THE FALSE PROMISE OF THE GENOMICS REVOLUTION FOR ENVIRONMENTAL LAW

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Toxics regulation has long been constrained by limitations on our ability to determine the risk presented by any given chemical. Toxicogenomics is a cutting-edge technology that, according to its many adherents, promises low-cost, effective, quantified risk measurement. If these claims are true, toxicogenomic technology will produce a revolution in chemical risk assessment and regulation. The promise of toxicogenomics, however, may never be fulfilled because of the inherent complexity and heterogeneity of biological systems and the importance of environmental, rather than genetic, factors in toxic susceptibility. This Article describes the implications of toxicogenomics for environmental law, offering a critical perspective on the benefits and shortcomings of this technology. It concludes that toxicogenomics is unlikely to transcend the current chemical risk assessment paradigm, but that it is a valuable development nonetheless for enhancing our understanding of scientific uncertainty.

I. Introduction

The limitations of chemical risk assessment methods, and particularly toxicology, have been the subject of countless reports, articles, and studies. Yet, despite years of debate and scientific effort, only a tiny fraction of the approximately 75,000 chemicals in commercial production have been subjected to even rudimentary toxicity testing. This lack of information persists in large part because the testing methods available to the Environmental Protection Agency (“EPA”) are woefully inadequate.

A new sense of hope, however, is emerging that the scientific uncertainties plaguing chemical risk assessment may soon be overcome. This surge of optimism has been inspired by the apparent success of genomics in the biomedical sciences. The guiding faith of those optimistic about change is that “a fundamental paradigm shift in the science of risk assessment” is now achievable through the application of genomics methods to

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3 Genomics is the study of chromosomes and their genes or, more broadly, the study of “the functions and interactions of all the genes in the genome”; genetics is the study of single genes and their effects. Alan E. Guttmacher & Francis S. Collins, Genomic Medicine—A Primer, 347 New Eng. J. Med. 1512, 1512 (2002).
environmental toxicology, a specialized field often referred to as “toxicogenomics.” 4

Genomics methods are expected to provide a new generation of simple, low-cost screening methods for determining whether a chemical is toxic, whether an individual is sensitive to certain toxins, and whether someone has been exposed to or harmed by a toxic substance. Above all, proponents of toxicogenomics claim that genomics methods will improve the “predictiveness, relevance and precision of toxicology” 5 and take the “guess work out of risk assessment” methods used to establish environmental standards. 6

Supporters of toxicogenomics have remarkably diverse affiliations, including environmental organizations, universities, industries, and federal agencies. Public health scientists and environmental activists have been among its most outspoken proponents. 7 The environmental group Friends of the Earth (“FOE”), for example, has written glowing reports on the potential of “the biomedical revolution [to] vastly improve our understanding of . . . the impacts of chemical exposures on [humans].” 8 Similarly, the private sector, though less effusive, 9 has supported government efforts to

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6 Olden & Guthrie, supra note 5.


9 Their enthusiasm is tempered by concerns that “premature data” could be misused by over-eager regulators, environmentalists, and trial lawyers. Neil Franz, Industry Keeps an Eye on Toxicogenomic Studies, Chem. Wk. Nov. 13, 2002, at 38 (quoting an American Chemistry Council representative worrying that “‘[t]here are some folks who can’t wait for this’ data to push for restrictions on chemicals”); see also Andrew Pollack, DNA Chip May Help Usher in a New Era of Product Testing, N.Y. Times, Nov. 28, 2000, at F2. (“Experts
integrate toxicogenomics into regulatory programs (e.g., the regulation of industrial chemicals, pesticides, and herbicides). Even representatives of the chemical industry, who are often the most critical of regulatory science (i.e., science used to support regulatory standards and decisions), have acknowledged that “toxicogenomics has ‘great value and potential.’” In short, major stakeholders across the spectrum have endorsed toxicogenomics.

The strong support for toxicogenomics is further reflected by significant changes in federal programs. Toxicogenomics represents the first high-profile scientific initiative in environmental toxicology since the proliferation of new environmental statutes transformed environmental law. Both the Food & Drug Administration (“FDA”) and the EPA have adopted preliminary policies supporting toxicogenomic methods. At the same time, the National Institute for Environmental Health Sciences (“NIEHS”) within the National Institutes of Health has initiated a major toxicogenomics program. In 1998, NIEHS launched the Environmental Genome Project (“EGP”), which will “investigate how genetic variation affects responses to environmental exposures” by characterizing genes linked to human disease. The new data and knowledge generated by the EGP will, it is hoped, enable environmental exposures that are major contributors to human disease to be fully characterized and ultimately eliminated.
The enthusiasm for toxicogenomics is understandable. The proclaimed
effects of toxicogenomics are extraordinary: it will dramatically improve
evaluations of chemical toxicity for low-dose exposures, allow screening of compounds for toxicity, enable toxicity testing for exposures to multiple chemicals, and provide methods for assessing harm to organisms beyond humans. These claims, however, ignore important biological constraints and threaten to devolve a silver-bullet mentality. This mentality has led environmental policy astray in the past. If such claims were true, toxicogenomics would be the ideal regulatory science. Yet, although it is true that science can overcome complex problems, it has had less success developing easy-to-apply methods for biological systems despite huge public and private investments. The complex nature of biology ought to give us pause or at least make us question high-flying claims.

Several factors provide grounds for skepticism. The optimism instilled by the genomics revolution in medicine is premised on reducing the study of human disease to identifying genes “for” specific human traits. Two assumptions typically underlie this view: (1) human disease is primarily a matter of genetic susceptibility, and (2) most genetic traits are simple. For a number of reasons, both assumptions are false. First, despite the intense interest in genomics, broad scientific consensus holds that most common diseases are more strongly linked to human-made and natural environmental exposures

19 Cynthia A. Afshari et al., Application of Complementary DNA Microarray Technology to Carcinogen Identification, Toxicology, and Drug Safety Evaluation, 59 CANCER RES. 4759, 4760 (1999); Olden et al., supra note 4; at 1966.
20 Marilyn J. Aardema & James T. MacGregor, Toxicology and Genetic Toxicology in the New Era of “Toxicogenomics”: Impacts of “-omics” Technologies, 13, 18 (2002); Simmons & Portier, supra note 4, at 904.
21 William D. Pennie et al., The Principles and Practice of Toxicogenomics: Applications and Opportunities, 54 TOXICOLOGICAL SCI. 277, 277 (2000); Richard A. Lovett, Toxicologists Brace for Genomics Revolution, 289 SCI. 536, 536 (2000) (asserting that toxicogenomics will reduce the costs and time associated with toxicity testing).
24 In the biomedical sciences, increased spending on basic research is not leading to more rapid discovery of new drugs; in fact, the rate of new drug development over the past decade has shown a significant decline. Food & Drug Administration, INNOVATION OR SINGULARITY: CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS 2 (Mar. 2004), available at http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf.
than to genetics. Second, genetic traits are complex and influenced by an individual’s surrounding genetic makeup—genes do not function in isolation. As a result, each gene associated with a toxic response or susceptibility will have a small, often variable effect, making detection of its causal role far more challenging.

This Article fills a significant gap in the literature by providing a critical appraisal of toxicogenomics. A further objective of the Article is to show that the recent embrace of toxicogenomics provides valuable insights into beliefs about science, and particularly biological science, that often prove to be faulty or misconceived. Part II of the Article begins by placing toxicogenomics in the broader context of environmental regulation and toxicology, and then turns to a general discussion of toxicogenomics and its application to toxicology.

Part III addresses the short-term implications of toxicogenomics for environmental law. It makes three claims. First, toxicogenomics will expose the extent to which the United States population is heterogeneous in its susceptibility to toxic exposures. In 1996, the Food Quality Protection Act (“FQPA”) set a precedent by recognizing the unique susceptibilities of children and infants, as well as other “major identifiable subgroups” of consumers. While this was a critical development, it ignored the complexity of toxic susceptibilities. I propose a biologically grounded alternative based on estimates of the distribution of susceptibilities across the population. Second, the rise of toxicogenomics may, quite unintentionally, alert policymakers and the general public to the modest effect that genetics have on human health—relative to environmental factors. This realization would be significant because public resources are being committed disproportionately to high-tech genomics-oriented medicine. A potential benefit

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29 Julian Peto, *Cancer Epidemiology in the Last Century and the Next Decade*, 411 Nature 390, 393 (2001) (“If many genes contribute to the large genetic effects that seem to underlie many common cancers, they may be discoverable only through advances in our understanding of carcinogenic mechanisms.”).

of recognizing the limits of genomics, I hope, will be a refocusing of attention on public health research. Third, toxicogenomics is not destined to cause the paradigm shift its proponents claim. Although toxicogenomics will provide important mechanistic information, the complexity of the underlying biological processes will preclude, at least for the foreseeable future, the type of strict quantitative analyses required in a regulatory setting.

Part IV examines more closely the acknowledged limitations of toxicogenomics and the systemic criticisms that have been mounted against it. This analysis highlights the gulf between the popularized version of genomics science and the far more complex, less deterministic reality with which scientists must contend. In doing so, it challenges the common portrayal of genes as rigid blueprints that determine an individual’s susceptibility to harmful environmental exposures and the general viability of toxicogenomics itself.

Part V argues that the policy debate over toxics regulation has failed to grasp the nature of the uncertainties inherent in the biological processes that govern toxic responses and susceptibilities. By undertaking a careful analysis of toxicogenomics, I hope to convey just how difficult the scientific problems are—difficulties beyond the usual litany of subjective judgments that are endemic to chemical risk assessment. In this light, toxicogenomics is most valuable for its capacity to enhance our understanding of these uncertainties, not because it will transcend them. This limited power mandates an approach that uses this increased knowledge about scientific uncertainties to coordinate research and improve regulatory science. I offer several pragmatic recommendations, one of which calls for abandoning the current ad hoc industry-based approach to toxicity testing in favor of a government-based research model.

II. THE PARALYSIS OF ENVIRONMENTAL TOXICS REGULATION AND THE PROMISE OF TOXICOGENOMICS

The limitations of risk assessment methods are a major source of controversy within environmental law. The basic problem for environmental regulation is that the uncertainties in risk estimates are frequently very large at the low exposure levels most relevant to regulatory standards. Scientists have found it difficult or impossible to reduce these uncertainties because the harm from most toxic chemicals at low exposure levels falls below the detection limits of existing toxicological animal-testing methods and human epidemiological studies.\(^\text{31}\) Scientists must therefore make

\[^31\] The limited sensitivity of existing methods is compounded by the fact that the effects of many diseases (e.g., cancer) lie latent for many years before their clinical effects are detectable. See, e.g., Kirk R. Smith et al., How Much Global Ill Health Is Attributable to Environmental Factors?, 10 Epidemiology 573, 573 (1999).
judgments, or educated guesses, about the behavior of a chemical’s toxicity at low exposure levels to fill this gap in the data.

These judgments, which are sometimes determinative of regulatory outcomes, have fueled the debate over chemical risk assessment. Among environmentalists, such judgments are viewed as matters of social value that lie outside the jurisdiction of scientific expertise, and they object to risk assessment methods that transform questions of policy into obscure technical details. On the other side, critics of regulation view risk assessment methods as the solution, not the problem. Critics object to the injection of fuzzy, ethics-oriented principles advocated by environmentalists (i.e., the Precautionary Principle) into what they view as otherwise rigorous analysis.

The high levels of uncertainty associated with risk assessment methods have very real consequences. Failures to protect workers against asbestos exposure prior to 1980 may eventually cause 250,000 additional cancers in Western Europe. This example, and many others, demonstrates the weakness of standard epidemiological methods as an early warning system. Moreover, scientists are pessimistic about the prospects of achieving major advances through improvements in current toxicological test methods.

According to its proponents, toxicogenomics offers a means to move beyond this impasse. First, a detailed understanding of genetic susceptibilities will allow scientists to gain a mechanistic understanding of the causes of human disease and the role that chemical exposures play in disease etiology. Second, recent research indicates that “genetic variability

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34 The Precautionary Principle is premised on the belief that “[i]f there is a potential for harm from an activity and if there is uncertainty about the magnitude of impacts or causality, then anticipatory action should be taken to avoid harm.” Carolyn Raffensperger, Introduction, in PROTECTING PUBLIC HEALTH & THE ENVIRONMENT: IMPLEMENTING THE PRECAUTIONARY PRINCIPLE 1, 1 (Carolyn Raffensperger & Joel A. Tickner eds., 1999).
35 See infra Part IV.A.
36 Peto, supra note 29, at 392.
37 Only “[a]bout a dozen specific occupation exposures and several complex mixtures, particularly the combustion products of coal, have [been demonstrated to] cause[] high risks of certain cancers (predominantly lung cancer) in heavily exposed workers.” Id. at 392. Similarly, apart from alcohol and aflatoxin (and a few local customs), no single dietary factor has been unequivocally demonstrated to be an important carcinogen or anti-carcinogen. Id. at 390.
38 Taubes, supra note 2, at 164. Epidemiological methods are hampered, for example, because exposure levels often cannot be directly measured, because the effect of a discrete exposure often cannot be separated from other overlapping exposures, and because small sources of risk fall below methodological detection limits. Rothman et al., supra note 4, at C2.
in human populations can affect the entry, absorption, activation, and 
detoxification of environmental toxins.” 40 Solid evidence thus exists linking 
genetic susceptibility to processes involved in chemical toxicity and risk. 
Third, genomics methods, particularly gene expression profiling, are 
believed to be more sensitive than traditional toxicological techniques. 41 
Toxicogenomic methods therefore ought to be of broad benefit and applicability 
to environmental toxicology.

To place toxicogenomics in the broader context of environmental toxes 
regulation, this Part of the Article discusses the debate over toxicity testing 
and risk assessment in environmental law, and then examines the emerging 
methods in molecular biology and toxicogenomics.

A. The Current State of Environmental Toxics Regulatory Science

Toxics regulation is intertwined with the long-standing debate over 
risk assessment, which is the broad analytical framework in which toxicological studies are utilized to establish environmental standards. 42 
The uncertainties inherent in risk assessment methods and chemical toxicology 
are by now infamous. 43 More than twenty years ago, the National Research 
Council identified almost fifty decision points in risk assessments for which 
“inferential options” necessitate choosing between several scientifically 
plausible alternatives that cannot be resolved given existing uncertainties. 44 
Legal scholars have frequently pointed to these inferential gaps to chal-
lenge the scientific authority of risk assessment methods and to criticize 
what they perceive as an overreliance on quantitative risk analysis in en-
vironmental standard setting. 45 To give just one example of the alleged

40 Christiani et al., supra note 17, at 526.
41 Aardema & MacGregor, supra note 20, at 16.
42 Risk assessment is typically portrayed as consisting of four distinct stages: 
(1) identification of the hazard; (2) estimation of the adverse effect as a function of dose; 
(3) estimation of the level of exposure; and (4) calculation of the composite risk. NATIONAL 
RESEARCH COUNCIL, RISK ASSESSMENT IN THE FEDERAL GOVERNMENT: MANAGING THE 
PROCESS 3 (1983) [hereinafter NRC]; MARK R. POWELL, SCIENCE AT EPA: INFORMATION 
in the Regulatory Process 8–9 (1999). Toxicology studies are utilized in stage two, 
although much debate remains about the degree to which these stages are separable.
43 Donald T. Hornstein, Reclaiming Environmental Law: A Normative Critique of Com-
parative Risk Analysis, 92 COLUM. L. REV. 562, 563 (1992) (noting that even EPA’s Sci-
entiﬁc Advisory Board has given only a qualiﬁed endorsement of risk assessment, and ac-
knowledging that data for conducting risk assessment can be very spotty and that “risk-
bearing can involve qualitative elements not easily indexed for comparison”).
45 Adam Babich, Too Much Science in Environmental Law, 28 COLUM. J. ENVTL. L. 
119, 126 (2003) (arguing that “current scientiﬁc theories about risk make a poor starting 
point for regulatory standard setting”); Devra Lee Davis, The “Shotgun Wedding” of Sci-
(describing the misuse and limitations of risk assessment in the context of judicial review);
Howard Latin, Good Science, Bad Regulation, and Toxic Risk Assessment, 5 YALE J. ON 
Reg. 89, 90 (1988) (“challeng[ing] the conventional view that scientific perspectives should 
dominate the risk-assessment process”); see also McGarity, supra note 32, at 729 (arguing
reductive biases, environmental risks of industrial chemicals are often reduced to assessments of human carcinogenicity, without any consideration of non-cancer risks, because so little is known about these other sources of harm. Criticisms of risk assessment methods cross ideological lines in the debate over environmental regulation. Justice Stephen Breyer, for example, has dutifully acknowledged the limitations of risk assessment methods and, in particular, toxicological testing:

The more frequently used animal studies are often more uncertain [than human studies]. The investigator applies a high dose of a supposed carcinogen to the animals; if they develop a higher than average number of tumors, the analyst tries to extrapolate backward to low doses in humans. What assumptions shall be made in doing so? What extrapolation model should be used? Risk analysts tend to use, for both animal and epidemiological studies, a linear model, which extrapolates backward on a straight line... Critics argue that to use such mathematical models is like saying “If ten thousand men will drown in ten thousand feet of water, then one man will drown in one foot of water”... The critics are right, in that there is no consistent scientific rationale for assuming a linear relation between dose and response. Some substances, such as cyanide, are proportionately as deadly in small doses as large ones; others, such as butter, are harmful only when consumed in large quantities; while still others, such as iodine, kill in high doses, are harmless in small doses, and in tiny doses are necessary for life. Science very often does not tell us which of these examples best applies.

46 Critics also charge that simplifying assumptions, such as functional linearity and continuity, are more misleading than enlightening and therefore should be critically re-evaluated. Lawrence H. Tribe, Policy Science: Analysis or Ideology?, 2 PHILO. & PUB. AFF. 66, 87–88, 92–93 (1972). In this regard, a great deal of attention has been directed at the values implicit in various simplifying assumptions in cost-benefit analysis (e.g., omitting any consideration of non-cancer risks and harm to the environment). See Frank Ackerman & Lisa Heinzerling, Pricing the Priceless: Cost-Benefit Analysis of Environmental Protection, 150 U. PA. L. REV. 1553, 1578–81 (2002); Lisa Heinzerling, Regulatory Costs of Mythic Portions, 107 YALE L.J. 1981, 2060–64 (1998).

47 Stephen Breyer, Breaking the Vicious Circle: Toward Effective Risk Regulation 44 (1993). The extrapolation model Breyer criticizes involves a simple linear ex-
Despite these weaknesses, Breyer is a strong proponent of risk assessment methods and toxicity testing.

Judgment unavoidably enters into toxicological assessments when the existing data are evaluated in the aggregate and decisions are made regarding the relative weight to be given to different toxicological studies. At the EPA, global assessments of existing data are made by committees of scientists that produce a consensus opinion on the potency of the toxic chemicals EPA regulates. When integrating the available data to arrive at a consensus opinion, scientists must consider a variety of qualitative experimental factors, such as whether the data are static from animal or human studies, the degree to which the conditions for the experiments were controlled, assumptions made to derive exposure levels, and any confounding exposures that could bias the results. Significantly, these judgments are made independently of quantitative estimates of toxicity, such as statistical significance. As a result, uncertainties in toxicological methods propagate through to the final assessment of a chemical’s toxicity, risk estimates of harm from specific chemical exposures, and the regulatory standard chosen.

Beyond the academic debate, the significant limitations and costs of toxicological methods have had substantial repercussions for environmental standard-setting. Of the approximately 75,000 chemicals subject to EPA regulation, only about six percent have been subjected to any toxicological testing. Even among the most heavily used chemicals, toxicity test-trapolation from animal study data down to zero.

48 EPA conducts this global analysis of existing data under its Integrated Risk Information System (“IRIS”) program. See What is IRIS, at http://www.epa.gov/iris/intro.htm (last visited Oct. 8, 2004) (on file with the Harvard Environmental Law Review); see also Powell, supra note 42, at 31–34. The first part of the process involves determining a chemical’s “reference dose,” which is the highest dose that its toxic effects are not observed, corrected for uncertainties in its derivation. EPA uses reference doses and modeling methods to calculate regulatory standards for each of the chemicals it regulates. As such, the IRIS toxicological reviews provide the final toxicological information used by EPA to calculate regulatory standards for toxic substances.

49 See, e.g., Breyer, supra note 47, at 43–44; Wagner, supra note 45, at 1621–27.

50 While a lower level of statistical significance may permit scientists to consider more data, because more studies will be “statistically significant,” it provides no guidance on the more important judgment of how the data are assessed relative to each other or as a whole to derive a quantitative estimate of a chemical’s toxicity. Randall Collins, Statistics Versus Words, 2 Soc. Theory 329, 337 (1984) (explaining that scientific judgments on the value of specific experimental results “count most, not some meeting of, or failure to meet, an arbitrary level of statistical ‘significance’”); Deborah G. Mayo, Error and the Growth of Experimental Knowledge 313 n.8 (1996) (noting that the exclusion of non-significant results actually creates a bias in the scientific literature because negative results are often not reported and thus not considered in meta-analyses of multiple experimental studies).

51 Current costs for conducting toxicity tests for a chemical average between $2 million and $4 million and entail several years of work. Thomas et al., supra note 1, at 1189.

52 Robert V. Percival et al., Environmental Regulation: Law, Science, and Policy 334 (4th ed. 2003) (“Only 6 percent of the [premanufacture notices] received annually by EPA have any toxicity data at all. . . .”); see also Thomas, supra note 1, at 1189 (noting that in 2001, 505 chemicals had been tested in longer-term studies under the National Toxicology Program, sixty-six in short-term tests, and one in a subchronic test; for the vast majority of the chemicals in commerce, testing them using existing methods will
ing is sparse—there are no publicly available toxicity data for fifty-seven percent of the chemicals used in the highest volumes, and developmental toxicity testing is available for just seven percent of them.\footnote{Philip J. Landrigan et al., Environmental Pollutants and Diseases in American Children: Estimates of Morbidity, Mortality, and Costs for Lead Poisoning, Asthma, Cancer, and Developmental Disabilities, 110 Envtl. Health Persps. 721, 721 (2002). Approximately 3000 high-volume chemicals are produced in or imported into the United States at over one million pounds per year. Percival et al., supra note 52, at 335.}

Further, lingering ambiguities in toxicological data have contributed to significant delays and disputes in determining the proper level of regulation for numerous compounds, including lead, mercury, vinyl chloride, and dioxin.\footnote{Gerald Markowitz & David Rosner, Deceit and Denial: The Deadly Politics of Industrial Pollution 137–38, 291–93 (2002); Powell, supra note 42, at 3–4, 122, 339–46; Wendy Thomas, Through the Looking Glass: A Reflection on Current Mercury Regulation, 29 Colum. J. Envtl. L. 145, 150–52 (2004) (noting that even today there is no consensus on what constitutes an unacceptable amount of mercury contamination).}

The limitations of toxicological methods have led many commentators to conclude that the uncertainties in these methods cannot be overcome.\footnote{See, e.g., Breyer, supra note 47, at 42–43; McGarity, supra note 32, at 733–34; Powell, supra note 42, at 127–28; Wagner, supra note 45, at 1619.}

Toxicogenomics is arguably the first scientific development that has inspired hope that new methods might actually resolve these uncertainties and make toxicology a truly quantitative science for determining chemical toxicity, exposure, and harm.\footnote{Development of new, independent experimental techniques such as those associated with toxicogenomics can help to resolve scientific uncertainties. A standard example of the power of complementary scientific methods involves the first observation of "dense bodies" in red blood cells. Ian Hacking, Representing and Intervening: Introductory Topics in the Philosophy of Natural Science 200–02 (1983). When dense bodies were initially observed, the scientist conducting the experiment believed they were an artifact of his observational method, here an electron microscope. Id. To test this hypothesis, he selected a different observational technique, a fluorescence microscope, which operated according to completely different physical principles. Id. The scientist then observed the dense bodies with the fluorescence microscope, refuting his original hypothesis that they were an artifact. Id. The logic behind this strategy is straightforward:

Two physical processes . . . are used to detect dense bodies. These processes have virtually nothing in common between them. They are essentially unrelated chunks of physics. It would be a preposterous coincidence if, time and again, two completely different physical processes produced identical visual configurations which were, however, artifacts of the physical processes rather than real structures in the cell.}

B. Molecular Epidemiology and the Rise of Genetics-Based Methods

A dispute over environmental contamination at the Midway Village housing complex in Daly City, California, represents one of the first at-
tempts to use evidence of genetic harm to humans as a means of demonstrating harm from toxic exposures. 57 A standoff between state regulators and Midway Village residents erupted in the early 1990s over chemical residues left over from a former Pacific Gas & Electric plant. 58 Residents organized to form a community group, Midway Residents for Environmental Justice, and lobbied state and federal authorities to remediate the site. Two groups of residents also filed liability suits for alleged health problems caused by the residual contamination. 59

These efforts were flagging by the late 1990s with few of the community’s demands having been addressed. The dispute reignited in June 1999, however, when residents’ claims received potentially powerful scientific support from a study conducted by the federal Agency for Toxic Substances and Disease Registry. The study detected heightened levels of chromosomal abnormalities among Midway Village residents. 60 Residents immediately seized on the results as direct evidence of the harm caused by the residual site contamination. Although the residents were ultimately unsuccessful in their legal actions, the 1999 study prompted immediate action by state and federal authorities, including additional environmental testing and ultimately further costly site remediation. 61

The use of chromosomal abnormalities to detect harm from chemical exposures stems from developments in molecular biology that began to be applied to environmental toxicology in the early 1980s. The integration of genetic data into toxicology, referred to as molecular epidemiology, focuses on identifying novel biological indicators, known as “biomarkers,” that provide very sensitive tests for toxicity, disease onset, and harmful chemical exposure. 62 This approach can screen for broad chromosomal abnormali-

57 Sara Shostak, Locating Gene-Environment Interaction: At the Intersections of Genetics and Public Health, 56 Soc. Sci. Med. 2327, 2337 (2003); Angelica Pence, Appeals Court Tosses Toxic Site Lawsuit; Neighbors Say They Have Been Sickened for Years, S.F. Chron., May 17, 2000, at A21; Angelica Pence, Tenants Blast State Toxics Agency; Midway Village Hopes for Relocation Dashed, S.F. Chron., Feb. 28, 2001, at A15. Activists in the Midway Village, Daly City, housing project alleged that polynuclear aromatic hydrocarbons (“PAHs”) in the soil beneath their homes were responsible for bloody noses, respiratory illnesses, nausea, rashes, infertility, memory loss, miscarriages, and cancers. Id.

58 Angelica Pence, Gene Defects for Neighbors of Toxic Site; Study Finds Aberrations in Chromosomes Among Daly City Project Residents, S.F. Chron., Jan. 19, 2000, at A1 [hereinafter Pence, Gene Defects].

59 Id. (noting that the first case was filed in 1991 against San Mateo County and PG&E, and the second was filed in 1993 against the federal government); Pence, Living on Toxic Ground, S.F. Chron., Jan. 20, 2000, at A1.

60 Pence, Gene Defects, supra note 58, at A1 (“The study detected a high number of chromosome aberrations in 32 of 34 residents ages 18 and under. Similarly, 19 of the 24 adults showed abnormal levels of irregularities in their DNA.”).

61 Pence, Living on Toxic Ground, supra note 59, at A1; Angelica Pence, Toxic Takeout; Ridding Midway Village of Tainted Soil—Again, S.F. Chron., Aug. 25, 2001, at A13 (reporting that further remediation of the site costing $3.5 million was conducted in August 2001).

62 William A. Suk & Samuel H. Wilson, Overview and Future of Molecular Biomarkers of Exposure and Early Disease in Environmental Health, in BIOMARKERS OF ENVIRONMENTALLY ASSOCIATED DISEASE, supra note 23, at 3, 4–6 (Samuel H. Wilson & William A. Suk
ties, simple genetic conditions, and exposure to certain types of chemicals. An example of a well-known biomarker in toxicology is lead blood level, which is used as a measure of harm caused by exposure to lead. Molecular epidemiology actually incorporates three strategies: (1) quantification of body burdens of chemicals (like lead), or their metabolites, to test for chemical exposure; (2) prediction of health effects based on detecting early changes in biochemical functions associated with chemical exposure; and (3) measurement of individual susceptibility to harm from chemical exposures across populations. To the extent feasible, molecular epidemiology uses non-invasive testing methods to make them as patient-friendly as possible and thus attractive for broad-scale monitoring.

Research in molecular epidemiology focuses on genes associated with protecting cells from harmful exposures. These typically include genes coding for proteins that metabolize environmental toxins, facilitate DNA repair, or aid cellular replication. Scientists believe molecular epidemiology will eventually allow them to develop tests for precursors of diseases.

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63 Olden & Guthrie, supra note 5, at 4.
65 Suk & Wilson, supra note 62, at 6–7. Newer methods use multiple markers to identify the specific stage of disease development and to screen for the particular mechanism(s) involved. Perera & Weinstein, supra note 7, at 520.
66 Suk & Wilson, supra note 62, at 9; Perera & Weinstein, supra note 7, at 517–18 (discussing the use of samples of blood, exfoliated cells, tissue, and body fluids for biomarkers for exposure, pre-clinical effects, and susceptibility); Perera, supra note 7, at 608 (explaining that monitoring blood lead levels is exemplary of this strategy). Other benefits attributed to molecular epidemiology include reduced reliance on animal studies and direct chemical testing at exposure levels relevant to regulation. Frederica P. Perera, Molecular Epidemiology: Insights Into Cancer Susceptibility, Risk Assessment, and Prevention, 88 J. Nat'l Cancer Inst. 496, 496 (1996); Perera & Weinstein, supra note 7, at 517–18.
67 Lawrence H. Lash et al., Genetics and Susceptibility to Toxic Chemicals: Do You (or Should You) Know Your Genetic Profile?, 305 J. Pharmacology & Experimental Therapeutics 403, 406 (2003); see also Rothman, supra note 4, at C3. Two important classes of proteins that metabolize environmental toxins are Phase I metabolizing enzymes (e.g., cytochrome P450s, N-acetyltransferases) and Phase II detoxifying enzymes (e.g., glutathione S-transferases (“GSTs”)); both classes have polymorphisms that increase or decrease the rate of these processes. William W. Au et al., Usefulness of Genetic Susceptibility and Biomarkers for Evaluation of Environmental Health Risk, 37 Envtl. Molecular Mutagenesis 215, 216 (2001); Frederica P. Perera, Environment and Cancer: Who Are Susceptible?, 278 Sci. 1068, 1070 (1997).
68 DNA-repair enzymes are critical because they correct genetic mutations caused by environmental toxins, and scientists estimate that their activity may vary from person to person by as much as 180–300 fold (i.e., the efficacy of one person’s DNA-repair processes could be 300 times greater than that of a more susceptible individual). Perera, supra note 67, at 1070; Peto, supra note 29, at 393 (explaining that the study of DNA repair genes and chromosomal aberrations is likely to be particularly important because they correlate well with increased susceptibility).
69 Simmons & Portier, supra note 4, at 903.
with delayed onsets, such as many forms of cancer.\textsuperscript{70} As a consequence, a
great deal of this research has focused on carcinogens.\textsuperscript{71} Scientists have
identified chemicals that harm genes or proteins essential to DNA repair
or that cause genetic damage by binding to DNA (creating a “chemical-
DNA adduct”) and inducing changes in genes that promote or suppress
tumor growth.\textsuperscript{72} These methods have been used, for example, to determine
that susceptibility to the toxic effects of certain pesticides is influenced by
mutations in an enzyme that facilitates their destruction\textsuperscript{73} and that ninety-
seven percent of workers who are highly sensitive to beryllium dust and
fumes, which can cause severe lung inflammation and malfunction, share
the same genetic mutation.\textsuperscript{74} Molecular epidemiologists have also discov-
ered that certain types of gene mutations are commonly found in a vari-
ey of cancers.\textsuperscript{75}

The prototype biomarkers relevant to environmental regulation (other
than lead blood level) are chemical-DNA adducts, which provide a direct
molecular-level link between toxic exposure and genetic effects, and chro-
mosomal aberrations like those identified in the Midway Village dispute.\textsuperscript{76}
Most biomarkers, however, are still in preliminary development,\textsuperscript{77} and they
have so far failed to detect important carcinogens outside a laboratory set-
ting.\textsuperscript{78} The most compelling results generated by molecular epidemiology
demonstrate the broad range of inter-individual variability in susceptibil-
ity to diseases such as cancer.\textsuperscript{79} The most significant challenge for mo-
lecular epidemiology remains avoiding potential sources of bias, particu-

\textsuperscript{70} Christiani, \textit{supra} note 17, at 529 (explaining that biomarkers may be used to identify
“upstream” signs of dose and early effects of cancer); Perera & Weinstein, \textit{supra} note 7, at
519, 521–22 (noting the existence of biomarkers for early-stage detection, such as chromo-
somal aberrations, small deletions, and point mutations); K. Husgafvel-Pursiainen, \textit{Molecu-
lar Biomarkers in Studies on Environmental Cancer}, 56 J. EPIDEMIOLOGICAL COMMUNITY
HEALTH 730, 730 (2002) (explaining that early-stage biomarkers eliminate the need to wait for disease
onset).

\textsuperscript{71} Perera, \textit{supra} note 66, at 499.

\textsuperscript{72} Id. at 496, 499; Peto, \textit{supra} note 29, at 394 (suggesting that promising research is
linking specific events in carcinogenesis to increased risk and, ultimately, quantifying risk
based on certain biomarkers associated with specific stage of carcinogenesis).

\textsuperscript{73} Au et al., \textit{supra} note 67, at 219; Olden, \textit{supra} note 5, at 5.

\textsuperscript{74} Olden, \textit{supra} note 5, at 5.

\textsuperscript{75} Perera, \textit{supra} note 66, at 500–02. For example, mutations in the gene for GST-M1,
which is a detoxifying enzyme, increases susceptibility to the carcinogen benzo[a]pyrene.
Michael L. Cunningham et al., \textit{Workshop Overview: Use of Genomic Data in Risk Assess-
ment}, 73 TOXICOLOGICAL SCI. 209, 212 (2003). Similarly, the P53 tumor-suppressor gene
has been found to be mutated in 40–50% of lung, breast, colon, and other common cancers.
Perera, \textit{supra} note 67, at 1069.

\textsuperscript{76} Perera & Weinstein, \textit{supra} note 7, at 518–19; Perera, \textit{supra} note 66, at 499. Other
examples of such biomarkers are chromium-DNA and polycyclic aromatic hydrocarbon-
DNA adducts. Suk & Wilson, \textit{supra} note 62, at 10.

\textsuperscript{77} Suk & Wilson, \textit{supra} note 62, at 10.

\textsuperscript{78} Perera, \textit{supra} note 66, at 496; Perera & Weinstein, \textit{supra} note 7, at 518; Peto, \textit{supra}
note 29, at 392 (noting that biomarkers so far have not provided quantitative estimates of
risk or been used on their own as a basis for diagnosis).

\textsuperscript{79} Perera & Weinstein, \textit{supra} note 7, at 517.
larly since associations between biomarkers and toxic exposures can be greatly influenced by numerous factors (e.g., time of testing, nutrition, method of measurement) in unpredictable ways.\(^80\)

C. Toxicogenomics: A Whole-Genome Strategy

Scientists believe that toxicogenomics will produce a new generation of more sensitive and reliable biomarkers.\(^81\) The central innovation in toxicogenomics is its ability to simultaneously measure the activity of thousands of genes (and ultimately the entire genome) without the need for first developing “any prior biological clue as to how they function.”\(^82\) Using gene-expression profiling—genomics’ experimental workhorse—the biological effects of a potentially toxic compound are assessed by identifying the genes that are activated (i.e., transcribed), or deactivated, upon exposure to the chemical.\(^83\) The relative rate of gene expression, measured by the number of copies detected of the transcribed gene, is assumed to be indicative of specific cellular reactions that arise in response to a chemical exposure.\(^84\) For example, if a chemical causes direct damage to DNA (e.g., polyaromatic hydrocarbons) or interferes with hormonal regulators (e.g., endocrine disruptors), a genome-wide assay of gene-expression levels following exposure should find aberrant expression levels altered from pre-exposure levels among those genes vulnerable to these chemi-

\(^{80}\) Rachel Nowak, Problems in Clinical Trials Go Far Beyond Misconduct, 264 SCI. 1538, 1540–41 (1994) (discussing the problems with and concerns about using surrogate marks, i.e., biomarkers, in epidemiological studies); M. Porta et al., Incomplete Overlapping of Biological, Clinical, and Environmental Information in Molecular Epidemiological Studies: A Variety of Causes and a Cascade of Consequences, 56 J. EPIDEMIOL COMMUNITY HEALTH 734, 734 (2002) (explaining that molecular epidemiological studies often fail to assess potential sources of bias); Paolo Vineis & Anthony J. McMichael, Bias and Confounding in Molecular Epidemiological Studies: Special Considerations, 19 CARCINOGENESIS 2063, 2066–67 (1998).

\(^{81}\) MacGregor, supra note 13, at 237; Suk & Wilson, supra note 62, at 5, 11.

\(^{82}\) Lander & Schork, supra note 27, at 2037; see also Richard D. Irwin et al., Application of Toxicogenomics to Toxicology: Basic Concepts in the Analysis of Microarray Data, 32 TOXICOLOGIC PATHOLOGY 72, 73 (2004) (noting that current microarrays can measure the activity of 20,000–25,000 genes simultaneously); Lash et al., supra note 67, at 407 (noting that “subsets of genes, rather than a single biomarker, can be used as more accurate predictors of toxicity”); Gary Zweiger, Knowledge Discovery in Gene-Expression-Microarray Data: Mining the Information Output of the Genome, 17 TIBTECH 429, 430 (1999) (explaining that thousands of genes can be examined at once using serial analysis of gene expression (“SAGE”), microarrays (“genechips”), and high-resolution two-dimensional gel electrophoresis coupled with mass spectrometry).

\(^{83}\) Mark R. Fielden & Tim R. Zacharewski, Challenges and Limitations of Gene Expression Profiling in Mechanistic and Predictive Toxicology, 60 TOXICOLOGICAL SCI. 6, 8 (2001).

\(^{84}\) When a gene is activated, its genetic sequence of nucleotides is transcribed (i.e., transferred) to a complementary molecule, messenger RNA (“mRNA”), which is then transported to a unit of the cell that uses the mRNA as a template for constructing the protein for which the gene codes. Lash, supra note 67, at 407. The number of mRNA generated during the transcription process correlates with the level of activity of the gene in question. \(Id.\)
Scientists believe that gene-expression profiling, by allowing them to monitor dynamic biological responses, will enable them to understand the underlying mechanisms of chemical toxicity and to identify new biomarkers for chemical susceptibility, exposure, or harm.  

Toxicogenomics encompasses three basic strategies: (1) identifying gene expression patterns that can be used as predictors of exposure or harm; (2) improving predictive accuracy in extrapolations from in vitro to in vivo tests and from animal models to humans; and (3) discovering gene expression patterns that reflect and predict specific, quantifiable toxic effects.  

The first goal represents the initial phase of implementing toxicogenomic methods; the latter two will require development of new analytical methods and detailed knowledge about the biological processes involved in toxic responses and disease.  

Each of these strategies relies on gene-expression profiles which are measured using gene-activity microarray tests. In its simplest form, a microarray is a glass plate on which thousands of short DNA segments (“gene probes”) are deposited in a matrix array. Each probe spotted on the plate is associated with a human gene. If a gene is active (i.e., being transcribed) when a microarray test is conducted, the messenger RNA (“mRNA”) molecules transcribed from the gene bind to the corresponding gene probes on the plate. The number of transcribed molecules that have bound to each probe is then measured. A single microarray can simultaneously measure the expression levels, and hence the activity, of literally thousands of genes. In the future, scientists believe they will be able to construct microarrays customized to detect exposure to specific groups of toxins.  

Toxicogenomics methods have virtues beyond simultaneous monitoring of many genes. As already indicated, one of the major obstacles confronting toxicology is eliminating bias and confounding factors in epidemiologies.  

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85 Simmons & Portier, supra note 4, at 904.
86 See Michael D. Waters et al., Toxicogenomic Approach for Assessing Toxicant-Related Disease, 544 Mutation Res. 415, 417 (2003).
87 Simmons & Portier, supra note 4, at 904.
89 Pierre Baldi & Wesley Hatfield, DNA Microarrays and Gene Expression: From Experiments to Data Analysis and Modeling 7 (2002).
90 See Olden & Guthrie, supra note 5, at 7.
91 Id. More specifically, gene screening involves the following: (1) mRNA from control and exposed animals or cell cultures is reverse transcribed and tagged with a fluorescent marker (red for treated and green for untreated controls); (2) labeled nucleic acid sequences are tested for binding to genomic DNA; (3) activity of a gene is correlated with the number of nucleic acid sequences that bind to the genomic DNA on a slide; and (4) once a gene is identified, its associated protein may be studied to determine its structure, function, and quantity using conventional methods. Id.
92 Typically, transcript differences (between normal and exposed subjects) of a factor of two or more can be consistently distinguished, and as few as one mRNA transcript per cell can be detected. Zweiger, supra note 82, at 430; see also Pennie et al., supra note 21, at 277 (noting the possibility of “quantitative assessment of changes in gene expression”).
93 Pennie et al., supra note 21, at 278.
logical studies, such as socioeconomic status and behavioral factors. Toxicogenomic methods provide a powerful experimental protocol for studying harmful environmental exposures while avoiding these problems. The protocol has two steps: first, identify a genetic mutation known to contribute to heightened environmental exposure, such as a malfunctioning gene involved in breaking down chemical toxins; second, conduct an epidemiological study consisting of (a) individuals with the genetic mutation who will, on average, be exposed to the toxin at higher levels or for longer periods of time, and (b) a control group of people without the mutation. Under this protocol, a positive association is established between a disease and the chemical exposure if a difference in disease rates is detected between individuals with the mutation and the control group. This approach takes advantage of the fact that an individual’s genetic makeup is independent of typical confounding factors that are problematic in epidemiology, particularly those whose ethical or practical constraints are at issue.

The intuitive appeal of linking gene expression levels to toxicological response can obscure important limitations of these methods. A central premise of toxicogenomics is that “gene expression profiling will identify mechanisms of action that underlie the potential toxicity of chemicals.” However, biologists know that changes in gene expression can be caused by a host of processes, such as defensive and adaptive responses, that are unrelated to toxicological harm. Further, chemical toxins frequently do not directly impact gene expression, as they may cause gene mutations that affect protein function without altering gene expression, or may not cause genetic mutations at all.
Detecting changes in gene expression levels may also be difficult. Large microarrays cannot detect all types of toxicological impacts, such as expression-level changes localized in a small number of cells or expression-level changes that are highly variable. For example, the pain reliever acetaminophen causes liver damage through non-specific (i.e., random) modifications of cellular proteins. Such non-specific toxicity causes gene expression levels to vary unpredictably according to the nature of the proteins affected and the degree of inactivation associated with the specific exposure. In the absence of a signature gene-expression pattern to associate with acetaminophen exposure, microarrays will lack a defining signal for detecting its toxic effects.

Proponents of toxicogenomics believe that these methodological constraints can be overcome with significant effort and resources. Initially, microarray data will operate as the first stage of a much more detailed set of experiments designed to determine whether observed gene-expression patterns are predictive or reflective of underlying toxic mechanisms. Contrary to proponents’ initial beliefs, establishing the link between a chemical’s toxicity and microarray data will require scientists to combine gene-expression data with information on the protein activity, metabolic processes, and physiological effects associated with the chemical exposure. Epidemiological population studies will also be necessary to provide a critical benchmark for scientific validity. To meet these challenges, scientists have endorsed an approach in which simple single-gene disorders will be studied first to obtain basic mechanistic information about different types of chemical toxicity; scientists will then use this information to study more complex toxic responses and susceptibilities.

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101 Fielden & Zacharewski, supra note 83, at 7.
102 Id.
103 See Pennie et al., supra note 21, at 280; Waters et al., supra note 86, at 416; Tennant, supra note 5, at A9.
104 Cunningham et al., supra note 75, at 210 (explaining that understanding protein functionality is key because many regulatory signals affect proteins post-translationally); Fielden & Zacharewski, supra note 83, at 9 (arguing that genomics data must be integrated with larger studies designed to assess effects at higher levels of biological organization (e.g., protein function and interactions metabolic processes)); Lash et al., supra note 67, at 405 (“[G]ene expression and proteomic microarrays are being used to map changes in mRNA and protein expression, whereas metabonomics is being used to assess changes in metabolite profiles. Of course, the most powerful approach is when all three of these complementary technologies are used to assess phenotype.”); Pennie et al., supra note 21, at 278. See also infra notes 248–250.
105 Caporaso, supra note 39, at 1547; Rothman et al., supra note 4, at C4 (arguing that epidemiological studies will provide “direct estimates of relative risk, absolute [observed] risk (penetrance), and the fraction of disease due to environmental exposures (i.e., genetic variants), and to their interactions”).
106 Guttmacher & Collins, supra note 3, at 1515–16, 1518 (predicting “genomics will most likely make its greatest contribution to health by revealing mechanisms of common, complex diseases”); Olden & Guthrie, supra note 5, at 6 (“[I]dentification and functional characterization of susceptibility alleles (i.e., genetic variants) are critical for understanding the pathways for development of human illness and for predicting risk to environmental
In the long term, scientists believe that toxicogenomics will become a knowledge-based science built on compilations of genomics data and computational bioinformatics tools.\textsuperscript{107} According to this vision, gene-expression profiles from exposed individuals or animal models will be used to identify unknown chemical exposures by comparing measured profiles against profiles contained in established databases.\textsuperscript{108} Through such comparative analysis, scientists will determine either the identity of the unknown toxin or, for novel chemicals, discover the mode or mechanism of toxic injury.\textsuperscript{109} Above all, scientists aspire to develop bioinformatics into a resource for reliably identifying “biomarkers of chemical exposure and predictive toxicology,” such that exposures may be detected prior to the onset of medically significant harm.\textsuperscript{110}

The flagship federal programs in toxicogenomics, the Environmental Genome Project (“EGP”) and the National Center for Toxicogenomics (“NCT”), incorporate an integrated approach to developing effective diagnostic and predictive toxicological test methods.\textsuperscript{111} The mission of the NCT is to build a comprehensive database of gene-expression profiles relevant to toxicological effects that can be used for testing chemical toxicity, exposure-induced harm, and chemical-specific individual susceptibility to toxic exposures.\textsuperscript{112} The EGP is more narrowly focused on research related to the effects of genetic variation on susceptibility and to environmental exposures.\textsuperscript{113} During its first phase, NIEHS will conduct experiments...
“to validate the concept of gene expression profiles as ‘signatures’ of toxicant classes, disease subtypes, or other biological endpoints.”114 If these proof-of-principle experiments are successful, NIEHS will standardize experimental protocols and establish data quality criteria.115 Initially, NIEHS plans to focus on profiling chemicals and disease processes that are either mutagenic or that harm key organs.116 So far, the initial proof-of-principle experiments conducted by NIEHS scientists are generating promising, although limited, results, and the Institute’s leadership is projecting a mood of optimism.117

III. REASSESSING THE PROMISE OF TOXICOGENOMICS FOR ENVIRONMENTAL LAW

The impact of toxicogenomics on environmental law stands to be more incremental than transformative. Unfortunately, the overselling of toxicogenomics may serve only to highlight its inability to provide the quantitative tests of chemical toxicity, susceptibility, and harm that its proponents have heralded. This failure has the potential to overshadow the benefits discussed below that are more likely to emerge from toxicogenomic research. Both the public and policymakers will need to be convinced that, although insights will occur incrementally, toxicogenomics adds an important new class of techniques for understanding biological mechanisms involved in chemical toxicity and that it is worth pursuing on this basis alone—although, not at the expense of other established methods.118

In the end, the research spawned by toxicogenomics may be as important for what it tells us we cannot know as it is for the knowledge that

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114 Waters et al., supra note 86, at 416; see also Aardema & MacGregor, supra note 20, at 15; Tennant, supra note 5, at A8.
115 Waters et al., supra note 23, at 814.
116 Lovett, supra note 21, at 536–37; Waters et al., supra note 86, at 419; Tennant, supra note 5, at A9 (reporting that this work will be complemented by the International Life Sciences Institute, which will focus on genotoxicants, hepatotoxicants, and nephrotoxicants).
117 Waters et al., supra note 86, at 419. The first experiments entailed using gene-expression profiling to identify known chemical toxins from several different classes based on their gene-expression “signatures” following an acute exposure to each compound. The experiments demonstrated that gene-expression methods can distinguish between two classes of toxins. Cunningham et al., supra note 75, at 210. The experiments found a high degree of accuracy for categorizing chemicals into the two distinct classes of compounds (correct for twenty-two of twenty-three compounds). Hisham K. Hamadeh et al., Gene Expression Analysis Reveals Chemical-Specific Profiles, 67 TOXICOLOGICAL SCI. 219, 228–29 (2002); Hisham K. Hamadeh et al., Prediction of Compound Signature Using High Density Gene Expression Profiling, 67 TOXICOLOGICAL SCI. 232, 233, 238–39 (2002). Further, in a second, parallel experiment, scientists found that only a limited number of gene transcripts (twelve transcripts) were needed to successfully identify the different classes of compounds. Thomas et al., supra note 1, at 1193–94.
118 Philosophy of Toxicology/Pathology Working Group of the NIEHS National Center for Toxicology acknowledges that “only through a strategic, incremental study of specific agents and specific toxic effects can the most appropriate ways in which to use toxicogenomics technology in toxicology be identified.” Paules, supra note 88, at A338.
it ultimately generates. As two observers have put it, “[c]urrent ‘complexity’
schools of thought may be faddish, but they have a point, and they have
amply shown that even relatively simple causation can be inferentially prob-
lematic” in biological systems.119 Even granting these limitations, how-
ever, the recent developments in toxicogenomics, and molecular biology
more generally, cannot be ignored and will impact environmental regulation
significantly. The discussion that follows examines the implications
of toxicogenomics for environmental law and policy.

A. Chemical Risk Standards for a Heterogeneous Population

Molecular epidemiology and toxicogenomics research will cause more
than the revision of regulatory standards and methods; it also stands to alter
how regulations are structured and set. Currently, government regulators
presume that variation in individual susceptibility to disease or harm from
chemical exposures across the population is relatively limited (i.e., it var-
ies by less than a factor of ten).120 Emerging molecular epidemiology and
toxicogenomic data suggest that this presumption is false. Recent studies,
for example, indicate that the efficacy of biological processes involved in
neutralizing the effects of toxic exposures vary by as much as eighty-five- to
five hundredfold across the U.S. population, with correspondingly high
variability in cancer risk.121 As public health scientists have argued, treating
the U.S. population as biologically uniform exposes population sub-
groups to unacceptable levels of risk.122

Research on variability in toxic susceptibility has focused on the dif-
fferences between children and adults, and it has been the unique suscep-
tibilities of children that have drawn attention to the issue.123 Both the
physiological immaturity of children and their often heightened level of
exposure contribute to increased susceptibilities.124 Infants and children are,
for example, subject to greater risks than adults when exposed to envi-

119 Weiss & Buchanan, supra note 26, at 178.
120 “Historically, EPA has generally applied an uncertainty factor of 100 to the results
of animal toxicity studies, to account for the fact that humans may be more sensitive than
test animals and certain human subpopulations may be especially sensitive.” Environ-
mental Protection Agency, 1996 Food Quality Protection Act: Implementation
Plan 12 (Mar. 1997). However, this uncertainty factor only applies to chemicals that are
presumed to have a threshold below which they are not harmful; non-carcinogens, for ex-
ample, are presumed not to have such a threshold. Gary Marchant, Genomics and Environ-
edu/files/Programs/Sci-Tech/Commentaries/marchantwhitepaper.pdf (last visited Nov. 15,
121 Perera & Weinstein, supra note 7, at 520.
122 Perera, supra note 7, at 608–09.
123 See, e.g., Environmental Protection Agency, Implementing the Food Qual-
ity Protection Act, at iii (Aug. 1999) (citing the strong evidence that children and in-
fants are uniquely vulnerable to risk from pesticide exposures).
124 Perera, supra note 67, at 1071.
ronmental toxins such as pesticides, air pollutants, and certain synthetic organic chemicals.\(^{125}\)

The broad variation in toxic susceptibilities demands that regulators utilize test methods that take individual differences into account. This will not be easy. Variation in toxic susceptibilities derives from simple genetic disorders, multigenic associations, developmental differences, epigenetic causes, environmental factors, and combinations of all five.\(^{126}\) Moreover, entire classes of enzymes (and their associated genes) are involved in cellular processes that mitigate the toxic effects of chemicals. As a result, even for relatively simple cases in which chemicals directly cause genetic damage, molecular buffering mechanisms can compensate for mutations that would otherwise adversely affect proteins involved in mitigating the effects of toxic compounds.\(^{127}\) Designing effective testing regimes is thus complicated by the range and unpredictability of variables that influence toxic susceptibilities.

The FQPA\(^{128}\) is arguably the first environmental statute that addresses population-wide variation in toxic susceptibilities.\(^{129}\) The FQPA includes specific provisions that address the unique biological susceptibilities of a population subgroup known to be more sensitive to certain types of chemical exposures.\(^{130}\) Focusing primarily on infants and children, the statute

\(^{125}\) Id. The causes of these difference “may include increased absorption and retention of toxicants, reduced detoxification and repair, the higher rate of cell [growth in children], and the fact that cancers initiated in the womb and in the early years have the opportunity to develop over many decades.” Id.


\(^{127}\) See infra Part IV.B. Toxic susceptibilities can also encompass a broad range of genetic variants because different combinations of genes and environmental factors will influence a person’s susceptibility at any given time. Id.

\(^{128}\) See supra note 30 and accompanying text.

\(^{129}\) The importance of population subgroups has been acknowledged in two other environmental statutes, but both provisions are limited to informational requirements. The Clean Air Act requires EPA to collect information on “measures which may be employed to . . . protect the health of sensitive or susceptible individuals or groups.” 42 U.S.C. § 7408(i)(1)(C) (2000). Similarly, the 1996 amendments to the Safe Drinking Water Act require EPA to conduct studies involving drinking water contaminants “to identify groups within the general population that may be at greater risk than the general population.” 42 U.S.C. § 300j-18(a)(1) (2000). See also Marchant, supra note 120, at 18–20.

\(^{130}\) Congress was, in part, responding to a 1993 National Research Council report that urged “the federal government [to] change some of its scientific and regulatory procedures to afford infants and children greater protection from possible adverse health effects of pesticides in their diets.” Press Release, National Academies, Changes Needed to Protect Children From Pesticides in Diet (June 28, 1993), at http://www4.nationalacademies.org/news.nsf/isbn/0309048753?OpenDocument (last visited Nov. 6, 2004) (on file with the Harvard Environmental Law Review); see also EPA, supra note 123, at 42. The central rationale motivating the call for reform was the “fundamental maxim of pediatric medicine . . . that children are not 'little adults.'” National Research Council, Pesticides in The Diets of Infants and Children 3 (1993). The report identified “quantitative and occasionally qualitative” differences in toxic susceptibilities between children and adults, and a woeful lack of data on infants and children. Id. at 3–5.
requires pesticide standards to be set at levels that protect them.\textsuperscript{131} Further, when (1) data demonstrate that a pesticide poses heightened risks to infants and children or (2) data are not available regarding a pesticide’s toxicity to infants and children, the FQPA affords EPA discretion to include an additional tenfold safety factor.\textsuperscript{132} The new tenfold safety factor is a default measure that may be altered only if reliable data demonstrate that a different standard would adequately protect infants and children.\textsuperscript{133}

The FQPA also extends certain protections to subgroups of individuals with heightened susceptibility. In setting pesticide standards, the statute states that EPA “shall consider, among other relevant factors . . . available information concerning the variability of the sensitivities of major identifiable subgroups of consumers.”\textsuperscript{134} Unfortunately, Congress failed to define the term “major identifiable subgroup” in the statute, and neither the legislative history nor the statute as a whole provides any useful indication of Congress’s intent regarding the criteria that should be used to define a major identifiable subgroup.\textsuperscript{135} Predictably, it did not take long before the interpretation of this term became a significant issue.

In 1998, the Natural Resources Defense Council (“NRDC”) and a number of other non-governmental organizations petitioned the EPA to identify farm children as a major identifiable subgroup.\textsuperscript{136} The strategy adopted in the NRDC petition is interesting insofar as it identifies a group based on its members’ physical characteristics, the developmental attributes of children and infants, and their unique environmental circumstances.

\textsuperscript{131} 21 U.S.C. § 346a(b)(2)(C)(i)(I)–(III) (2000). The agency must consider (1) whether consumption patterns among infants and children render them more subject to exposure than the population at large; (2) whether infants and children are especially susceptible to pesticide residues, “including neurological differences . . . and effects of in utero exposure;” and (3) whether, and to what extent, infants and children face unique cumulative effects from pesticide residues and other substances with similar mechanisms of toxicity. Id.

\textsuperscript{132} 21 U.S.C. § 346a(b)(2)(C) (2000) (limiting this additional tenfold safety factor to chemicals with “threshold” effects, meaning that harm does not occur below a certain threshold level of exposure).

\textsuperscript{133} ENVIRONMENTAL PROTECTION AGENCY, DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTOR(S) IN TOLERANCE ASSESSMENT 12 (Feb. 2002) (“EPA must apply the default 10x safety factor unless EPA concludes, based on reliable data, that a different safety factor would protect the safety of infants and children.”). This safety factor is in addition to the two standard tenfold uncertainty factors that EPA has historically used to take into account, especially, inter- and intra-species differences in toxic susceptibilities. Id. at A-3.

\textsuperscript{134} 21 U.S.C. § 346a(b)(2)(D)(vii).


\textsuperscript{136} National Resources Defense Council et al., Petition for a Directive that the Agency Designate Farm Children as a Major Identifiable Subgroup and Population at Special Risk to Be Protected Under the Food Quality Protection Act (1998), available at http://www.ecologic-ipm.com/farmkids.PDF (last visited Nov. 6, 2004) (on file with the Harvard Environmental Law Review). The petition drew on extensive studies and a report written by NRDC scientists showing that farm children are disproportionately subject to higher pesticide exposure levels. Id. As of March 2003, EPA had not responded to the petition. See Cook, supra note 135, at 1138.
Moreover, the physical characteristics are based on the developmental processes particular to infants and children, which are already formally recognized in the FQPA. In effect, it is the carefully documented environmental factors and living conditions of the group that define it. These features of the petition make it clear that no attempt was made to define a major identifiable subgroup based on novel physical characteristics, such as a genetic predisposition. Farm children were both politically salient and scientifically established as a distinct subgroup with unique susceptibilities and environmental exposures.

The NRDC petition rightly focuses on the defining environmental conditions of the group. The many problems already described with resolving genetic susceptibilities make it very unlikely that a major identifiable subgroup could be established on a genetic basis. First, given that simple genetic disorders are rare, genetic subgroups in most cases simply would not be large enough. Second, for complex genetic disorders, the impediment will lie in identifying the specific genetic attributes that define the subgroups because they will be so variable and context-dependent. Accordingly, the FQPA approach premised on defining major identifiable subgroups cannot address the variation in toxic susceptibility caused by more subtle and complex individual genetic differences.

An alternative approach is needed to address the variability in toxic susceptibilities that recent scientific developments in molecular biology and genomics have exposed. I would urge that simple and complex genetic susceptibilities be addressed separately. The subgroups of individuals with simple genetic susceptibilities to toxic exposures (e.g., susceptibility to harm from beryllium exposure) will be, relatively speaking, easier to define and identify. Thus, an approach based on “identifiable subgroups” is viable for such simple genetic susceptibilities—assuming they must be dealt with separately because complex genetic differences fail to cover them. The more challenging question is what kind of protection to afford small subgroups in a regulatory setting. This raises important ethical considerations and has been the subject of a great deal of scholarly

137 See NRDC et al., supra note 136, at 1–3.
138 Admittedly, “major” remains undefined, but if children and infants are treated as the prototype for major identifiable subgroups, the few hundred to few thousand people who are likely to suffer from a rare genetic disorder will fall far below this benchmark.
139 It may be possible to define subgroups based more on mechanistic failures, such as the lower metabolic rates found in molecular epidemiological studies. However, even the impact of biochemical processes can be highly dependent on the specific conditions and chemical toxin. In some cases, for example, a lower metabolic rate can be detrimental because it allows the toxin to remain active, but in other cases a high metabolic rate actually increases toxicity, such as where a chemical’s metabolite actually causes the harm. Perera, supra note 66, at 501–02.
140 Perera, supra note 67, at 1072 (urging that “[w]herever possible, for each toxicant of concern, risk assessments should present the estimated range of risk across the population as well as risks to identified sensitive populations . . . ”).
debate. I will not attempt to address such questions here because they are beyond the scope of this Article.

Defining effective legal rules for complex genetic susceptibilities is made especially difficult because the variation in susceptibility is so unpredictable. As a result, individuals often will not know where they fall within the distribution of susceptibilities and the distribution itself may not be a simple one. Given the uncertainties that already exist in toxicological testing methods, an approach based on identifying specific population subgroups will fail. The most viable approach is to incorporate another safety factor into estimates of chemical toxicity, but one that is roughly commensurate with the measured (or estimated) variability in individual toxic susceptibility across the U.S. population as a whole. Initially, data will no doubt be limited, requiring that a default factor (like that already used in the FQPA) be used or that multiple factors be developed based on classifying chemicals according to their mode of action. As scientists' mechanistic understanding of chemical toxicity improves and better epidemiological data are collected, default safety factors can be replaced. Consistent with the Subsection that follows, research ought to be directed at chemicals to which the public is exposed the most or that pose particularly significant risks.

The complexity inherent in toxic susceptibilities is also important because it defuses many of the difficult questions raised by simple genetic disorders. The nature of complex toxic susceptibilities precludes reducing them to well-defined genetic attributes. Focusing on observed susceptibilities, as opposed to genetics, will counteract propensities for the debate to lapse into a divisive form of genetic essentialism. Toxic susceptibilities do not fit simple binary categories of genetically normal and aberrant. To the contrary, the complexity of toxic susceptibilities precludes systematic categorizing and ought to dispel apprehensions that the current fixation on genetics could cause the burden to be placed on individuals with susceptibilities to protect themselves, rather than on industry or the government. It also stands to expose the importance of environmental and behavioral


142 Mohrenweiser, supra note 27, at 141–42 (“For complex diseases, an almost continuous gradient of individual risk exists within the population.”).

143 Mechanistic information of detoxification pathways, while not fully quantitative, will allow safety factors to be refined. For example, if scientists find that an important detoxification process has a highly variable level of efficacy across the U.S. population, the estimated variability could be used to derive an appropriate safety factor for chemical exposure. This type of information is already becoming available. See Perera & Weinstein, supra note 7, at 522.

144 Christiani, supra note 17, at 531.
factors, thereby reinforcing the necessity of addressing socioeconomic and environmental contributors to toxic susceptibilities. Recent developments in molecular epidemiology and the growing use of toxicogenomic methods have exposed the fallacy in environmental regulations that presume small variation in human susceptibilities to chemical toxins. While the innovations of the FQPA mark a major step forward, the statute’s reliance on recognizing major identifiable subgroups cannot address the complex, and prevalent, sources of variation in susceptibilities to toxic exposures. The scientifically grounded proposals advocated here correct major deficiencies in the FQPA approach and should be incorporated into amendments to the FQPA statute, as well as any future legislative efforts designed to address individual variation in toxic susceptibilities.

B. The Limited Influence of Genetics on Public Health

Ironically, one of the more powerful insights of genetic research is the dominant role environmental factors (e.g., poor diet, smoking, environmental pollutants) play in determining human health. According to broad scientific consensus, most common diseases are much more closely associated with human-made and natural environmental factors than genetic susceptibilities. Scientists estimate that the drop in cancer rates caused by eliminating certain environmental factors could be as high as eighty to ninety percent. By contrast, diseases with a strong genetic com-

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146 In epidemiological studies, environmental factors include any cause of disease that is not genetic, although specific researchers may refine the scope depending on the circumstances. Smith, supra note 31, at 573–77.

147 See e.g., Richard S. Cooper & Bruce M. Psaty, Genomics and Medicine: Distraction, Incremental Progress, or the Dawn of a New Age?, 138 ANN. INTERNAL MED. 576, 578 (2003) (“The primary disease-producing forces are rooted in our technologically based lifestyle and the resulting patterns of consumption, behaviors, and environmental exposures.”); Perera, supra note 66, at 496; I. Bernard Weinstein, The Origins of Human Cancer: Molecular Mechanisms of Carcinogenesis and Their Implications for Cancer Prevention and Treatment, 48 CANCER RES. 4135, 4135 (1988) (“Epidemiological studies provide evidence that environmental factors (external agents such as chemicals, radiation, and viruses) play a major role in the causation of the majority of human tumors.”); Willett, supra note 26, at 696 (“[T]he majority—probably the large majority—of important cancers in Western populations are due to environmental rather than genetic factors.”).

148 Hubbard & Wald, supra note 126, at 83, 91 (“Environmental carcinogens, such as chemicals, radiation, and probably viruses, are responsible for between 70 and 90 percent of cancers.”); Olden, supra note 5, at 4 (finding that strictly genetic disorders account for 21 to 42% of the risk of contracting the ten most common cancers, while non-uniform environmental factors account for 58 to 92% of this risk); Perera, supra note 66, at 496; see also Willett, supra note 26, at 695–96 (stating that non-genetic factors have high attributable risks, often of 80 to 90%); Rothman, supra note 4, at C2 (“estimat[ing] that 75–80% of all cancer in the United States is due to environmental factors and is, thus, potentially avoidable”). The contribution of environmental factors to human disease is demonstrated by geographical differences in disease incidence, variation in disease trends over time, and studies of disease patterns in immigrant populations. See Peto, supra note 29, at 390.
ponent are estimated “to account for less than 5% of major cancers and coronary heart disease.” These statistics confirm what we already know from the underlying biology, namely, that genetic variation constitutes one risk factor among many for common diseases.

This statement applies equally to individual environmental causes of disease. Although often lost in the debate over toxics regulation, individual environmental risk factors each have a relatively small effect on one’s lifetime risk of contracting a disease. Their aggregate impact on levels of mortality (or morbidity) becomes significant because the number of people exposed is large. In the United States, for example, smoking is associated with approximately eighty percent of the cases of lung cancer. Yet a smoker’s lifetime risk of lung cancer is “only” ten percent. The disparity in these numbers arises because the number of people who contract lung cancer is small, relatively speaking, while the number of people who smoke is quite large. Further, given that smoking is a leading environmental risk factor, the ten percent lifetime risk of lung cancer is a high-water mark; most pollutants will present a much lower lifetime risk.

The variety of risk metrics commonly used and debates over the relative importance of environmental risk factors also cloud public understanding.

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149 Willett, supra note 26, at 696; Olden, supra note 5, at 5; Perera & Weinstein, supra note 7, at 517; see also Peto, supra note 29, at 393. This statistic suggests, as some commentators have concluded, that toxicogenomics will, at best, marginally benefit public health because its major value is in identifying and treating rare genetic disorders. Cooper & Psaty, supra note 147, at 578 (predicting that “[treatment of common diseases] will only be minimally improved through genetic screening.”); Kathleen Ries Merikangas & Neil Risch, Genomic Priorities and Public Health, 302 SCI. 599, 601 (2003).

150 American Thoracic Society, What Constitutes an Adverse Health Effect of Air Pollution?, 161 AM. J. RESPIRATORY CRITICAL & CARE MED. 665, 668 (2000) (observing that even seemingly “minute individual risks may be significant from the standpoint of population exposures.”).

151 WORLD HEALTH ORGANIZATION, THE WORLD HEALTH REPORT 2002: REDUCING RISKS, PROMOTING HEALTHY LIFE 64–65 (2002) (stating that smoking is estimated to cause ninety percent of the cases of lung cancer in men and seventy percent of the cases in women in industrialized countries). Smoking is also estimated to cause “one-third of all cancer deaths in developed countries.” Peto, supra note 29, at 394.

152 Peto, supra note 29, at 394. Lung cancer is the single largest cause of mortality from smoking in the United States, implying that the lifetime risks for other diseases caused by smoking are substantially less. Id. at 391. In the United States, lung cancer accounts for thirty-nine percent of the deaths from smoking; the only other disease associated with smoking that is comparable in risk is heart disease, which accounts for thirty-six percent. Id.

153 In 2000, 22.2% of the U.S. population was classified as current smokers, 24.4% as former smokers, and 53.4% as non-smokers. Ali H. Mokdad et al., Actual Causes of Death in the United States, 2000, 291 J. AM. MED. ASS‘N 1238, 1239 (2004). This implies that well over a hundred million people have smoked or smoke in the United States. By contrast, about 170,000 new cases of lung cancer were expected to be diagnosed in 2002, and approximately 152,000 Americans died in 1999 from lung cancer. Centers for Disease Control and Prevention, The Burden of Chronic Diseases and Their Risk Factors: National and State Perspectives 2002, at http://www.cdc.gov/nccdphp/burdenbook2002/02_lungcancer.htm (last visited Oct. 9, 2004) (on file with the Harvard Environmental Law Review).

154 Peto, supra note 29, at 394 (“[M]ost causes of cancer are likely to increase risk by a small[,] amount . . . .”).
Blanket claims are frequently made that harm to public health from environmental pollutants in the air and water are of marginal significance. While it is true that the major sources of mortality and morbidity in the United States derive from smoking, poor diet, physical inactivity, and alcohol, they do not represent the full picture. First, evidence suggests that environmental pollutants may aggravate the impacts of the other major risk factors. Again, this is natural because biological responses to specific risk factors are sensitive to the other environmental factors present.

Second, the impact of environmental pollutants on major diseases, such as cancer, respiratory conditions, and cardiovascular disease is significant in absolute terms. Scientists from the U.S. Centers for Disease Control and Prevention estimate that 55,000 deaths in the United States are attributable to toxic agents, which is more than the number of people that the same scientists estimate are killed annually in automobile accidents and almost twice the number of people killed annually by guns. Further, many of the most serious diseases confronting children are believed to have a significant environmental component. In a recent study of the costs associated with harm to children from environmental pollutants in the United States, scientists estimated that the annual costs were $2 billion for asthma, $9.2 billion for neurobehavioral disorders, and $45.4 billion for lead poisoning. In each case, environmental pollutants present small lifetime risks and may account for a small fraction of all cases. Nevertheless, even with conservative estimates and limited data, both the number of people af-

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155 See, e.g., Bruce N. Ames & Lois S. Gold, Pollution, Pesticides and Cancer Misconceptions, in WHAT RISK?: SCIENCE, POLITICS & PUBLIC HEALTH 173 (Roger Bate ed., 1997) (arguing that the important causes of cancer are smoking, diet, chronic infections, and hormonal factors, not environmental contaminants).

156 Mokdad et al., supra note 153, at 1239–40. At the global level, similar environmental factors dominate, with high blood pressure, smoking, alcohol, child malnutrition, and unsafe sex among the major contributors. Majid Ezzati et al., Selected Major Risk Factors and Global and Regional Burden of Disease, 360 LANCET 1347, 1347 (2002).

157 Peto, supra note 29, at 392 (noting that both “indoor and outdoor air pollution from fossil fuels may also contribute to the risk of cancer in smokers”).

158 Id. at 391. (describing how the health effects of smoking in the United States and China differ markedly—whereas in the United States heart disease is associated with thirty-nine percent of the deaths from smoking, the same rate in China is nine percent).

159 Mokdad et al., supra note 153, at 1241; RICHARD J. JACKSON & CHRIS KOCHTITSKY, CREATING A HEALTHY ENVIRONMENT: THE IMPACT OF THE BUILT ENVIRONMENT ON PUBLIC HEALTH 7 (2002) (noting that during the summer of 1997, for example, air pollution resulted in more than six million asthma attacks and 53,000 hospitalization for asthma treatment); Aruni Bhatnagar, Cardiovascular Pathophysiology of Environmental Pollutants, 286 AM. J. PHYSIOLOGY—HEART & CIRC. PHYSIOLOGY H479, H482 (2003) (“The totality of the evidence . . . strongly supports the view that exposure to environmental toxins significantly increases [cardiovascular disease]”); Luis Cifuentes, Hidden Health Benefits of Greenhouse Gas Mitigation, 293 SCI. 1257, 1257 (2001) (citing studies with findings indicating that the reduction of emissions from coal-fired power plants alone would avoid 18,700 deaths and three million lost work days in the United States).

160 Mokdad et al., supra note 153, at 1241–42.

161 Landrigan et al., supra note 53, at 721.

162 Id. at 732–34, 726.
fected and the costs add up because of the large populations affected.\textsuperscript{163} More importantly, the crucial point remains that environmental factors, whether lifestyle- or pollutant-based, overwhelm the attributable risks from genetic susceptibilities.

Along with the overemphasis of genetic factors, it is also ironic that environmental health science is modeling itself more after high-tech medicine, which is moving farther away from a public health approach by touting “personalized medicine.”\textsuperscript{164} If one were to consider the relative benefits to society historically, it is strange that individualized, high-tech medicine has eclipsed traditional public health measures. Advances in aggregate human health have historically followed advances in basic public health medicine, such as improvement in sanitation, reductions in environmental exposures and improvements in living conditions, rather than major technological advances.\textsuperscript{165} As one author argues:

Contrary to what we are usually taught in school, mortality rates from almost all known infectious diseases were already decreasing in the industrialized world many decades before the offending bacterial or viral agents were identified. Deaths from such serious scourges as tuberculosis, scarlet fever, measles, and whooping cough were on the decline long before vaccines or drugs that are effective against these diseases were developed . . . . this decline [is attributable] to innovations in agriculture and transportation that increased the availability of different foods and so improved nutrition, and to sanitary measures that provided more healthful water and better sewage disposal and housing.\textsuperscript{166}

Ninety percent of the decrease in the death rate from tuberculosis, for example, occurred prior to the introduction of a drug therapy.\textsuperscript{167} Even life-expectancy increases in the United States derive mostly from reduction in infant mortality rates, which disproportionately lowered the population average.\textsuperscript{168}

These observations are not intended to suggest that society has not benefited enormously from technological advances in medicine or to deny that toxicogenomics offers a fruitful area of research. Rather, they are in-

\textsuperscript{163} Mokdad et al., supra note 153, at 1241.
\textsuperscript{165} HUBBARD & WALD, supra note 126, at 59; see also LEOWONTIN, supra note 126, at 43–44; JACKSON & KOCHTITZKY, supra note 159, at 5 (“Much of the improvement in disease death rates in the last century can be attributed to basic environmental public health actions”).
\textsuperscript{166} HUBBARD & WALD, supra note 126, at 59; see also LEOWONTIN, supra note 126, at 43–44.
\textsuperscript{167} LEOWONTIN, supra note 126, at 44.
\textsuperscript{168} Id. at 42.
tended to highlight the importance of public health approaches and to challenge the federal government’s focus on genomics research. NIEHS is making a major commitment to toxicogenomics based on often unrealistic expectations.\textsuperscript{169} Further, beyond the questionable objectives of NIEHS in launching the EGP, research in the environmental sciences must be balanced, both with respect to substantive areas covered and the relative likelihood of success. Indeed, substantive breadth is critical to toxicogenomics research itself, which is advanced by good epidemiological data.\textsuperscript{170} The rising fervor over toxicogenomics threatens to create an imbalance by focusing attention on a narrow, high-risk research program whose benefits will take years to realize and are likely to be indirect and research-oriented.

Broader, well-established public health research exists that ought to receive at least equal support.\textsuperscript{171} A good example of this type of research is the National Children’s Study (“NCS”), which is a large-scale prospective epidemiological study that “will examine the effects of environmental influences on the health and development of . . . children across the United States.”\textsuperscript{172} The NCS promises to be particularly powerful because of its study size (100,000 individuals) and its prospective approach, which will allow environmental exposures and perinatal factors to be assessed based on more solid data.\textsuperscript{173}

Yet, despite the support of a broad coalition of industry, public health, and research groups, funding for the NCS is currently in jeopardy.\textsuperscript{174} Large prospective studies that focus on environmental factors affecting human health are essential for all of the reasons discussed above, not the least of

\begin{thebibliography}{9}
\bibitem{169} See \textit{infra} Parts III.C., IV.
\bibitem{170} Rothman et al., \textit{supra} note 4, at C4 (arguing that epidemiological studies “are well-suited to identify the effects of common [genetic variants]”).
\bibitem{172} The National Children’s Study, at http://www.nationalchildrensstudy.gov/ (last visited Nov. 6, 2004) (on file with the Harvard Environmental Law Review). The NCS will follow more than 100,000 children from before birth until they reach age twenty-one. See Rob Stein, \textit{Following Children to Identify Health Risks; Study Will Examine Genes, Environment}, \textsc{Wash. Post}, Apr. 27, 2004, at A19.
\bibitem{173} Stein, \textit{supra} note 172; Gertrud S. Berkowitz et al., \textit{The Rationale for a National Prospective Cohort Study of Environmental Exposure and Childhood Development}, 85 Env’tl. Res. 59, 59 (2001).
\bibitem{174} Joel Kirkland, \textit{ACC Asks Congress to Fund National Child Health Study}, \textsc{Chem. News & Intel.}, May 5, 2004 (discussing how the Bush Administration proposed funding is grossly inadequate and describing the coalition of stakeholders lobbying on behalf of the NCS); Erica Check, \textit{Huge Study of Children Aims to Get the Dirt on Development}, 432 \textsc{Nature} 425, 425 (2004) (noting that $50 million has been allocated to plan the NCS, but Congress is yet to fund the program itself); Allison Freeman, \textit{Coalition Calls for Funding Boost for Children’s Health Study}, 10 Env’t & \textsc{Energy Daily}, May 4, 2004.
\end{thebibliography}
which is the paucity of data now available. Moreover, by focusing on broad public exposures, as opposed to individual susceptibilities and narrow technological strategies, public health studies serve the critical purpose of raising public awareness and understanding about the importance of environmental quality to their health.

In any research program opportunity costs must be balanced. A critical liability of the current infatuation with toxicogenomics is its potential to further distort research priorities in the environmental health sciences, which are already encumbered by inadequate support. It is therefore essential that policymakers and scientists alike promote an accurate understanding of toxicogenomic methods and that they foster a more reasoned, scientifically grounded approach to integrating toxicogenomics into environmental regulatory science. The Subsection that follows seeks to provide a realistic appraisal of genomics science and its potential for advancing environmental regulatory policy.

C. The Practical Limits of Toxicogenomics

Toxicogenomics is destined neither to cause a paradigm shift in toxicology nor be vitiated by toxicogenomics’ limitations. Toxicogenomics will undoubtedly establish a new class of analytical methods, but it is unlikely to generate quantitative tests of chemical toxicity, susceptibility, and harm. Insights will nevertheless emerge incrementally as toxicogenomic methods reveal important biological mechanisms involved in chemical toxicity. As such, toxicogenomics will aid scientists’ efforts to obtain qualitative knowledge about these mechanisms. Two matters of par-
ticular importance that will be illuminated are estimates of the interindividual variability in susceptibilities to toxic exposures,\(^\text{181}\) which was discussed above, and extrapolations from animal models to humans.\(^\text{182}\) Further, development of a mechanistic understanding of the metabolic processes that break down toxic chemicals will provide basic information for understanding biological responses to low-level toxic exposures. This information will improve toxicological experiments using traditional epidemiological methods and promote the creation of new methods.

Toxicogenomics also stands to provide important information on different modes of toxicity, which will assist scientists in identifying the structural elements of chemicals that make them harmful. This mechanistic information may help to determine whether a toxic threshold exists for exposure to particular chemicals—although quantifying what the threshold is will remain elusive. The end result may be a qualitative classification scheme for chemical toxicity that employs a combination of mechanistic knowledge and epidemiological testing.\(^\text{183}\) Equally importantly, improved mechanistic knowledge may enable scientists to develop effective treatment regimes.

Even under the best of circumstances, toxicogenomics will have important practical limitations.\(^\text{184}\) "The best cases will involve rare genetic disorders that will marginally benefit the public, but will certainly have profound benefits for certain individuals.\(^\text{185}\) Arguably the most significant constraint is therefore toxicogenomics’ poor track record and low likelihood of success with more common, complex toxicological responses and susceptibilities. From a public health perspective, knowledge gained from

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\(^\text{181}\) Perera & Weinstein, supra note 7, at 517 (noting that significant advances have already been through work in molecular epidemiology).

\(^\text{182}\) MacGregor, supra note 13, at 244 (describing how toxicogenomic methods may aid in the development of biomarkers that enable comparison of toxic responses between animal models used in toxicity testing and humans); Olden et al., supra note 4, at 1965 (noting that knowledge of toxicological processes in humans and animals will “be very useful for extrapolating from . . . surrogate models [i.e., animals] . . . to humans.”).


\(^\text{184}\) Experience in drug development ought to be particularly sobering. Despite enormous incentives to develop better methods for early detection of toxicity—just “a 10-percent improvement in predicting failures before clinical trials could save $100 million in development costs per drug”—drug companies continue to struggle in their efforts to develop effective test methods. FDA, supra note 24, at 8.

\(^\text{185}\) See supra Part II.B. In some cases, even relatively rare genetic disorders can have a significant impact, such as the recent finding that a mutated growth factor receptor is strongly associated with lung disease that responds remarkably well to the drug gefitinib. See Jean Marx, Why A New Cancer Drug Works Well, In Some Patients, 304 Sci. 658, 658 (2004). Although the drug is effective for only ten percent of patients, it stands to have a significant market because lung cancer kills about 160,000 Americans each year. Id.
studying simple genetic disorders should be leveraged to understand more common and complex conditions. However, the extent to which such opportunities will arise remains, at best, uncertain. The other important limitation from a regulatory standpoint is that toxicological data will not be deterministic—associations between genetic mutations or gene activity and harm will be probabilistic.

The significance of these limitations is illustrated by the highly touted discovery of the strong association of the BRCA1 and BRCA2 genes with breast and ovarian cancer. The BRCA genes represent a best-case scenario for applying genomics methods because they involve single genes that have a large impact on risk. But, consistent with the low rates of such disorders, approximately ninety percent of women with breast cancer do not have the high-risk mutations in either of these genes. At the same time, the estimates of the cancer risk for women with cancer-linked BRCA variants (eighty-five percent for breast cancer; forty-five percent for ovarian cancer) are subject to significant uncertainties, as other factors are also clearly involved. Accordingly, even if a test is positive, it is not clear how doctors should counsel women given the underlying uncertainties, the lack of effective measures of prevention, and the probabilistic nature of the information. These qualifications have understanda-
bly led patients and doctors to view genetic testing skeptically. One can only imagine how such uncertainties would invite controversy and agency paralysis in a regulatory setting.

The impulse to revitalize environmental toxicology that toxicogenomics has inspired is clearly a positive step that acknowledges the need for fundamental change. Federal agencies, however, are staking a great deal of political and scientific capital on the transformative potential of toxicogenomics when significant uncertainties remain about its methods. The preceding Sections analyzed these uncertainties and the many limitations that are likely to impact the degree to which environmental regulators can utilize toxicogenomics. The major problems critics have identified with toxicogenomics, and genomics methods generally, have prompted scientists to redouble their efforts and to broaden their research program. Scientists are also beginning to apply complex mathematical models to the study of biological systems. With this multifaceted approach, proponents of toxicogenomics believe they will be able to gain a precise understanding of even the most complex biological processes.

The potential flaw in this approach is that it may involve something akin to the blind leading the blind, as none of these techniques is currently well-established. It is one thing to expand scientific knowledge by taking advantage of complementary methods, which on their own are well established, to resolve uncertainties. It is quite another, however, to apply several weak methodologies, none of which rests on solid empirical or theoretical grounds, with the hope that a similar level of determinacy and insight can be achieved. From a regulatory standpoint, these problems suggest that toxicogenomics methods will take years to refine, and they raise serious questions about their viability as regulatory tests in the long run.

Critics of toxicogenomics are correct to point out that “because of evolution, genetics is involved in everything; but because of evolution by phenotype, not everything is genetic.” The genomics revolution, even in its

\[\text{tions About the Use of Genetic Tests in Populations, 357 LANcET 710–11 (2001).}\]

\[\text{Cooper & Psaty, supra note 147, at 577 (“[T]he available empirical data support the argument against a clinical role for susceptibility testing for chronic disease.”); Hubbard & Lewontin, supra note 28, at 1192–93.}\]

\[\text{As discussed further below, the genomics revolution has expanded to include protein function, metabolic processes, and cutting-edge technologies in physiological imaging. Waters et al., supra note 23, at 811; see also infra Part IV.A.}\]

\[\text{See infra Part IV.B.}\]

\[\text{Indeed, if anything genomics is better developed and technically simpler than the other “-omic” fields, which often involve even more complex regulatory processes. Weiss & Terwilliger, supra note 187, at 154 (asserting that there is no reason to “expect the network of regulatory pathways to be less complex than the genetic heterogeneity with which we currently struggle”).}\]

\[\text{Even the most committed proponents of toxicogenomics, such as the scientists involved in the Environmental Genome Project at NIEHS, are beginning to acknowledge that progress will be made incrementally and that application of toxicogenomic methods in a regulatory setting are at least a decade away. See, e.g., Waters et al., supra note 23, at 816, 822.}\]

\[\text{Weiss & Buchanan, supra note 26, at 178; see also Richard C. Lewontin, The...}\]
broadly integrative form, has tended to marginalize factors other than genetics that are equally, and often more, important in determining toxic responses and susceptibilities. The discussion in Part IV below shows that the complexity of toxicological responses must be dealt with on its own terms. Biology does not fit into a simple Newtonian model of science in which genes are the elementary objects that define the system as a whole. Toxicogenomic methods fall short in part because genes play a limited causal role in biological systems, which is a fact of biology that no amount of statistical pyrotechnics can overcome. Developing effective testing for chemical toxicity will ultimately require scientists to address these more complex processes. This issue is examined in detail in the next part, which provides a more thorough explanation of how biological complexity limits the power of genomics methods.

IV. A Critique of Toxicogenomic Methods: Taking Natural Selection Seriously

The distinctive power of genomics methods—monitoring thousands of genes simultaneously—comes at a significant price. The vast quantities of data generated by genomics studies raise extremely challenging problems for data analysis. The process of discerning the meaningful data from

TRIPLE HELIX 120 (2000) (“[V]ariation in size, shape, physiology, and behavior cannot be traced to any well-defined variation for a particular gene, if they are influenced by genes at all.”).

197 Weiss & Terwilliger, supra note 187, at 156.

198 Lewontin, supra note 196, at 113–14:

It is not new principles that we need but a willingness to accept the consequences of the fact that biological systems occupy a different region of the space of physical relations than do simpler physico-chemical systems, a region in which the objects are characterized, first, by very great internal physical and chemical heterogeneity and, second, by a dynamic exchange between processes internal to the objects and the world outside of them. That is, organisms are internally heterogeneous open systems.

199 Biological signaling processes that control cellular responses to environmental exposures, for example, involve networks that “defy analyses based on intuition” and that lack necessary experimental data. Upinder S. Bhalla & Ravi Iyengar, Emergent Properties of Networks of Biological Signaling Pathways, 283 Sci. 381, 386 (1999).

200 Mohrenweiser, supra note 27, at 142 (noting that the complexity of biological systems must be “conquered” if the potential of toxicogenomics is to be realized); Richard Strohman, Maneuvering in the Complex Path From Genotype to Phenotype, 296 Sci. 701, 703 (2002) (objecting to policies that “continue to see complex phenotypes as primarily derivable from genomic and proteomic databases”). Biomedical scientists also acknowledge the need to come to terms with complex biological processes. Geoffrey Duyk, Attrition and Translation, 302 Sci. 603, 603–04 (2003) (arguing that the shrinking number of drugs being discovered is attributable to the failure of scientists to address biological complexity in a systematic manner).

201 Baldi & Hatfield, supra note 89, at viii (“The bioinformatics solutions to problems associated with the analysis of data on this scale are a major current challenge.”); Irwin et al., supra note 82, at 72 (“The amount and complexity of the data means that con-
the masses of background noise requires the development of novel statistical methods that are computationally intensive and complex.\(^{202}\) Given these analytical hurdles, it should come as no surprise that successful applications of toxicogenomic methods have involved relatively simple cases.\(^{203}\) The narrow range of genomics successes has begun to prompt questions within the scientific community about the viability of applying genomics methods to more complex conditions.\(^{204}\) These concerns have been heightened by an increasing number of published reports in which prior experimental results derived from genomics measurements could not be reproduced.\(^{205}\) This Part of the Article delves into some of the likely reasons for these problems.

To begin, it is important to appreciate the contrasting public and scientific images of human genetics. In its most simplistic form, the public image of human genetics is that genes determine the person and control his susceptibilities to chemical toxicity and disease.\(^{206}\) This view is analogous to the claim that the food one eats fully determines who one is and founding factors can easily be missed and potential[ly] important changes may be overlooked.”); Lash et al., supra note 67, at 405 (“[B]ioinformatics is still struggling with the most appropriate means to analyze such large data sets.”).

\(^{202}\) Baldi & Hatfield, supra note 89, at 55–56 (discussing the multidimensional nature of biological systems and the sophisticated probabilistic methods that are being used to analyze them). Somewhat ironically, “[t]he selection of candidate genes has many parallels with identifying and ranking risk factors in an epidemiological study. In both arenas, investigators must choose, from a very large number of potential factors, those factors that are most likely to be involved in the [observed trait].” Tabor et al., supra note 183, at 3.

\(^{203}\) The much-vaunted advances made by genomics in medicine are also almost exclusively directed at rare, simple genetic disorders. Cooper & Psaty, supra note 147, at 577 (noting that “[t]o date, both [gene expression] studies and genome-wide scans have identified only weak and inconsistent genetic signals” for common diseases in the United States such as cardiovascular disease and cancer); David F. Horrobin, Realism in Drug Discovery—Could Cassandra Be Right?, 19 NATURE BIOTECH. 1099, 1099 (2001); Robert F. Service, Surviving the Blockbuster Syndrome, 303 SCI. 1796, 1799 (2004) (“The plain truth is that many of the most dramatic scientific advances that have recently been made in the lab have not transformed medical care.”) (quoting FDA Commissioner Mark McClellan). The significant technical obstacles that genomics is confronting are reflected both in the number of new drugs making it to market, which is lower than ever despite significant financing, and in the low success rate of new-drug development by the pharmaceutical and biotechnology industries. Jonathan Rees, Complex Disease and the New Clinical Sciences, 296 SCI. 698, 698 (2002).

\(^{204}\) See, e.g., Horrobin, supra note 203, at 1099.

\(^{205}\) Ahsan & Rundle, supra note 145, at 1429; Julian Little et al., The Human Genome Project Is Complete: How Do We Develop A Handle for the Pump?, 157 AM. J. EPIDEMIOLOGY 667, 669 (2003); Kirk E. Lohmueller et al., Meta-Analysis of Genetic Association Studies Supports a Contribution of Common Variants to Susceptibility to Common Disease, 33 NATURE GENETICS 177, 177 (2003); Weiss & Buchanan, supra note 26, at 171–72; Kenneth M. Weiss & Andrew G. Clark, Linkage Disequilibrium and the Mapping of Complex Human Traits, 18 TRENDS IN GENETICS 19, 22 (2002); Willett, supra note 26, at 696.

\(^{206}\) This description of the public understanding of genetics is arguably oversimplified in the sense that most people are aware of the basic debate over “nature versus nurture”—that is, over the respective roles of biology and environment in determining human traits. In another sense, the description is not an oversimplification because, much the same way soft variables (i.e., unquantified factors) tend to be ignored or marginalized in regulatory analysis, so too are non-genetic factors ignored once a genetic association is identified.
what one does. Literally speaking, we certainly are constructed out of what we eat, but it is equally true that we are much more than these constituent parts—traits and characteristics emerge at the level of the organism that cannot be easily reduced to the elements that make them up.\textsuperscript{207} It is also true that under certain circumstances what we eat (or do not eat) may determine our behavior or fate (e.g., starvation, poisons, pharmaceuticals), but it would be absurd to infer from these instances that humans are fully determined by what they eat. The relationship between an individual’s genetic makeup and her toxic susceptibilities is no different; some susceptibilities to toxic compounds have strong genetic influences (the minority as it turns out) and many have relatively weak or diffuse genetic influences that are often causally complex.\textsuperscript{208}

The challenges entailed in unraveling this complexity are exhibited by the genetic variation found in DNA repair genes, which play an essential role in neutralizing the effects of mutagenic chemicals. Over four hundred and fifty variants of the genes involved in DNA repair have been identified in genetic screens intended to be representative of the U.S. population.\textsuperscript{209} The large number of low-frequency variants discovered suggests that they are the primary source of genetic variation in the U.S. population.\textsuperscript{210} The implication of the large number of variants for toxicogenomic methods is sobering:

The complexity of the problem to be addressed in associating genetic variation with risk becomes apparent when it is realized that these repair pathways require the activity of 20–40 different proteins to complete the repair process. Thus, given the large number of different variant[s], the typical individuals will be variant for 10–15 proteins required for repair of a specific class of damage. But, these typical individuals will not have similar pathway genotypes as these 10–15 variants will be drawn from a pool of 100–200 different [genetic variants].\textsuperscript{211}

These results lead to the conclusion that, because it is the integrated functionality of the system of DNA repair genes that determines individual risk, linking specific genetic variants to increased susceptibility is made ex-

\textsuperscript{207} Weiss & Buchanan, supra note 26, at 178.
\textsuperscript{208} A number of cancers, for example, have been associated with genetic variations in tens of genes. Id. at 172. Further, the relationship between genetics and disease can be complicated by much more mundane factors, such as physiological differences that may aggravate or neutralize the effect of a genetic mutation. See, e.g., Cohen, supra note 180, at 5–6 (describing how basic physiological differences between animal models and humans are determinative of whether certain chemicals heighten this risk of bladder cancer and concluding that “[g]enomics will contribute little to this risk assessment”).
\textsuperscript{209} Mohrenweiser, supra note 27, at 139.
\textsuperscript{210} Id. (The average frequency of any single genetic variant is four percent, and only 15 of the 450 have an estimated frequency of greater than forty percent).
\textsuperscript{211} Id.
tremely difficult by the huge range of possible combinations and the small impact that any given genetic variant is likely to have.

The human genome and the processes involved in transcribing genes are also far more complex than popularized versions of genetics would lead one to believe. First, “less than two percent of the human genome codes for proteins, while more than fifty percent [consists of] repeat sequences of several types” that have a currently undefined function. Second, genes themselves are oddly constructed—most are not unbroken segments of DNA code, but instead are interspersed with long segments of non-coding DNA. Third, there are critical processes that are not genetically controlled, yet alter the activity of a gene or its protein product. These structural and dynamic features make even the process of identifying genes non-trivial, let alone the effort needed to link genes to specific toxic responses or susceptibilities. Moreover, cellular processes can include complex feedback mechanisms, involving multiple biological pathways, that influence gene expression patterns. These complex “epigenetic” dynamics are a distinguishing feature of biological systems that cannot be understood by focusing

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212 Guttmacher & Collins, supra note 3, at 1514.
213 Id. In fact, different coding sequences of a gene may be linked together in a variety of ways, such that the 30,000–35,000 genes in the human genome code for more than 100,000 proteins. Id.
214 Id. (offering as examples the signals that turn genes on and off and molecules that activate and deactivate critical proteins). These alternate control mechanisms have emerged because “[t]he evolution of additional complex attributes is essentially an organizational one,” not a product of major genetic modifications. Gerald M. Rubin et al., Comparative Genomics of the Eukaryotes, 287 Sci. 2204, 2214 (2000). Current evidence suggests that “the majority of phenotypic variation between individuals (and species) results from differences in the control architecture, not the proteins themselves.” John S. Mattick & Michael J. Gagen, The Evolution of Controlled Multi-tasked Gene Networks: The Role of Introns and Other Noncoding RNAs in the Development of Complex Organisms, 18 Molecular Biol. Evolution 1611, 1612, 1622–23 (2001); see also David K. Gifford, Blazing Pathways Through Genetic Mountains, 293 Sci. 2049, 2050 (2001); Baldi & Hatfield, supra note 89, at 141–42.
215 A test of gene detection methods on the Drosophila genome, for instance, were mixed. The accuracy of the methods used to find genes varied between 5% and 95%, and they incorrectly identified up to 55% of the genes studied. Teresa K. Attwood, The Babel of Bioinformatics, 290 Sci. 471, 471 (2000).
216 A recent issue of the journal Science contained a special section on “Mathematics in Biology,” and other recent articles have also highlighted the rising importance of mathematical modeling and the study of complexity in biological systems. Gilbert Chin et al., Biology by the Numbers, 303 Sci. 781, 781 (2004); Ronald N. Germain, The Art of the Probable: System Control in the Adaptive Immune System, 293 Sci. 240, 244 (“[I]t is now time to add the power of mathematics, systems analysis, and quantitative cell-based modeling” to the study of complex biological systems (e.g., the immune system).); Hiroaki Kitano, Systems Biology: A Brief Overview, 295 Sci. 1662, 1662 (2002); Robert F. Service, Exploring the Systems of Life, 284 Sci. 80, 83 (1999) (arguing that scientists will need to develop complex models for biological systems). This focus on modeling is motivated both by the needs of genomics research and the realization that biological systems often operate more as networks, with different pathways interacting, than as systems driven from the smallest level up by the same fundamental forces.
solely on genes. They also cannot be ignored because epigenetic processes play an important role in toxicological processes such as carcinogenesis.

The Subsections that follow discuss the important limitations of toxicogenomic methods. The discussion begins by examining problems that even proponents of toxicogenomic methods have acknowledged. It then turns to addressing the more systemic deficiencies of toxicogenomic methods that a number of well-known, though still often marginalized, critics of the genomics revolution have raised. Interestingly, the split between scientific proponents and critics of toxicogenomics resembles that between proponents of risk assessment and their (mostly environmentalist) critics in environmental law.

A. Selective Challenges in Toxicogenomic Methods

Even ardent advocates of toxicogenomics acknowledge that major advances in genomics methods and information will be necessary before they can be applied in a regulatory context. The challenges of establishing toxicogenomics as a reliable method for regulatory purposes range from low-level experimental impediments, to significant analytical problems, to deeper constraints imposed by the biological processes themselves.

At the most basic level, toxicogenomics lacks rigorously validated experimental methods and modes of data analysis. This lack of standardization is a significant obstacle to progress given the numerous sources of

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217 “Epigenetics is the study of heritable changes in gene expression that occur without a change in DNA sequence.” Alan P. Wolfe & Marjorie A. Matzke, Epigenetics: Regulation Through Repression, 286 SCI. 481, 481 (1999); see also Rebecca E. Watson & Jay L. Goodman, Epigenetics and DNA Methylation Come of Age in Toxicology, 67 TOXICOLOGICAL SCI. 11, 11 (2002). “[A]daptive epigenetic inheritance challenges the ‘central dogma’ that information is unidirectional from DNA to protein” and that epigenetic processes are unimportant in assessing potential chemical toxicity. Id. Examples of epigenetic phenomena include silencing of tumor genes through chemical modifications, short double-stranded RNA (RNAi) segments that mediate gene expression, and DNA-DNA, DNA-RNA, and RNA-RNA interactions that trigger gene silencing. Wolfe & Matzke, supra note 217, at 483.

218 Perera & Weinstein, supra note 7, at 521 (explaining that many carcinogenic chemicals act “through indirect genotoxic or epigenetic mechanisms”).

219 Cunningham et al., supra note 75, at 214; Robert Millikan, The Changing Face of Epidemiology in the Genomics Era, 13 EPIDEMIOLOGY 472, 476–77 (2002); Lash et al., supra note 67, at 405 (noting that the search for associations of multigenic variations will be costly and technically challenging, particularly given the current limits of bioinformatics and the lack of experimental standardization).

220 At the experimental level, many of the limitations found in simplified experimental models and animal studies also apply to toxicogenomics, such as extrapolating results from in vitro studies or animal testing to humans. Cunningham et al., supra note 75, at 211, 214 (recognizing that significant variability in the gene-expression profiles exists between animals and humans); Pennie et al., supra note 21, at 278–79 (noting that changes in expression profiles may not reflect the response of affected organs in vivo, where toxicity is specific to a species, strain, sex, or route of exposure, in vitro testing is unlikely to be a reliable approach).

221 Baldi & Hatfield, supra note 89, at xi–x, 31–32, 49–51, 53, 55; Cunningham et al., supra note 75, at 211.
instrumental variability in toxicogenomic microarrays and the broad range of platforms that scientists are using. Standardized methods for constructing microarrays and analyzing data are urgently needed and are a high priority for NIEHS, but a great deal of work is still needed in this area.

Precise control of genetic material is a necessity for toxicogenomics because its methods require the manipulation and analysis of vast quantities of genetic material. These high volumes require a mapping system for identifying genetic segments, which can consist of multiple genes, a specific gene, or a gene fragment. Because genes are large molecules and mutations can arise in different sections of a gene, simply relying on their unique structure for identification purposes does not work. Instead, scientists either track the mutation itself, using it as a locator tag, or they rely on short, novel sequences that are commonly found in the general population, referred to as “genetic markers,” as locator tags for mapping genetic mutations in a genome. The more prevalent a genetic marker is,
the more useful it will be to scientists because it can be used in large population studies. Use of a rare genetic marker for mapping purposes is analogous to relying on faulty map designations that are routinely removed from the spot they were intended to identify and randomly transferred to a completely new location.\textsuperscript{226}

Toxicogenomic testing is not possible when reliable genetic markers are not available in a given region of the genome—if genetic sequences cannot be tracked, they cannot be tested. These gaps can arise for a number of reasons. First, no genetic marker is universal, and the rates at which specific genetic markers occur will vary from population to population.\textsuperscript{227} Second, the most prevalent genetic markers will be the oldest, as it takes time for markers to spread throughout a population.\textsuperscript{228} Older genetic markers, however, can shift position in the genome, breaking their association with the DNA segment they are used to tag.\textsuperscript{229} As a result, for such older genetic markers a certain number of misidentifying tags will be present. The extent of these problems was confirmed in a recent study that found many genes do not have a consistent set of common genetic markers from which scientists can draw.\textsuperscript{230} While more genetic markers will no doubt be discovered, their identification and reliability is an important limiting factor in the application of toxicogenomic methods.\textsuperscript{231}

\textsuperscript{226} This discussion presumes that genetic markers are being used as indirect tags for segments of DNA. Rare genetic markers are, by contrast, extremely useful as direct markers of rare, monogenic disease-causing genetic variants, such as the mutations associated with certain types of breast cancer.

\textsuperscript{227} See Weiss & Terwilliger, supra note 187, at 152; Christopher S. Carlson et al., Additional SNPs and Linkage Disequilibrium Analyses are Necessary for Whole-Genome Association Studies in Humans, \textit{33 Nature Rev. Genetics} 518, 518 (2003) (explaining that the 2.7 million genetic markers available would detect nearly eighty percent of the common genetic variants in European populations but only fifty percent of those common in African American populations).

\textsuperscript{228} Elizabeth Pennisi, A Closer Look at SNPs Suggests Difficulties, \textit{281 Sci.} 1787, 1789 (1998); Weiss & Clark, supra note 205, at 19 (noting that common gene variants have more time to recombine and can have weaker associations than rarer, newer, or more geographically localized variants).

\textsuperscript{229} Weiss & Clark, supra note 205, at 19. Genetic recombination involves the mixing of different segments of a gene between its maternal and paternal copies during sperm and egg formation, thereby breaking down the correlation between a genetic marker and gene variants that inflate disease risk. Pennisi, supra note 228, at 1787. Such recombination makes it far more difficult to expose genetic associations with disease. \textit{Id.}

\textsuperscript{230} J. Clairborn Stephens et al., Haplotype Variation and Linkage Disequilibrium in 313 Human Genes, \textit{293 Sci.} 489, 492 (2001) (reporting that closely associated extended chromosomal segments for targeted genetic markers were often absent or of limited range). The reliability of genetic markers is reduced by gene conversion and recombination, which is dictated by highly stochastic processes for which there is wide variability across the genome. Weiss & Clark, supra note 205, at 19. As a result, the reliability of any given genetic marker must be assessed empirically, requiring further analysis that will require substantial additional resources and present its own set of obstacles. \textit{Id.} at 19, 23.

\textsuperscript{231} Carlson et al., supra note 227, at 520 (“[T]here is no simple way to develop an optimal subset [of genetic markers] without knowledge of [genetic variant] frequencies and
Arguably the most fundamental obstacle scientists confront is ensuring that their studies are based on unbiased, representative samples. Genetic differences between subgroups in a population being sampled, for example, can lead to spurious correlations between a disease present at higher frequency in a subgroup and a genotype (i.e., specific genetic variant) that also happens to be more common in that subgroup. This leads to false positive results because in most cases the trait and genotype will not be causally related. Moreover, these experimental challenges are made all the more acute because large sample sizes, which are more likely to have distinct subpopulations, are needed for statistical reasons.

Bias may also be introduced by subtle external factors, such as seasonal variations in sunlight, or internal molecular influences, such as hormone levels, that are often difficult to anticipate. This variability stems from chemical toxins acting through multiple mechanisms, which are dependent on dose, timing, and duration of exposure. Yet a central premise of gene-expression testing is that expression levels are stable (i.e., have a characteristic “signature”) under a variety of experimental conditions. Further, toxicogenomic testing is often conducted without knowing the cell type(s), or in some cases, organ(s) affected by a toxin. However, if a toxin affects gene-expression levels in only certain cells or organs, the change in expression levels of those specific cells may be obscured by gene expression in the more numerous unaffected cells. This leads to a chicken-
and-egg problem: one needs to have a mechanistic understanding of a chemical’s toxicity to know what cells or organs it affects but needs this very information to be able to conduct a meaningful gene-expression experiment to begin to understand the mechanism in the first place. To the extent that gene expression is subject to such influences, discovery of consistent patterns, or fingerprints, of toxic response or susceptibility will remain frustratingly elusive.\footnote{Mohrenweiser, supra note 27, at 138 (noting that even in the case of direct genetic mutation by a chemical, “[t]he pattern of DNA damage induced by an agent is often complex” and “the damage does not usually provide a unique ‘signature’ that can be employed for identifying exposure to a specific agent”).}

Complex diseases present daunting challenges for toxicogenomics and only a handful of complex susceptibilities have been successfully studied.\footnote{See Glazier et al., supra note 82, at 2345–46 (observing that there are fewer than ten instances in which complex genetic traits have been studied); Guttmacher & Collins, supra note 3, at 1518; Tabor et al., supra note 183, at 1–2.} The central reason is simple, namely, the causal connection of any one gene to a complex disease will be relatively weak and thus difficult to prove.\footnote{Cunningham et al., supra note 75, at 212; Hartman et al., supra note 28, at 1001; Lander & Schork, supra note 27, at 2044 (noting that no systematic approach exists for designing experiments with sufficient statistical power for complex diseases because the optimal design is dependent on the complexities themselves, which are necessarily unknown at the outset); Taubes, supra note 2, at 164–65 (explaining that current efforts to study weaker, more prevalent, sources of harm are pushing epidemiology to its limits, and arguably beyond). Dissecting the underlying genetic “causes” is made even more challenging because most complex susceptibilities have heritabilities of less than fifty percent, making it much more difficult to conduct complementary generational studies. See Weiss & Terwilliger, supra note 187, at 153.} Identifying relevant genes is made difficult because the expression level (or change in it) of any single contributing gene may be barely measurable.\footnote{Fielden & Zacharewski, supra note 83, at 7; Lander & Schork, supra note 27, at 2037 (explaining that the multigenic nature of complex toxin-induced diseases means that any single mutation will “affect the probability of disease, but not fully determine the outcome,” making toxicogenomic studies much more difficult because a mutation “may be present in some unaffected individuals or absent in some affected individuals”).} Indeed, specific genes associated with complex traits may also contribute so marginally to toxic susceptibility that it will make little sense to treat them as meaningful predictors of either harm or toxicity. Making matters worse, fewer genetic markers exist as the number of mutation sites a marker is used to tag increases.\footnote{See Cunningham et al., supra note 75, at 212 (noting that the number of potential genetic markers is limited for complex traits); Hartman et al., supra note 28, at 1001 (cautioning that genetic markers may work well for rare Mendelian traits, but much care is warranted in seeking to apply them to study complex traits); Horrobin, supra note 203, at 1100; Lander & Schork, supra note 27, at 2037 (recognizing that “it is often impossible to find a genetic marker that shows perfect cosegregation with a complex trait”); Temple et
tions in multiple genes are causally linked to a disease, the parallel epidemiological studies may require impractically large study sizes to obtain sufficient populations in each genetic subgroup. In such cases, elementary statistics may argue for a strategy that aggregates genetic subgroups. The upshot of this problem is that rather than being a more powerful approach, the results from toxicogenomic studies may actually be more difficult to verify than standard methods for most conditions of regulatory significance.

These constraints have led scientists to adopt a broader, integrated approach that incorporates data from proteomics, metabonomics, and physiological studies. Without such an integrated approach, scientists would have a very low likelihood of successfully studying the mechanisms that underlie toxic responses and susceptibilities given the complexities identified above. There have also been some significant advances in molecular imaging technology, which allows scientists to observe real-time cellular processes in vivo, and methods for in vivo testing of protein struc-

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al., supra note 223, at 808; Willett, supra note 26, at 696.

Ahsan & Rundle, supra note 145, at 1431–32 (“[T]he large possible combinations of genotypes will require an impractical study size to meaningfully examine their effects.”); Willett, supra note 26, at 696 (suggesting that genomics data “may still be less useful than simply measuring serum [levels of a hormonal biomarker], which summarize[] all the genetic and environmental determinants”). Acknowledging these limitations, some avid proponents of toxicogenomics concede that the benefits of genomics methods will be indirect and “discovery” focused, as their primary role will be in aiding identification of useful molecular biomarkers. MacGregor, supra note 13, at 240.

See Ahsan & Rundle, supra note 145, at 1431–32; see Clayton & McKeigue, supra note 186, at 1357–58.

Clayton & McKeigue, supra note 186, at 1359.

Nicholson et al., supra note 99, at 153, 160 (“The realization that obtaining the genome sequence of humans or other species does not in itself explain the fundamental nature of many disease processes has triggered a marked increase in interest in approaches that relate gene expression to phenotypic outcome.”); Baldi & Hatfield, supra note 89, at ix (“[A]rray data must be integrated with sequence data, with structure and function data, with pathway data, with phenotypic and clinical data, and so forth. New biological discoveries will depend strongly on our ability to combine and correlate these diverse data sets along multiple dimensions and scales.”).

Proteomics is the study of proteins in biological systems, particularly their functionality and the levels at which they are produced—cells typically contain thousands of different proteins. Pennie et al., supra note 21, at 278. Currently, the power of proteomic methods is far less developed than that of genomics techniques, but the field is rapidly developing. See N. Leigh Anderson et al., Proteomics: Applications in Basic and Applied Biology, 11 CURRENT OP. BIOTECH. 408 (2000) (describing how proteomics will follow genomics as the new dominant technology in biology for the new century).

Metabonomics involves the study of chemical metabolism (i.e., biological breakdown of chemicals, including foreign toxins) using methods that allow visualization of tissue-wide patterns of chemical metabolites. Waters et al., supra note 86, at 418. Important, “[m]etabolic changes are real world end points, whereas gene expression changes are not; [gene expression levels] merely indicate the potential for an end-point change.” Nicholson, supra note 99, at 153.

See Fielden & Zacherewski, supra note 83, at 7–8. It is important to note, however, that the process of combining these different sources of information (genomic, proteomic, metabolic, etc.) is far from trivial and successful examples of this approach are still relatively rare. See Mark Gerstein et al., Integrating Interactomes, 295 Sci. 284, 285 (2002).
ture and function that will be critical to this work.\textsuperscript{252} If successful, imaging methods will enable scientists to monitor the impact and pathways of toxins in affected organs and physiological processes.\textsuperscript{253} These methods may offer another view of biological mechanisms important to toxicology and essential to toxicogenomic methods.

\textbf{B. Objections to Genetic Reductionism in Genomics Science}

Critics of toxicogenomics, and the Human Genome Project more generally, believe the problems discussed in the previous Subsection are superficial manifestations of much deeper theoretical defects. They reject the core genomics dogma that toxic susceptibilities derive directly from genetic mutations and that toxic responses and susceptibilities can be understood by tracking gene activity levels before and after toxic exposures.\textsuperscript{254} For them, it makes no sense to measure gene-expression levels when the influence of genetics on individual toxic responses and susceptibilities is highly attenuated. Their opposition to genomics methods is based on the view that “almost all human diseases are complex context-dependent entities to which our genes make a necessary, but only partial, contribution.”\textsuperscript{255} They consider the current fixation on genetics to be a case of scientists treating everything as though it were a nail because they have a hammer. In short, enthusiasm for genomics methods, rather than a considered understanding of biology, is driving the science.\textsuperscript{256}

These critics’ arguments center on the complex, indirect nature of the interactions between genetics and human disease. Two central points stand out: (1) genes do not have a fixed (either negative or positive) impact on human health, and (2) a weak causal association exists between a person’s genetic makeup and his responses and susceptibilities to most toxic exposures.\textsuperscript{257} One of the most important principles that has emerged from

\textsuperscript{252} Harvey R. Herschman, \textit{Molecular Imaging: Looking at Problems, Seeing Solutions}, 302 Sci. 605, 606–07 (2003); Lash et al., supra note 67, at 405 (observing that major advances have been made in “validating \textit{in vivo} probes for assessing phenotype in relatively noninvasive manners”).

\textsuperscript{253} Herschman, \textit{supra} note 252, at 605–06 (reporting that newly developed molecular imaging technologies allow noninvasive and repetitive study of “the mechanisms underlying normal development and disease”).

\textsuperscript{254} Weiss & Terwilliger, \textit{supra} note 187, at 151 (explaining that critics reject the view “that the genetic determinants of complex traits are tractable, and that knowledge of genetic variation will materially improve the diagnosis, treatment or prevention of a substantial fraction of cases of the diseases that constitute the major public health burden of industrialized nations”).

\textsuperscript{255} Strohman, \textit{supra} note 200, at 701; \textit{see also} Rees, \textit{supra} note 203, at 699.

\textsuperscript{256} Lewontin, \textit{supra} note 196, at 128 (acknowledging that scientists focus on questions they can answer with existing methods, creating a dialectic between method and theory); \textit{see also} Elliot Sober & Richard C. Lewontin, \textit{Artifact, Cause and Genic Selection}, 49 Phil. Sci. 157, 158–59 (1982).

\textsuperscript{257} See Weiss & Terwilliger, \textit{supra} note 187, at 152 (arguing that the central inferential problem is that a specific genotype does not imply a specific phenotype nor does a specific
biology is the dependence of a gene’s function on other genes and on environmental factors. According to this principle, known as the “genetic theory of relativity,” a gene may be highly beneficial “on one genetic background and be virtually lethal on another.” As a consequence, genes will typically have multiple effects that are dependent on one’s genetic background and the environment in which one lives.

The context-dependence of genetic traits is evident in even simple single-gene diseases, which often exhibit wide inter-personal variation in their clinical impacts. The effect of the genetic mutation that causes sickle cell anemia provides a simple example of this variability. Sickle cell anemia is illustrative because it has counterbalancing effects—it both degrades the functioning of red blood cells and makes carriers resistant to malaria. Symptoms consequently range from severe anemia for individuals with two copies of the mutation, to none for individuals with two normal copies of the gene who are not exposed to malaria, to beneficial malarial resistance for individuals with one mutated and one normal copy of the gene who are exposed to malaria. For complex diseases, the variation will be more intricate because a number of interacting genes will be involved. The end result is the same. Genes do not have fixed effects that are invariant between individuals with different genetic backgrounds or across different environments. This variation creates several significant problems for genomics. First, it negates the central genomics mission of ascribing fixed toxic susceptibilities to genes. Second, it introduces another source of variability that further undermines genomic methods designed to fingerprint disease states and toxic effects using gene-expression patterns.

The relationship between genetic makeup (“genotype”) and disease or toxic susceptibility (“phenotype” or observed trait) is also not a simple one. First, natural selection acts directly on phenotype, but only indirectly

\[ \text{phenotype imply a specific genotype; they are not equivalent or even necessarily correlated).} \]

\[ \text{258 Sober & Lewontin, supra note 256, at 159; Glazier et al., supra note 27.} \]

\[ \text{259 Mark S. Boguski, Biosequence Exegesis, 286 Sci. 453, 454 (1999). Some scientists have argued that, “[i]f only 1 in 10,000 of the [mutations] present in the human population has some [tangible] effect, then there would be more than enough unique combinations of these polymorphisms to assure that every human being (with the exception of identical twins) should have a unique [set of susceptibilities];” Hartman et al., supra note 28, at 1001.} \]

\[ \text{260 Hartman et al., supra note 28, at 1001 (explaining that in nature no wild type exists; all disease and chemical toxin susceptibilities are “arbitrarily defined [at a] point along a spectrum”); Little et al., supra note 205, at 669; Weiss & Buchanan, supra note 26, at 167.} \]

\[ \text{261 Ernst Mayr, The Objects of Selection, 94 Proc. Nat’l Acad. Sci. USA 2091, 2092 (1997); Sober & Lewontin, supra note 256, at 165–67.} \]

\[ \text{262 Millikan, supra note 219, at 474 (recognizing that a huge gap exists between genotype and phenotype because unmeasured genetic and environmental factors can influence expression); Strohman, supra note 200, at 701–02 (explaining that the progression from genotype to phenotype extends over four basic levels of control—genome to transcriptome, transcriptome to proteome, proteome to dynamic system, dynamic system to phenotype—“each . . . level [of which] is defined by a dynamic system of self-organizing proteins, the output of which is governed by laws that are still poorly understood”).} \]
on genotype (i.e., underlying genetic attribute).\(^\text{263}\) This distinction is important because the indirect relationship between natural selection and genotype allows genetic drift (i.e., selectively neutral genetic variation) to propagate over time.\(^\text{264}\) Genetic drift impacts genomics methods by decoupling genotype from phenotype, such that while a phenotype may remain fixed under the pressures of natural selection, the underlying genotype may vary significantly.\(^\text{265}\) Accordingly, it generally will not be possible to infer genotype from an observed phenotype, as the same phenotype can arise from multiple genotypes.\(^\text{266}\) Genetic drift introduces another source of variability into genomics methods—multiple gene-expression patterns may be associated with a single disease state or toxic effect.\(^\text{267}\) The absence of a unique, or even well-defined, genotype-phenotype relationship complicates the process of filtering out spurious gene-expression patterns from the meaningful signatures of toxicity, susceptibility or harm in toxicogenomic testing, and may erode the association altogether.

Second, biological processes actively buffer phenotype from variations in genotype.\(^\text{268}\) A genetic mutation that, for example, inhibits the activity of an important metabolic enzyme may be neutralized by other processes that counteract the impact of the mutation on the enzyme’s function or by redundancies built into the specific metabolic process.\(^\text{269}\) Buffering mechanisms may also cause specific genotypes to be associated with diverse phenotypes depending on the individual’s genetic background and environ-

\(^{263}\) Ahsan & Rundle, supra note 145, at 1429–30; Mayr, supra note 261, at 2093; Weiss & Buchanan, supra note 26, at 160. Natural selection may also act on gene complexes, rather than single genes, which will further attenuate its impact on any single gene. Sober & Lewontin, supra note 256, at 159, 170–71 (arguing that selection pressure must be understood as a combination of the biology of the organism and the physical characteristics of the environment).

\(^{264}\) Hartman et al., supra note 28, at 1001 (“Genetic variation is abundant in all natural species, and most is expected to be neutral or nearly neutral with respect to fitness.”); Sober & Lewontin, supra note 256, at 173–74 (suggesting that the conditions under which genetic selection exists are very narrow; genetic variation proliferates even though it has no effect on the phenotype of an organism).

\(^{265}\) Hubbard & Lewontin, supra note 28, at 1192 (noting that appearance of the same trait in different people need not be associated with the same genetic polymorphism (e.g., 200 different nucleotide variations appear to produce hemophilia B)); Weiss & Buchanan, supra note 26, at 164. In fact, “even strong [natural] selection favoring a specific phenotype closely tied to specific genes does not usually purify [genetic] variation.” Id. at 171.

\(^{266}\) Weiss & Buchanan, supra note 26, at 165. Moreover, once the classical binary (abnormal, wild-type) classification scheme is abandoned, substantial phenogenetic equivalence and a broad genotype-phenotype distribution results from numerous genetic variants. Id. at 168.

\(^{267}\) Id. at 165.


\(^{269}\) Suzanne L. Rutherford, From Genotype to Phenotype: Buffering Mechanisms and the Storage of Genetic Information, 22 BioEssays 1095, 1095 (2000) (suggesting that many ways exist in which phenotypes are buffered from perturbation by genotypic and environmental variation).
mental conditions.\textsuperscript{270} The prevalence of genetic buffering is driven by the important role it plays in natural selection. Genetic buffering allows “a reserve of neutral genetic variation” to build up in a population under stable conditions.\textsuperscript{271} This genetic reserve is critical to a species’ resiliency to environmental change and altered natural selection pressures because it provides a genetic reservoir upon which species can draw in response to changed circumstances.\textsuperscript{272} For toxicogenomics, genetic buffering weakens the association between gene-expression patterns and toxic susceptibility by further disassociating genotype from phenotype.\textsuperscript{273}

Third, a simple one-to-one relationship does not exist between genotype and phenotype because they are separated by intervening epigenetic and stochastic (i.e., random) processes.\textsuperscript{274} For example, epigenetic processes can determine whether or not a gene is activated and have been shown to play a significant role in the toxicity of certain compounds.\textsuperscript{275} Similarly, numerous non-genetic factors are affected, or even triggered, by chance events that lead to phenotypic variation.\textsuperscript{276} This innate uncertainty leads

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\item Hartman et al., \textit{supra} note 28, at 1001 (noting that “[t]he diversity of phenotypes produced by identical mutations in different strain backgrounds has been attributed to suppressors, enhancers, and modifiers”); Hubbard & Lewontin, \textit{supra} note 28, at 1192 (recognizing that having the same DNA nucleotide sequence in a gene does not guarantee that different people will display the same phenotype; for example, autosomal dominant retinitis pigmentosa display a range of effects from complete blindness to completely functional vision); Rutherford, \textit{supra} note 269, at 1095 (observing that the genotype of essential biochemical pathways, for instance, can be disrupted in some strain backgrounds with minimal phenotypic effect, while in other genetic backgrounds the organism is severely affected).
\item Rutherford, \textit{supra} note 268, at 263.
\item \textit{Id.} (explaining that this reserve “builds up in populations under normal conditions and could be expressed as heritable phenotypic variation during periods of environmental change”); Rutherford, \textit{supra} note 269, at 1096 (noting that genetically or environmentally perturbed states reveal “increased phenotypic variation due to the expression of cryptic genetic differences that are not normally apparent”). Hidden genetic variants may also increase health risk under specific conditions (e.g., certain genetic variants heighten the risk of lung cancer from smoking). Rutherford, \textit{supra} note 269, at 1097.
\item Rutherford, \textit{supra} note 269, at 1095. An important problem for genomics methods is that they cannot distinguish between cases in which a phenotype arises because of limited genetic variation, because of a high degree of buffering, or because the trait is constrained in some other way (e.g., biochemical constraints). \textit{Id.} at 1102.
\item Elizabeth Pennisi, \textit{Behind the Scenes of Gene Expression}, 293 Sci. 1064, 1065 (2001) (describing how epigenetic deactivation of tumor-suppressor genes can cause cancer); Watson & Goodman, \textit{supra} note 217, at 12–13 (describing how chemical modifications to DNA that affect gene activity have been connected to chemical toxicity).
\item Rutherford, \textit{supra} note 269, at 1100 (explaining that “developmental noise,” for example, is not well understood, but it is believed to arise when gene expression is triggered by a small number of molecules, making it sensitive to random fluctuations in their num-
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“each genotype [to] specify a number of different phenotypes depending on the environment; in a given environment, a probability function determines the mapping between any particular genotype and a set of phenotypes.”\textsuperscript{277} The unequal susceptibility to disease exhibited by twins with the same genetic backgrounds is an example of epigenetic variability.\textsuperscript{278} Moreover, growing evidence indicates that stochastic processes are integral to disease-response mechanisms.\textsuperscript{279}

All three of these factors—natural selection acting on phenotype (not genotype), active genetic buffering, and stochastic biological processes—expose the many obstacles to obtaining meaningful information from the gene-expression testing methods upon which toxicogenomics is based. Each of these processes complicates the interpretation of toxicogenic gene-expression studies by attenuating and, in some cases, eliminating the connection between gene-expression levels and the biological processes relevant to the toxicological responses and susceptibilities that scientists are attempting to monitor and understand.

Two additional factors compound the problems described above. First, most human health conditions involve complex biochemical processes and multiple genes;\textsuperscript{280} the simple cases in which toxicogenomic methods have been applied successfully are the relatively rare exceptions in a more complex world.\textsuperscript{281} Second, the most important diseases in environmental toxicology have late onsets, which are even less likely “to be genetic in the traditional deterministic sense of the term.”\textsuperscript{282} This additional barrier arises

\begin{itemize}
  \item \textsuperscript{277} Rutherford, supra note 269, at 1100.
  \item \textsuperscript{278} Cohen, supra note 180, at 4 (noting that the maximum concordance of disease among identical twins was thirty percent in a recent large study, suggesting that “[i]f individuals with the same DNA sequences have only a concordance of less than 1 in 3, what chance would we have of making confident disease predictions in individuals just knowing their DNA sequences?”); Rutherford, supra note 269, at 1100 (“For diseases that have a clear genetic component such as schizophrenia, given that one member of a pair of identical twins is affected, the probability that the other twin is affected is only on the order of 50%.”).
  \item \textsuperscript{279} Germain, supra note 216, at 240–41; Hartman et al., supra note 28, at 1001 (noting that diseases or toxic susceptibilities can be influenced differentially by environment factors, stochastic events, or interactions with other genes); Rutherford, supra note 269, at 1100.
  \item \textsuperscript{280} Vineis at al., supra note 190, at 709–11 (suggesting that mutations in genes coding for proteins that metabolize environmental toxins are prototypical of common, but weakly associated, genetic defects that affect individual susceptibility to toxins); Weiss & Buchanan, supra note 26, at 174 (concluding that the evidence to date indicates “that [simple genetic] variants with major effects on risk are the exception, not the rule”).
  \item \textsuperscript{281} Even simple organisms, such as yeast, display a high degree of complexity in their gene-gene interactions. In one recent study, scientists found an average of 34 gene-gene interactions per mutant gene based on an analysis of 143 genes in yeast mutants. Lee Hartwell, Robust Interactions, 303 Sci. 774, 775 (2004). As the author acknowledges, “[f]or those interested in uncovering the genetic basis of disease susceptibility in the human population, this result is daunting.” Id.
  \item \textsuperscript{282} Weiss & Terwilliger, supra note 187, at 156; see also Peto, supra note 29, at 390 (reporting that some studies suggest, for example, that cancer risks in old age may depend
because the late onset of toxin-induced diseases makes them selectively neutral because they do not impede reproduction, which may also explain why many were rare until relatively recently.\textsuperscript{283} The end result is that there is less reason to believe that measuring gene-expression levels will be particularly informative about toxic responses and susceptibilities.\textsuperscript{284}

The many impediments to applying toxicogenomics methods suggest that the problem is not specific to genomics methods, but one of confronting basic characteristics of complex biological processes.\textsuperscript{285} In this light, toxicogenomics proponents’ claims that understanding rare, single-gene disorders will advance understanding of common complex diseases appear speculative and, in any event, they fall far short of their paradigm-shifting vision.\textsuperscript{286} Similarly, recent proof-of-principle experiments employing gene-expression profiling demonstrate only that “when there is an association with a single risk [gene], one can identify this by using multiple [genetic] markers which are [physically associated with it].”\textsuperscript{287} Contrary to the claims of NIEHS scientists, these experiments begin with the stars completely aligned in favor of success and, as such, indicate little about the viability of toxicogenomic methods in a practical regulatory setting.\textsuperscript{288}

It would be a mistake, however, to conclude that these critics reject genomics methods altogether. The primary target of their opposition is the genetic reductionism that genomics has fostered. Ultimately, they agree that a multi-faceted approach must be adopted because no single method (genomics or otherwise) can generate all of the necessary information on its own.\textsuperscript{289}

\begin{thebibliography}{99}
\bibitem{283} Weiss & Terwilliger, \textit{supra} note 187, at 153. Type 2 diabetes, for example, has become much more severe in recent times, implying that environmental factors dominate. \textit{Id.} at 154. Further, even the pandemic among certain Native American tribes, which clearly has a genetic component, is still dominated by environmental factors because it was rare in the same populations sixty years ago. Weiss & Buchanan, \textit{supra} note 26, at 175.

\bibitem{284} Nelson Freimer & Chiara Sabatti, \textit{The Human Phenome Project}, 34 \textit{NATURE REV. GENETICS} 15, 16 (2003) (“[T]here is still relatively little known about how to integrate this effort with investigation of environmental influence on phenotypes.”); Strohman, \textit{supra} note 200, at 701 (suggesting that scientists are particularly ignorant of the interplay between disease and environmental factors); Weiss & Terwilliger, \textit{supra} note 187, at 153 (“[G]enetic factors are not likely to explain [common, chronic] diseases in the usual causal sense.”).

\bibitem{285} Weiss & Terwilliger, \textit{supra} note 187, at 151.

\bibitem{286} \textit{Lewontin, supra} note 196, at 115 (“[T]he internal heterogeneity of organisms [makes it] very dangerous to extrapolate from a few convenient examples to the whole of biology.”).

\bibitem{287} Weiss & Terwilliger, \textit{supra} note 187, at 155.

\bibitem{288} According to some critics, the proper inference to be made from these experiments is that toxicogenomics should be geared to toxins with strong, simple genetic influences, as more common (and important) complex chemical toxicities will remain out of reach. \textit{Id.}

\bibitem{289} \textit{Lewontin, supra} note 196, at 115 (“The full explanation of the path between gene and organism needs to include known phenomena that influence the way in which the string of amino acids coded by the gene becomes a protein, that is, a folded three-dimensional structure.”); \textit{Id.} at 117 (“Similarly, the shape and internal arrangement of cells must become a central feature of the explanations of development.”); Strohman, \textit{supra} note 200, at 702–03 (arguing in favor of balancing metabolic control with genetic-oriented research); Tabor et al., \textit{supra} note 183, at 6. Scientists also plan to use comparative, inter-species genomics

Critics have placed particular emphasis on conducting detailed functional analyses of genes, proteins, and their associated biological processes. Where critics differ most markedly from proponents of toxicogenomics is in their pessimism that toxicogenomics will generate quantitative methods for chemical testing.

V. Confronting Biological Complexity in Environmental Regulatory Policy

Chemical risk assessment is premised on developing quantitative estimates of a chemical’s toxicity. The challenge of this task is reflected in the acknowledged limitations and numerous critiques of risk assessment methods discussed in Part II, many of which focus on the difficult judgments involved in deriving quantitative risk estimates. The obvious validity of these critiques is further borne out by the complex interactions described in the preceding Part. As we have seen, the intricate biology of toxic responses is highly context-sensitive (i.e., both environmental and genetic factors), which makes it very difficult to develop a consistent measure of a specific chemical’s toxicity.

Careful analysis of human genetics also reveals that toxicological processes have inherent sources of indeterminacy. Outside relatively rare limiting cases, human toxic susceptibilities are multifactorial, such that an individual’s genetic background contributes to his susceptibilities to toxins in unpredictable ways. This variability is compounded by the fact that environmental factors, which play a dominant role in human health, are understood even less than genetic contributors. These impediments make development of precise quantitative tests even more remote.


Cohen, supra note 180, at 5–6 (predicting that toxicogenomic methods will contribute significantly to risk assessment methods, but basic biochemical, physiological and epidemiological methods will remain essential); Weiss & Terwilliger, supra note 187, at 154.

See supra Part IV.B. Chronic human ailments, such as cancer and asthma, tend to have particularly complex etiologies. Further, because chemical toxins play important causal roles in chronic human diseases, most harmful chemicals will also be associated with toxic responses and susceptibilities that are complex. While it is true that the most toxic chemicals could be associated with disease mechanisms that are genetically simple, with a minority accounting for the far more numerous complex conditions, this is wildly unlikely. First, many toxins have already been linked to complex conditions such as cancer, developmental defects, and neurological impairments. Second, precisely because simple genetic conditions are relatively easy to detect (e.g., the simple mutation associated with berylliosis), one would expect that if simple genetic traits dominated toxic responses and susceptibility that they would be discovered much more readily than they have.

Id.

Freimer & Sabatti, supra note 284, at 16 (“[T]here is still relatively little known about how to integrate this effort with investigation of environmental influence on phenotypes.”); Strohman, supra note 200, at 701 (scientists are particularly ignorant of the interplay between disease and environmental factors).

This complexity raises further questions about whether the significant uncertainties
This qualified understanding of toxicogenomics does not negate its value. While the quantitative precision some had hoped for will remain out of reach, regulatory science will benefit significantly from toxicogenomic methods and data. However, realizing these benefits will require regulators to confront the fundamental indeterminacies of toxicological mechanisms—not just the limits on scientists’ ability to study them. This will entail abandoning research objectives premised on developing fully quantitative test methods, as this level of precision will not be attainable and stands to distort research priorities.

The great potential of toxicogenomics resides instead in the suite of methods it will bring to bear on functional analyses of genes, proteins, and their associated biological processes. These qualitative mechanistic insights will, in turn, enable scientists to refine and strengthen the models (i.e., functions for toxic dose-responses, metabolic processes, and animal-to-human extrapolations) employed to derive chemical risk estimates, reducing their uncertainties and making them less dependent on highly discretionary judgments.

This final Part of the Article re-examines the current debate over risk assessment in light of these technical constraints. It also proposes several strategies for managing the uncertainties inherent in toxicological processes. Two distinct questions are addressed: (1) procedurally how to structure the process of making scientific judgments, and (2) how to prioritize data collection and research. The first question has garnered most of the attention of legal scholars and is the central subject of the long-standing battle over risk assessment between regulatory critics and environmentalists. The second question, which has received surprisingly little attention, is arguably more tractable and in greater need of attention and creative policy development. It is the focus of the recommendations that follow.

A. The Circular Logic of the Debate over Toxics Regulation

The debate over toxics regulation and risk assessment is dominated by two opposing factions: environmentalists, who appeal to the Precautionary Principle, and regulatory critics, who raise alarms about bogus scientific judgments. The efficacy of molecular epidemiological methods is limited for diseases with complex etiologies and more traditional methods for assessing toxicity have their own well-known shortcomings. Rothman, supra note 4, at C2.

Olden & Guthrie, supra note 5, at 4 (rescuing the “predictiveness, relevance and precision of toxicology”).

See supra Part IV.B.

Indeed, an important goal of EPA’s Computational Toxicology program is to obtain this type of mechanistic information and to apply it to its risk assessments models. ENVIRONMENTAL PROTECTION AGENCY, A FRAMEWORK FOR A COMPUTATIONAL TOXICOLOGY RESEARCH PROGRAM IN ORD, 12–13, 20–23 (2003), available at http://www.epa.gov/comptox/publications/comptoxframework06_02_04.pdf.

The Precautionary Principle embodies the old adage “Better safe than sorry” by
ence and perverse economic dislocations. 299 Both factions utilize a strategy that seeks to shift the burden of proof to their opponent. Environmentalists claim that industry must demonstrate that its products are safe before they are permitted to be sold, while regulatory critics argue that the benefits of regulation must be shown to outweigh the costs before regulation is justified. 300

These burden-shifting strategies have polarized the debate over how best to contend with scientific uncertainty. 301 This is true even though environmentalists and regulatory critics each seek to temper their positions with principles for resolving whether or not to regulate in a given situation. The regulatory critics’ cost-benefit approach requires one to assess the costs and benefits of regulating a chemical when it is entirely unclear whether or not it poses a risk. Similarly, the environmentalists’ Precautionary Principle entails applying a balancing test that requires the potential level of harm, degree of scientific uncertainty, and likely alternatives for a product or action to be weighed to determine the appropriate regulatory strategy. 302

At some level, both of these approaches are circular, as they ultimately rely on the existence of some measure of the risk posed. The basic problem is that they are trying to achieve the impossible—to propose a general set of principles, whether ethical or economic, for resolving regulatory decisions for which an essential piece of information, the level of chemical toxicity, is missing or too uncertain to be meaningful.

These attempts at principled responses are understandable given the alternatives. One risks lapsing into a defeatist attitude, on the one hand, placing protection of public health and the environment above other interests even when evidence of harm is not proven definitively. Frank B. Cross, Paradoxical Perils of the Precautionary Principle, 53 WASH. & LEE L. REV. 851, 851 (1996); see also Raffensperger, supra note 34.

299 See Risks, Costs, and Lives Saved, supra note 33; see also Cross, supra note 298, at 859–61; Graham, supra note 33, at 41–43 (current head of the Office of Information and Regulatory Affairs at the Office of Management and Budget discussing the merits of a risk assessment and cost-benefit analysis in environmental regulation).


301 Gaskins, supra note 300, at 148–52, 161–68 (“[T]he safest role for scientists in public discourse is to play the hard-nosed skeptic. This strategy forces the opponent to bear the burden of proving scientiﬁc facts, preferably under an unattainable standard of proof.”)

or a blindly speculative approach, on the other, that treats data as an end in itself regardless of whether it has any likelihood of resolving the risks posed by a chemical. Clearly, no good is served by abandoning hope that more research and new information will improve our understanding of toxicological mechanisms or generate improved methods for chemical testing. Yet, the basic biological processes display important fundamental uncertainties. Reading just a few articles on biological complexity is enough to shake one’s confidence in scientists’ ability to resolve basic uncertainties in toxicological processes.\footnote{See, e.g., Kitano, \textit{supra} note 216, at 1662; Service, \textit{supra} note 216, at 80–81.}

Moreover, if the biological sciences are forced into the field of mathematical complexity, which by many accounts is where they are headed, the analysis will be raised to much higher levels of unintelligibility—each toxicological analysis will be akin to a small-scale climate model.\footnote{Kitano, \textit{supra} note 216, at 1662.} One is left with limited hope of forward movement any time soon and the even less agreeable option of abandoning scientific methods altogether.

The severity of the technical impediments leaves little doubt that, given current knowledge and scientific methods, the toxicity of most chemicals will remain subject to large uncertainties, regardless of whether significant investments of time and money are poured into integrated toxicogenomics research. This level of uncertainty leaves regulators with tenuous scientific grounds for regulatory decision-making.

Actually, the situation is plainly worse than that—it leaves no \textit{principled} basis to make regulatory determinations whatsoever. Any attempt at clear-cut line drawing based on putative toxicity raises a substantial risk of being either under- or over-inclusive because the status of a large number of chemicals is likely to remain uncertain. It is therefore predictable that the debate over toxics regulation has centered to such a high degree on allocating the burden of proof—the biological origins of toxicological processes impede development of reliable quantitative estimates of chemical toxicity. Moreover, there are few, if any, signs that dramatic advances will be made in the near future.

These findings stand to reinforce the view among legal commentators that chemical risk assessment, and particularly toxicology, is an archetype of trans-science.\footnote{Professor Wendy Wagner has carefully identified many of the trans-scientific judgments made when interpreting the results of animal studies for purposes of determining a chemical’s toxicity: “Extrapolating [the high-dose] results to potential effects of low levels of the substance on humans then presents the next two trans-scientific junctures, which are often collapsed into one. First, an extrapolatory model must be selected that will predict low-dose effects on animals based solely on high-dose data. Although there are several scientifically plausible extrapolatory models, the choice of one model over another cannot be resolved by science and thus must be determined by policy factors. This policy choice will have significant implications for the level ultimately chosen as adequate to protect public health. Second, since the similarities between animals and humans with regard to their sensitivity to carcinogens are largely unknown and incapable of being studied directly, a
science and yet which cannot be answered by science.”306 The term trans-science typically establishes a boundary for scientific expertise; certain questions simply do not have a scientific answer, either because of technical or practical constraints. Moreover, once a question is declared trans-scientific, science is presumptively owed less (perhaps no) deference and other factors, particularly societal values, are elevated for consideration. Under this scheme, any quantitative estimate that is reliant on embedded qualitative judgments, as opposed to direct empirical support, is therefore branded trans-science.

Trans-science has had a high degree of currency in the debate over chemical risk assessment. This intuitive appeal, however, obscures the term’s unavoidable vagueness and circularity. Trans-science is meaningful only at the extremes.307 The question whether the sun will rise tomorrow is clearly a matter of scientific fact, not one of policy. But beyond such simple cases, determining what is science and what is policy is often far from clear. For example, it may seem clear that estimating the toxicity of a chemical is precluded because of practical constraints, and thus should be treated as trans-science. However, is the choice between two experimental models, neither of which is fully accurate, a matter of policy or science? Scientists make innumerable decisions like these and, because of their own limited knowledge, also make many implicit judgments that they may not even be able to articulate. Moreover, it is often just these sorts of narrow questions that are of greatest importance in chemical risk assessments.

The ambiguity of the term “trans-science” should really come as no surprise. Categorical terms cannot avoid the uncertainties inherent in the underlying methods and substantive knowledge any more than continuous quantitative risk metrics, which have been the subject of extensive critiques. The basic problem with risk assessment methods is straightforward: none of the science is all that solid. In this context, competing efforts to shift burdens of proof and to promote specific analytical approaches, policy choice must again be made. Wagner, supra note 45, at 1626.

306 Alvin M. Weinberg, Science and Trans-Science, 10 Minerva 209, 209 (1972). Weinberg describes three categories of trans-science: (1) resolving the question would be “impractically expensive,” (2) “the subject-matter is too variable to allow rationalisation according to the strict scientific canons established within the natural sciences,” and (3) the “issues themselves involve moral and aesthetic judgements [sic].” Id. at 213. The three categories correspond, respectively, to “low-level insults” (effects), social science, and “choice in science.” Id.

307 David E. Adelman, Scientific Activism and Restraint: The Interplay of Statistics, Judgment, and Procedure in Environmental Law, 79 Notre Dame L. Rev. 497, 531–32 (2004) (arguing that the line between science and trans-science is either incoherent or so biased toward most science being characterized as trans-science that the distinction is an empty one). The physicist Alvin Weinberg, who coined the term “trans-science,” acknowledged that the “border between trans-science and science is elusive” and that “in fact, the essence of the matter is often to define just where the line between the two lies.” Weinberg, supra note 306, at 218–219, 221.
whether quantitative or value-based, naturally reflect the interests of the stakeholders, who want to control the criteria for resolving regulatory decisions and who has primary responsibility for making them. Gradual scientific progress is still our best bet for resolving or diminishing such differences. Nevertheless, while toxicogenomics holds out the promise of locating some solid ground, much uncertainty will remain. The challenge, as always, will be to make the best use of the technical insights that toxicogenomics, and other related scientific developments, will generate.

B. Managing Scientific Uncertainty Pragmatically

Toxics regulation demands that some kind of line-drawing be done and that quantitative estimates of toxicity be made. Currently, decision-making is largely left up to a consensus process that utilizes scientific advisory panels. Many problems have been identified in expertise-based systems of setting standards for chemicals. The scientific consensus process is often engulfed by politics, the division between technical matters and policy questions is often hopelessly vague, conflicts of interest and ideological bents frequently compromise the perceived objectivity of committees, and the process is time-consuming. While these types of problems are often found in human institutions, people have become increasingly dismayed by the increased politicization of regulatory science.

The Delaney Clause is probably the best-known alternative to a scientific consensus process in the environmental regulatory context. It obviates the need for scientific judgment by effectively setting a zero-tolerance threshold if any incriminating data on a chemical is brought to light. The Delaney Clause does not, however, represent a particularly promising strategy, as it was the subject of fierce opposition for decades because it ignores regulatory costs and benefits. These defects ultimately led to its demise in a series of amendments contained in the FQPA that removed the zero-threshold standard. Furthermore, it is all but inconceivable that a similar strategy could be successful given the current regulatory climate.

The Delaney Clause also illustrates the extreme measures that must be taken to avoid difficult scientific judgments in chemical risk assessments. Given the practical constraints, the technical nature of the issues, and the attendant scientific uncertainties, the scientific consensus model is our best (or least worst) option. Churchill’s famous statement that “democracy is the

308 See supra note 48.
311 PERCIVAL ET AL., supra note 52, at 454.
312 Id. (noting the Delaney Clause was amended to omit “pesticide chemical residues in raw or processed foods.”)
worst form of government, except for all of those others that have been tried from time to time,”\textsuperscript{313} therefore, is apt here.\textsuperscript{314} As Sheila Jasanoff, a prominent science policy and legal scholar, has acknowledged, the critical offsetting virtue of scientific advisors is that “they inject a much-needed strain of competence and critical intelligence into a regulatory system that otherwise seems all too vulnerable to the demands of politics.”\textsuperscript{315} Stated otherwise, reliance on scientific advisors does not eliminate politics; it affords the best conditions for minimizing and counterbalancing the negative influence of politics.

Much greater latitude for regulatory reform exists for structuring regulations and prioritizing regulatory decision-making and research. Two particularly promising approaches offer a middle ground between the Delaney Clause and the traditional regulatory system: (1) imposing regulatory standards pragmatically based on whether certain classes of chemicals, industries, or exposures are believed to raise greater potential risks, and (2) establishing a second tier in the regulatory system with a separate low-threshold standard that triggers a relatively limited set of regulatory requirements.\textsuperscript{316}

Both of these approaches ought to receive more serious consideration. EPA has already, in effect, adopted this second approach in its High Production Volume Chemical Challenge, under which chemical companies have agreed to conduct basic toxicity testing for more than two thousand high-production-volume chemicals.\textsuperscript{317} EPA’s focus on high-volume chemicals is long overdue and makes good sense from the standpoint of potential risks.


\textsuperscript{314}This qualified endorsement of EPA’s scientific consensus process is premised on advisory committees maintaining high standards of openness, avoiding conflicts of interest among their members, and adequately reflecting the diversity of views in the scientific community.

\textsuperscript{315}Jasanoff, supra note 309, at 1.

\textsuperscript{316}This kind of approach has been adopted in several state and federal statutes. The best example of this approach in the environmental context is a provision of California’s Proposition 65, which requires businesses that expose members of the public to known carcinogens or reproductive toxins to warn them of the exposure unless they can demonstrate that the exposure “poses no significant risk.” Percival et al., supra note 52, at 474–77. Under Proposition 65, the standard for level of exposure is low (no significant risk) and the regulatory requirement is limited (notice to those exposed). Similar strategies have been advocated in the criminal and immigration law contexts. See Donald A. Dripps, Constitutional Theory for Criminal Procedure: Dickerson, Miranda, and the Continuing Quest for Broad-But-Shallow, 43 WM. & MARY L. REV. 1, 73–75 (2001) (arguing that “broad-but-shallow” rules ought to be developed in criminal procedure given the volume of criminal cases and that any rule based on a broad constitutional principle will invariably be both over- and under-inclusive); see generally James C. Hathaway & R. Alexander Neve, Making International Refugee Law Relevant Again: A Proposal for Collectivized and Solution-Oriented Protection, 10 HARV. HUM. RTS. J. 115 (1997) (calling for a strategy of limited rights for refugees that are broadly applicable, as opposed to an absolute right of asylum that states invariably seek to avoid and that lead to results that are often contrary to the interests of many asylum seekers).

\textsuperscript{317}As of 2000, EPA had received commitments from companies to voluntarily test 2,011 chemicals.
and efficiency.\textsuperscript{318} However, this kind of approach could be implemented using criteria other than volume (e.g., number of people potentially affected, heightened levels of average exposure, impacts on vulnerable subpopulations, etc.) to prioritize data collection for other chemicals. Efforts should be made to explore alternative criteria.

The second approach—low-threshold and limited regulation—offers some particular advantages of its own. First, it can take advantage of a simple default rule, similar to that found in the Delaney Clause, without invoking broad opposition because the burden it imposes is limited. The success of California’s Proposition 65, which imposes only notice requirements, rests on this careful balancing of risk threshold and burden imposed.\textsuperscript{319} Second, it offers a different regulatory framework in which to navigate between the pitfalls of mechanically requiring chemical testing versus passively accepting ignorance about chemical risks. By establishing a second-tier threshold, this regulatory model demands that a consistent minimum level of information be collected, without invoking much more elaborate measures that may be difficult to justify. This basic information also can provide the basis for subsequent regulatory judgments.

The challenge of determining how much data to collect in the face of the broad uncertainties that exist in toxicology represents a perennial regulatory dilemma. Indeed, part of what I hope to have conveyed through the detailed discussion of toxicogenomics is some sense of just how challenging the underlying science can be. This is also a problem that EPA and NIEHS are ill equipped to address, as most toxicity testing is conducted and controlled by industry scientists. EPA and NIEHS support relatively modest research programs, and EPA is subject to statutory limits on the types and quantities of data it can require of chemical producers. These constraints lead toxics research to be scattershot and driven by immediate regulatory or political demands.

The technical challenges detailed above demand a more coordinated and refined approach to chemical testing than the current regime allows. The only strategy that has the potential to achieve this is a major federal program in environmental toxicology, preferably supported by a registration fee for regulated chemicals.\textsuperscript{320} This approach acknowledges the obvious, namely, that chemical toxicology still involves questions of basic science. It also allows a more targeted, long-term research program to be established, as opposed to ad hoc chemical-by-chemical projects. Research,

\textsuperscript{318} Landrigan et al., \textit{supra} note 53, at 721 (stating that children are most threatened by high-production volume chemicals because they “have the greatest potential to be dispersed in air, water, food crops, communities, and homes”).

\textsuperscript{319} See \textit{supra} note 316.

\textsuperscript{320} While it is true that a registration fee will inevitably be viewed as a tax on industry, objections may be assuaged insofar as a government program would remove the burden on industry to conduct toxicological testing itself. It also could be designed to spread the costs of toxicological research more evenly or equitably across the industry as a whole.
for example, could be targeted at particularly promising areas, or more likely prioritized to avoid areas subject to large, unavoidable uncertainties, and federally supported researchers would be given primary responsibility for selecting the compounds for study.\textsuperscript{321} At the same time, relatively routine, regulation-related work could still be overseen by EPA scientists, or even industry, and be driven by pressing regulatory needs and priorities.\textsuperscript{322}

An added advantage of this approach is that it would provide the necessary resources for development of a significant group of independent university and government researchers. This benefit is particularly important because a common concern about the field of toxicology, and regulatory science more generally, is the dominance of industry-affiliated scientists.\textsuperscript{323} These concerns have gained heightened currency following the recent wave of allegations from the scientific community about the politicization of science in the regulatory process.\textsuperscript{324} A consistent source of funding would also lessen the pressures on agency scientists to oversell new scientific developments, such as those associated with toxicogenomics, to secure financial and political support for their work.

The emergence of toxicogenomics represents a unique opportunity to launch a major federal program in environmental toxicology. The broad-based enthusiasm for toxicogenomics is extraordinarily rare in this branch of environmental science and offers a powerful vehicle for garnering support. Further, unlike the past when the science was stalled, toxicogenomic methods, even granting their limitations, hold the promise of clear gains in understanding and knowledge. These advances stand to improve characterizations of dose-response relationships, extrapolations from animals to humans, and estimates of rates at which chemicals are metabolized (i.e., broken down).\textsuperscript{325} If successful, this new information will significantly reduce the uncertainties in chemical toxicity estimates and minimize the influence of often divisive judgments in chemical risk assessments.

This current alignment of factors is unprecedented. Toxicogenomic methods provide much-needed grounds for confidence that a new federal program will have significant value. EPA and NIEHS are already devoting significant resources to toxicogenomics, evidencing substantial sup-

\textsuperscript{321} Examples of promising areas include DNA-chemical adducts and research on genes important to chemical detoxification and DNA repair. See supra Part II.A & .B.

\textsuperscript{322} A strategically targeted approach like that used in EPA’s High Production Volume Chemical Challenge could readily be incorporated into this model.


\textsuperscript{324} See supra note 310.

\textsuperscript{325} See supra note 297 and accompanying text.
port from within these agencies. Furthermore, important parallel efforts using traditional epidemiological methods, such as the National Children’s Study, have the potential to both complement and support these newer programs. Finally, the strong appeal of genomics, and biotechnology generally, among the public and politicians can be leveraged to support a more integrated and efficient research program in environmental toxicology.

If pragmatism means anything, it represents a healthy respect for opportunism. Toxicogenomics has given environmental toxicology a new lease on life, even though it is not the perfect solution that its advocates have envisioned. As such, it represents a rare opportunity to refashion and rationalize federal environmental toxicology programs that ought to be exploited to the fullest extent possible based on a realistic understanding of its potential benefits.

VI. Conclusion

The Environmental Genome Project is the first high-profile scientific initiative in environmental toxicology to receive broad stakeholder and government backing since the transformation of environmental law in 1970s. Federal support for toxicogenomics research represents a unique opportunity for environmental toxicology to benefit from a major infusion of resources. However, toxicogenomics is being sold as the perfect solution to all that ails environmental toxicology and regulatory risk assessment. Its advocates claim that toxicogenomics will resolve complex problems definitively using simple-to-apply, highly reliable, low-cost methods. This Article provides a critical appraisal of these claims and exposes the less deterministic aspects of genetics. While important as a research tool, toxicogenomics will not achieve the quantitative precision its proponents ascribe to it.

Toxicogenomics nevertheless has important implications for environmental law. First, toxicogenomic methods demonstrate that susceptibility to toxic exposures are highly variable from person to person and that environmental law must take this variation into account. Toward this end, the Article identifies important statutory omissions and recommends several necessary refinements.

Second, the deep-seated uncertainties inherent in environmental toxicology reveal the futility of the current fixation on burdens of proof that dominates the literature on toxics regulation. The difficult judgments entailed in assessing chemical toxicity belie such a legalistic approach. Improvements in regulatory policy are more likely to be achieved by a strategy that shifts chemical toxicity testing away from ad hoc reliance on

industry to a government-based research model and toward more pragmatic regulatory strategies.

Third, genomics research stands to expose the dominant influence that environmental factors, both human-made and natural, have on human health. This fact and the significant limitations of toxicogenomics methods themselves demand a more balanced, less technology-driven approach to research in the environmental health sciences. After all, while it is true that the genomics revolution is realigning medicine, basic biological disciplines, and regulatory science, it is also true that these new technologies cannot succeed on their own. Consistent with the central objectives of this Article, the transformation occurring in the biomedical sciences represents a unique opportunity to reassess how science can be most effectively used to protect human health and enhance environmental regulation.