove that the substances are harmful, but rather on the industry to prove that the chemicals pose, "no significant risk (for cancer), or [is] sufficiently below the no observable effect level (reproductive toxins)." Garrett, *supra* note 116, at 545.

[194] *Id.* at 557.

[195] *The Agency for Toxic Substances and Disease Registry (ATSDR): Problems in the Past, Potential for the Future?: Hearing Before the H.R. Subcomm on Investigations & Oversight*, Mar. 12, 2009, http://democrats.science.house.gov/Media/File/Commdocs/hearings/2009/Oversight/12mar/Hearing_Charter.pdf.

However, the House Science Committee, Subcommittee on Investigations and Oversight, issued a recent report highly critical of the ATSDR:

> Time and time again ATSDR appears to avoid clearly and directly confronting the most obvious toxic culprits that harm the health of local communities throughout the nation. Instead, they deny, delay, minimize, trivialize or ignore legitimate concerns and health considerations of local communities and well respected scientists and medical professionals.[196]

Further, Committee Chairman, Congressman Brad Miller accused the ATSDR of practicing bad science and having, "a keenness to please industries and government agencies that prefer to minimize public health consequences of environmental exposures."[197]

Agency capture and bad science is always a concern with government regulators. One possible solution is to invite early involvement of the Institute of Medicine (IOM) and task it with forming a panel of experts to evaluate the nature of epigenetic risk and to help set priorities upon which substance classes to focus.[198] The IOM has proven to be a credible source of advice, utilizing doctors, statisticians, economists, and other researchers to establish scientific and policy consensus on complex issues such as Agent Orange, breast implants, and vaccine injuries.[199] Further, since the IOM is outside of

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[196] *Id.*

[197] Rita Beamish, *Agency to Improve Reporting of Neighborhood Toxics*, ASSOCIATED PRESS, Mar. 12, 2009, http://abcnews.go.com/Politics/wireStory?id=7070328.

[198] John Graham, former head of the Office of Information Regulatory Affairs (OIRA) under President George W. Bush, advances the argument of using the IOM to help set regulatory agencies' priorities. *See* Graham, *supra* note 7, 530 ("Justice Stephen Breyer has suggested that a small cadre of lifesaving specialists be housed inside the Executive Office of the President and granted vast priority-setting powers. Professor Sunstein has advocated that OIRA become more involved in priority setting. Although these ideas are certainly worth exploring, I believe that part of the solution must come from a credible source outside of government [referring to the IOM].") Inst. of Med., About the IOM, http://www.iom.edu/About-IOM.aspx (last visited May 3, 2010) (describing the IOM mission as follows: "The Institute of Medicine serves as adviser to the nation to improve health. Established in 1970 as the health arm of the National Academy of Sciences, the Institute of Medicine is a nonprofit organization that works outside of government to provide unbiased and authoritative advice to decision makers and the public.").

[199] During private practice as a products liability litigator and as an intern at the Federal Judicial Center, I dealt with Agent Orange, breast implants, and vaccine injury litigation, and frequently relied on IOM reports as objective, scientific consensus statements on these topics.

government and vets its experts for issue neutrality (meaning that the experts are not involved with industry or litigation on a particular issue), the IOM is sheltered from political and industry pressures.[200] The IOM's recommendations can then help set out the initial tasks of this new epigenetic agency.

Once researchers have developed a core of epigenetic knowledge that allows them to accurately predict the types and probabilities of certain diseases related to epigenetic mechanisms, it seems entirely appropriate to shift the burden of providing *specific* epigenetic safety data onto manufacturers. The onus of uncertain risk should not be placed on diffuse consumers who are in no position to generate such information. In the context of epigenetic harm, as the scientific community continually learn more about this process and particularized risks, administrative agencies can adjust the intensity of regulations based upon the particular knowledge level of any given substance. As discussed below, the framework I suggest would have four different levels of regulations that are adaptive to researchers' understanding of epigenetic harm and its effect on human health and capabilities: (i) disclosure; (ii) labeling; (iii) epigenetic tax and permit system; and (iv) restricted uses or total ban. By adopting an iterative and sliding-scale approach, this framework respects the need to ground regulations upon scientific findings, but rejects a binary approach that imagines only action or inaction based upon the presence or absence of scientific proof.

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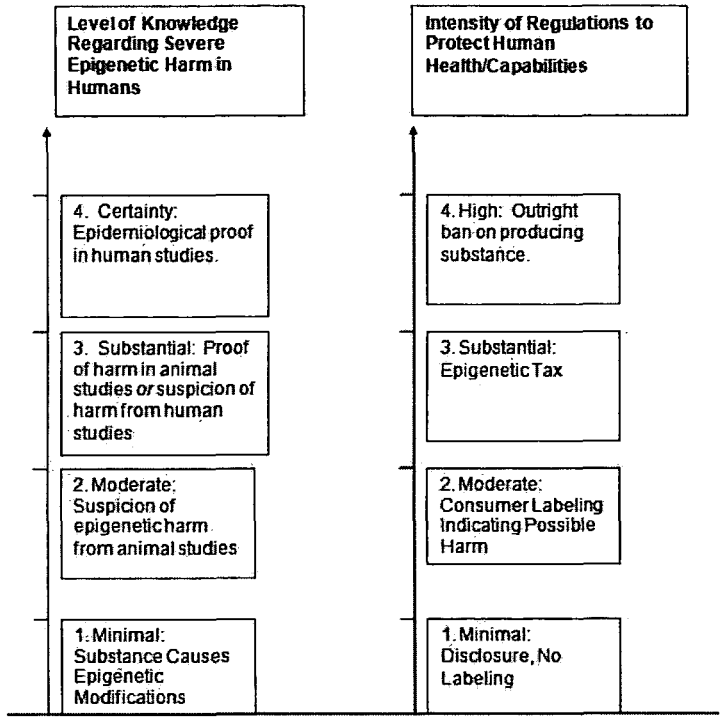
[200] *See* Inst. of Med., *supra* note 198.

Figure 2. Adaptive Regulatory Framework



A. Level 1: Disclosure Standard

Paracelsus was a chemist and physician in the 1500s and is considered the father of toxicology, the study of poisons. He is often quoted for the dictum, "dose makes the poison," which remains one of the bedrock principles of toxicology. In other words, any substances, even those seen as innocuous, can be harmful in a great enough dose. Thus, fresh water can be poisonous in large enough doses, causing seizures and even death.[201] Going back to Jirtle's *agouti* mice experiment (discussed *supra*), the dose of folate rich foods proved to be very beneficial to those particular mice, turning off the effect of a harmful gene. However, recalling the Ireland folate supplementation debate, the fear is that while a little folate might be beneficial, too much of this substance might turn off helpful tumor suppressor genes

[201] *See* Melissa Conrad Stöppler, Hyponatremia (Low Blood Sodium), http://www.medicinenet.com/hyponatremia/article.htm (last visited May 3, 2010).

and increase the risk of certain cancers – hence, dose determines whether the substance is helpful or harmful.

Therefore, an important threshold question, regarding chemicals and consumer products, is whether such substances cause significant epigenetic markings or modifications. The ability of a substance to cause epigenetic marking is not an indication of harm *per se*, and might even prove beneficial, as in the *agouti* experiment. However, for an individual, it would be important to know if one was accumulating too great a dose of any particular type of epigenetic marking from an overall combination of substances. In the same way that an Ames test provides an inexpensive and quick way to assay whether a substance has mutagenic potential (and hence cancer-causing potential),[202] it is not difficult to imagine that a similar testing model can be developed to measure the potential of a substance to cause epigenetic modifications. Positive evidence of epigenetic modifications could then indicate the need for more robust testing in animal models.

Under my proposal, the burden to demonstrate the extent of epigenetic modifications a chemical substance causes would be placed on manufacturers. This information would then be required to be disclosed to the appropriate government regulatory agency.[203] This regulatory approach would be consonant with the EU's regulation of manufactured chemicals, the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), which was adopted in December 2006.[204] The goal of REACH is to "provide a high level of protection of human health and the environment through earlier and improved identification of the inherent properties of chemical sub-

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[202] The Ames test was developed in the 1950's by University of California Berkeley researcher Bruce Ames. The test uses a strain of *salmonella* bacteria that can be grown cheaply, yielding results in only one day. Bruce N. Ames et al., *An Improved Bacterial Test System for the Detection and Classification of Mutagens and Carcinogens*, 70 PROC. NAT'L ACAD. SCI. 782 (1973).

[203] Rather than relying on manufacturers own tests which might be subject to bias or obfuscation, the government can require testing be done by certified labs which are audited by the government. As illustrated by the Georgia peanut scandal, relying on private testing facilities that are not overseen by the government can be problematic as manufacturers might direct their business to labs that will give them favorable results, thus creating incentives for labs to perhaps have lax standards if they are not subject to oversight. Another tactic used by the offending peanut manufacturer was to not report repeated test results that showed presence of salmonella and only report tests that were negative. *See* Lyndsey Layton, *Peanut Processor Knowingly Sold Tainted Products*, WASH. POST, Jan. 28, 2009, at A1. A regulation that took away discretion from manufacturers from selectively reporting test results and made disclosure of all tests by certified labs to the government mandatory could solve this "cherry-picking" problem.

[204] *See generally* Council Regulation 1907/2006, 2006 O.J. (L 396) 1 (EC).

stances."[205] The mantra of REACH is "no data, no market," meaning all chemicals must be registered in order to be merchantable in the EU.[206] REACH not only targets substances in isolation, but also in compounds and articles containing chemical substances where it is foreseeable that such substances will be released during normal usage.[207] What if multiple companies make the same chemical – do these companies need duplicative laboratory and animal tests? REACH allows for substance information exchange forums (SIEF) to be set up so that companies can voluntarily share data on identical substances. In the case of animal testing, REACH mandates information-sharing in order to reduce redundancy of these tests.[208] As discussed above, it is clear that U.S. regulatory agencies have the potential legal authority to shift the burden of testing onto manufacturers in a regime similar to REACH and could mandate the generation of basic epigenetic information.

Once an epigenetic profile of a substance is generated, should this information be required on a product's label? The appropriate answer seems to be "no." In the abstract, this information is likely not useful to the average consumer and might only cause fear and confusion in consumers should they automatically assume that epigenetic markings are *per se* harmful.[209] This information is most helpful and important to regulatory agencies for consideration of how much follow-up testing should be done on particular substances. Analogizing to the Ames test, a positive result on this assay does not mean that a substance is necessarily carcinogenic and a negative test does not mean that a substance is not carcinogenic. However, the Ames test has proven to be a helpful screen in identifying potential carcinogens which would indicate the need for further in-depth testing. The epigenetic equivalent of the Ames test should be viewed in the same manner.

The case for regulating manufactured chemicals which cause epigenetic changes seems clear, but what about "natural" substances like

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[205] Isabelle Laborde, *REACH: The New European Union Chemicals Regulations*, 23 NAT. RESOURCES & ENV'T 63, 63 (2009).

[206] *Id.*

[207] *Id.* at 63-64. This regulation also applies to chemicals manufactured for export only to rebut charges that this is a protectionist scheme by the EU. For US manufacturers, falling behind this standard could prove costly and limit their overall market access, in the same manner that falling behind higher fuel standards in the rest of the world crippled the competitiveness of American car manufacturers.

[208] *Id.* at 64.

[209] As behavioral scientists have noted, providing more information does not always lead to better understanding by the recipient as the individual might experience "cognitive dissonance," or difficulty in incorporating new information that does not correspond to their previous understanding.

food products? Should regulators punt on epigenetic regulation of these substances and only focus on synthetic chemicals? As Sunstein points out in his critique of the precautionary principle, the reason many view artificial or processed substances as being less safe than natural substances is due to the cognitive bias of believing in the "benevolence of nature."[210] However, we know that many natural products can be harmful; for example, tuna may harm pregnant women (due to high mercury content) and natural licorice can cause severe hypertension and potassium deficiency.

One response might be that traditional food products have become "traditional" through a natural process of empiricism. That is, for thousands of years, humans have been figuring out what is safe and not safe to ingest or put on their body by trial and error. Thus, an underlying logic justifies trusting the safety of natural products as opposed to newer synthetic products. However, going back to Jirtle's *agouti* mice experiment, the dramatic change in epigenetic programming that he accomplished was not through administration of complex synthetic compounds, but through simple vegetables like onions, beets, and leafy vegetables. Therefore, there is a serious rationale to generate more knowledge about the epigenetic effects of everyday foodstuffs. The question then becomes "who should be responsible for generating epigenetic safety information regarding food products?" Should a small family farm have the same burden placed on it as industrial food giants like Con-Agra or Archer Daniels Midland? Here it seems more efficient and practical to have the U.S. Department of Agriculture perform testing on bulk distributors of fruits, vegetables, grains, and meats, and to exempt smaller farms from such requirements.[211] However, for processed or packaged food companies, it is rational to place this burden on them, as Company A might process their creamed corn in a completely different manner than Company B. This would add a *de minimis* burden, as food companies already are required to test the general safety of their products.

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[210] *See* Sunstein, *supra* note 167.

[211] It is common for public health regulations, such as nutritional labeling requirements for restaurants, to distinguish between large and small business operators. *See* New York State Rest. Ass'n v. New York City Bd. of Health 556 F.3d 114, 121 (2d Cir. 2009) (The court upheld state law mandating the chain restaurants provide nutritional information to customers. The law did not apply to smaller, non-chain restaurants.).

B. Level 2: Labeling Standard

Once researchers can publish data in peer-reviewed journals that a substance can cause epigenetic harm in something more robust than a simple petri dish assay, such as in more than one species of laboratory animal, then it seems warranted for an epigenetic risk agency to require labeling of their products to state this result. The labeling statement can be as simple as "Animal Studies have demonstrated evidence of epigenetic harm caused by this product." If manufacturers can reference or conduct independent human epidemiological studies that do not demonstrate evidence of harm, then manufacturers could add the truthful disclaimer that evidence of harm in human studies has not yet been established. The intent of allowing this disclaimer is that it provides manufacturers with an incentive to fund independent research on human populations.

One response might be that, even without the human studies disclaimer, labels are an inherently weak form of regulation, and allowing disclaimers makes the labels even weaker.[212] However, the virtue of standards one and two under this framework is that they intentionally do not exert a very powerful effect. Stronger measures that could drastically reduce or eliminate the viability of products would be difficult to justify given that the evidence of harm contemplated to trigger these measures is also comparatively weak. So what is the point of having intentionally weak regulations? The value of such regulations is the provision of early notice to manufacturers and end-users that they might want to start considering the development or use of alternative products. This scheme should mitigate the "no suitable alternative" problem highlighted in the EPA's attempt to ban asbestos.[213]

C. Level 3: Epigenetic Tax and Permit System to Protect Human Capabilities

The tort system is predictably ill-suited to regulate epigenetic harm, and a purely utilitarian regulatory scheme fails to address qualitative differences in epigenetic harm. So how can one practically address the problem of epigenetic risk? Under Nussbaum's conception of the CA, the general way to formulate policy questions is to ask what one values and seek to protect through collective action:

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[212] *See* John Abramson, *The Reliability of Our Medical Knowledge as a Product of Industry Relationships*, 35 HOFSTRA L. REV. 691, 697-98 (2006).

[213] *See* Corrosion Proof Fittings v. EPA, 947 F.2d 1201, 1215-17 (5th Cir. 1991).

> In all cases, however, a political scheme will not realize the goals of the CA unless it identifies a core group of entitlements that deserve to be protected stably, regardless of majority whim, and then asks carefully whether people face unequal obstacles to the enjoyment of their basic entitlements, devoting particular attention to traditionally disadvantaged groups.[214]

As Nussbaum explains, the CA suggests that the government make a "short list" of individual entitlements or capabilities that will be protected equally for all citizens.[215] Ensuring adequate education, healthcare, and political liberty are typical entitlements put forth by CA proponents. Using this list, one can prioritize which epigenetic harms pose the greatest threat to developing our human capabilities and which harms are inequitably distributed. Then one can attach greater penalties (taxes) or barriers (permits) to producers of epigenetic harm that undermines our human capabilities or to producers of harm that disparately impacts some discrete group. In this way, an epigenetic regulatory agency can calibrate a tax and permit system to reflect qualitative decisions to protect capabilities in an equitable and non-arbitrary fashion.

The government can set up a permit scheme based upon a manufacturer's ability to disclose epigenetic risk data about its products or activities. Thus, development and disclosure of epigenetic safety information will allow a company to sell their goods in their marketplace or operate their factories. While industry might protest vigorously, a permit scheme for consumer goods, similar to prescription drugs receiving FDA market approval, can convey significant benefit to a manufacturer, certifying the product for the marketplace and erecting barriers to less sophisticated or responsible competitors who take shortcuts.[216] An important consideration is the duration of the

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[214] Nussbaum, *supra* note 12, at 57.

[215] *Id.* at 20 ("The CA, by contrast, is quite abstemious: it identifies a very short list of core entitlements that should be secured to all citizens as basic entitlements of a just society. Beyond that short list, the CA does not make sweeping claims about the overall good. It allows people to make their own choice based on their different views of the good life. Moreover, since the core entitlements are understood as capabilities, rather than as actual functions or actions, giving one of them to a person does not require him or her to use it.").

[216] Loretta Chao, *More Firms Tied to Tainted Formula: China Officials Say Industrial Chemical was in Baby Food*, WALL ST. J., Sept. 17, 2008, at A23 (describing recent scandal involving food products from China adulterated with melamine); Austin Ramzy, *China's Melamine Woes Likely to Get Worse*, TIME, Nov. 4, 2008, http://www.time.com/time/world/article/0,8599,1856168,00.html; U.S. Food & Drug

permit. Since scientific knowledge can fluctuate rapidly as new data is gathered, a permit's time span should be linked to the progression of knowledge within the field. For epigenetics, this might mean a default permit for ten years, which would nevertheless allow the permit agency to call for a special review in light of new information, especially if a firm has not disclosed or neglected to perform additional research within a decade time frame.

Epigenetic taxes can be structured to create incentives for firms to compete with each other on the development of risk information. For example, if Company A and Company B make the same product X, but Company A develops more epigenetic risk information on X, it could receive a discounted tax assessment compared to Company B. In addition to incentivizing research, this strategy addresses free rider concerns related to which parties should bear the cost of safety testing. Safety information exchanges, as envisioned by the EU and its REACH legislation, can also address efficiency concerns related to redundant testing.[217]

D. Level 4: Restricted Uses and Outright Ban

If scientific studies ultimately prove that certain substances cause severe epigenetic harms that are not reversible, the appropriate regulatory action would be to ban such substances from general use. Once again, under a CA focus, harms that have greater deleterious effects on individuals' abilities to make free choices or that limit the scope of their life options are considered to be relatively more severe than other harms. Prioritizing epigenetic harms is important, because a ban on one substance predictably could lead to the use of risky substitutes.[218] Thus, under the framework I propose, regulatory agencies would need to rank the epigenetic harms caused by substances, especially when substitution of one substance for another is likely.

Given the strength of this regulatory measure, it is appropriate to demand that the corresponding level of scientific knowledge be equally strong: reproducible, peer-reviewed scientific studies demonstrating a significant increase in epigenetic risk. As discussed above, I hesitate to suggest a relative risk threshold of 2.0 as the necessary thre-

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Admin., Melamine Contamination in China, *available at* http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm179005.htm (last visited May 3, 2010).

[217] *See* Laborde, *supra* note 205, at 63.

[218] *See* Cass R. Sunstein, *Health-Health Tradeoffs*, 63 U. CHI. L. REV. 1533, 1541-42 (1996) (arguing that regulatory bans can lead to risky substitutes). Of course, Sunstein would likely calculate the tradeoffs in a different manner as he is a strong proponent of cost-benefit analysis.

shold for a regulatory ban. For example, if the relative risk of a substance causing epigenetic developmental defects is only 1.9, I think it should be within an agency's discretion to ban such a substance. The insistence on reproducible and peer-reviewed data is distinguishable because one needs to know if any measured risk is legitimate and not due to chance or poor scientific methodology. In contrast, deciding on whether to enact a regulatory ban based upon a 1.9 or 2.0 relative risk is a quantitative, not qualitative, decision.

The issue of paternalism versus libertarianism in the banning of substances is especially thorny when epigenetics enters the equation. For example, adopting the libertarian view, one can argue that so long as individuals are given notice that a certain substance is harmful, they should be allowed the freedom to choose whether they want to risk exposure. However, given the multi-generational persistence of epigenetic markings, notice and choice are necessarily absent for future generations suffering from epigenetic risk acquired before they even came into existence. This in turn raises the issue of generational justice and the extent to which the present generation is held responsible for risks that will be passed on to future generations. As in the debate regarding climate change regulations, talking about protecting future generations that would not come to be even during our own lifetime makes the case for taking action more difficult and attenuated. However, with epigenetic risk as with catastrophic climate change, one is talking about taking decisive action against harms that might affect our generation directly as well as generations born during our lifetime.

CONCLUSION

This article explores the meaning of epigenetic risk and why addressing it from a legal and policy perspective is critical. Epigenetics is a rapidly evolving field, and no doubt researchers will develop more knowledge about how one acquires and pass on epigenetic marks, about the impact such marks on human disease and development, and about the extent to which medicine can manipulate or modify the epigenetic effects. Viewing the issue from the CA framework, the imperative for addressing epigenetic risk is not merely the biological or medical concerns involved, but more generally the underlying fairness and justice of the American social contract. How one develops mentally or physically has a tremendous impact upon one's set of capabilities and hence the ability to choose a life of one's own making. Of course, there is no such thing as absolute freedom from biological or social constraints – some people will innately be more physically fit or intelligent than others. However, with epigenetics, one considers how much of these biological constraints are "innate" as opposed to

externally manufactured. The CA prompts one to ask questions such as: what impact do particular epigenetic risks have on one's ability to exercise free choices, are these risks avoidable, and how are such risks distributed across society?[219]

Addressing epigenetic risk poses some of the same challenges as addressing global climate change. The more variables and complex interactions that must be accounted for, the less likely scientific researchers will establish "conclusive proof" of cause and effect or neatly quantify the costs and benefits of an action. Additionally, as with global climate change, scientific uncertainty will be used as a basis for undermining the legitimacy of measures and regulations aimed at reducing epigenetic risk. The adaptive framework I propose holds that the growing evidence that particular environmental exposures cause epigenetic risks cannot be ignored and that overall uncertainty about epigenetics should first result in knowledge-generating policies rather than inaction. As data regarding epigenetic risks accrues, this framework accounts for such learning and enables the intensity of any epigenetic-based regulation to be rationally tied to existing knowledge. The stakes are high, given evidence that potentially avoidable epigenetic risks are not only causing disease, but also harming the capabilities writ large of present and future generations.

[219] The epigenetic effects of social interactions (e.g., parent-child bonding, bullying, discrimination) is a fascinating area of inquiry, but as stated in the Introduction, is outside the scope of this article. Obviously, regulating social interactions raises quite different jurisprudential and political concerns than regulating exposures to chemical substances.