Genetics and Environmental Law: Redefining Public Health

Jamie A. Grodsky
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Jamie A. Grodsky

The sequencing of the human genome and introduction of high-speed gene expression profiling technologies are revolutionizing our understanding of the interplay of genes and the environment. This Article develops a novel and provocative framework for thinking about the implications of the genetic revolution for the U.S. environmental regulatory system. Professor Grodsky employs the concept of "public health" as a lens for analyzing emerging issues, and demonstrates how scientific advances may erode the distinction between public and individual health. Future claims of genetically susceptible individuals and groups may challenge the legal definition of the "public" to be protected by environmental law. Likewise, the Article demonstrates how the meaning of "health," and legally significant threats to health, may be questioned as new techniques reveal earlier evidence of toxic harm. These developments strike at the core of the Environmental Protection Agency's public health mission. The Article analyzes and synthesizes diverse elements of the changing scientific landscape, providing a new framework for understanding the science as well as the law. Professor Grodsky examines implications for environmental standard setting, as these potentially beneficial, enormously complex, and increasingly controversial scientific developments may modify estimates of individual and public health risk attributable to toxic exposure.

The Article also sounds a cautionary note. It evaluates scientific roadblocks that must be overcome if the new science is to benefit law and regulation rather than generate scientific uncertainty. This new, exciting, and potentially perilous terrain in environmental law has only begun to be perceived by policymakers.

INTRODUCTION

Since James Watson and Francis Crick demonstrated the structure of DNA in 1953,1 scientific and technical advances in molecular biology and

genetics have brought about dramatic shifts in the fields of epidemiology\(^2\) and toxicology,\(^3\) the cornerstones of environmental risk assessment.\(^4\) Incorporation of the tools of molecular biology into these fields in the past two decades has provided new subcellular insights into the effects of toxic substances on living organisms. Relying on genetic and other molecular "biomarkers," scientists have begun to identify a continuum of health effects elicited by toxic exposure, effects detectable long before clinically observable disease. This ability to identify and study intermediate events has supplanted a metaphorical "black box" that hobbled earlier scientific investigations.\(^5\) Likewise, new genetic technologies\(^6\) are revealing a range of human susceptibilities to environmental harms, suggesting that certain groups and individuals may be genetically predisposed to bear a disproportionate share of environmental risk.

Since the 1990s, advanced computers, robotics, and other new technologies have enhanced scientists' ability to gather molecular and genetic

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2. "Epidemiology is the study of health effects in groups of people." Paul A. Schulte, *A Conceptual and Historical Framework for Molecular Epidemiology*, in *Molecular Epidemiology: Principles and Practices* 3, 10 (Paul A. Schulte & Frederica P. Perera eds., 1993). Epidemiologists generally are concerned with the causes, prevention, and control of disease in populations. The introduction of molecular biology techniques into this field in the 1980s has augmented the traditional focus, as these techniques may permit more direct observation of environmental exposures, effects, and susceptibilities on an individualized basis.

3. Toxicology is the science of evaluating the effects of toxic substances on humans and other organisms. "The science of toxicology... is an applied science that attempts to define the harm that chemicals can cause to humans and, most importantly, it is an integral part of the risk assessment process." Lewis L. Smith, *Key Challenges For Toxicologists in the 21st Century*, 22 *TRENDS IN PHARMACOLOGICAL SCI.* 281, 281 (2001). As the title of a leading treatise indicates, toxicology has been defined broadly as "the science of poisons." *Casarett and Doull's Toxicology: The Basic Science of Poisons* (Curtis D. Klaassen ed., 6th ed. 2001).


5. See *infra* notes 15-27 and accompanying text.

6. The terms "genetics" and "genomics" frequently are distinguished but also have overlapping meanings. Genetics is defined most broadly as "the science of heredity." *Campbell et al., Biology: Concepts and Connections* G-11 (3d ed. 2000). Genetics has been defined more specifically as "the study of single genes and their effects," while genomics is defined as "the study of the functions and interactions of all the genes in the genome." Alan E. Guttmacher & Francis S. Collins, *Genomic Medicine—A Primer*, 347 *NEW ENG. J. MED.* 1512, 1512 (2002). However, "genomics" is a relatively recent term, first appearing in 1987 to mark the advent of a new scientific journal. See Victor A. McKusick & Frank H. Ruddle, *A New Discipline, A New Name, A New Journal*, 1 *Genomics* 1 (1987) (editorial).
information related to toxic exposure, early injuries, and differential genetic susceptibilities to environmental agents. These new technologies, including DNA “microarrays,” represent the second generation of the Human Genome Project and are providing a virtual explosion of information on gene-environment interactions. The emerging fields of “toxicogenetics” and “toxicogenomics” are devoted exclusively to this research.\footnote{See infra notes 89-107 and accompanying text.}

As the ability to detect subtle responses to chemicals improves, and as we gain more refined information about particularly susceptible populations exposed, we will be required to make the following policy choices: (1) Does the government have a responsibility to ensure that the most genetically sensitive citizens are protected by our environmental regulations? (2) When are molecular and genetic responses to toxic exposure sufficiently predictive of future disease to warrant regulatory action? These questions present formidable regulatory line-drawing problems, particularly where genetically susceptible groups represent a small fraction of the overall population and where the predictive value of genetic data remains less than absolute. Although the new information must be validated and clinically tested before it can be considered for practical application, recent scientific and technological advances ultimately may require us to reassess the way we regulate to protect the environment and public health. These developments have only recently reached the regulatory radar screen.

The Environmental Protection Agency (EPA) is invested with a dual mandate: to protect the environment and public health.\footnote{“The mission of the U.S. Environmental Protection Agency is to protect human health and to safeguard the natural environment—air, water, and land—upon which life depends.” U.S. Environmental Protection Agency, Agency Mission Statement, Office of the Federal Register, National Archives and Records Administration, The United States Government Manual 377, 378 (2003-04).}

Reflecting this mission, many environmental statutes require estimates of public health risk as part of the standard-setting process. For example, the Clean Air Act requires standards for the nation’s most pervasive air pollutants to be set at levels that, allowing an “adequate margin of safety,” are “requisite to protect the public health.”\footnote{Clean Air Act, 42 U.S.C. § 7409(b)(1) (2000).} The availability of new genetic data will require us to reconsider what it means to protect the public’s health under the Clean Air Act and other environmental statutes. This rethinking also will have significant implications for workplace safety, product liability, health law, and disability law. This Article explores new challenges to the herculean task of setting “health-based” environmental standards, as well as other standards based, at least in part, on estimates of public health risk. I argue that advances in molecular biology and genetics may call into question the legal definitions of “public” as well as “health.”
As to the meaning of "public," the growing technical ability to assess risk on an individualized basis suggests that the classic population-based public health paradigm may need to be revisited. Research may show that existing standards establishing "safe" levels of air and water pollutants, industrial chemicals, and pesticides are insufficiently protective of certain genetically defined constituencies. I suggest that the polygenic nature of genetic susceptibility will reveal a continuum of susceptibilities to the effects of particular chemicals, further complicating the picture. A central question for scholars and policymakers is whether EPA is statutorily mandated or institutionally capable of protecting newly identified, genetically susceptible individuals and groups. Such protection may prove to be exceptionally challenging because these groups may be smaller and more difficult to identify than are groups currently recognized. Moreover, groups defined on the basis of genetic susceptibility will include, or cut across, other groups—including those protected by the Constitution or other law.

As new technologies set the stage for personalized testing for genetic susceptibility, toxic exposure, and early evidence of injury, newly emerging constituencies will likely petition for enhanced regulatory protection or seek private legal remedies to fill putative regulatory gaps. I suggest that, over time, more widespread access to personalized environmental risk information could transform the politics of environmental protection.

Regarding "health," I illustrate the regulatory significance of the fact that new genomic technologies are blurring the boundary between health and disease. As research identifies subclinical events in the disease process elicited by chemical exposure, the line between health and disease becomes murky. Society will be forced to decide whether these early, possibly predictive events should qualify as legally actionable harms or "adverse health effects" for regulatory purposes. Put another way, society must decide when, in the continuum from exposure to disease, early indicators of future harm are sufficiently predictive to qualify as harms in themselves—particularly where early intervention could thwart the ultimate disease. As technology allows us to perceive adverse health effects in closer temporal proximity to the chemical exposures that caused them, our conception of "latent" harms may change. As harms traditionally viewed as latent arguably become patent, society may need to reevaluate current mechanisms for addressing latent risks. Unless or until genetic clues are validated as predictors of susceptibility or cause-effect relationships in the disease process, however, they will present additional problems of scientific uncertainty that will further complicate regulatory choices.

Although it is perhaps easiest to visualize how the new scientific information may support claims for more stringent environmental protection, a better understanding of the mechanisms of toxicity at the genetic and molecular levels also may enable more finely calibrated risk assessments,
allowing regulators to substitute hard data for overly protective risk assumptions and ultimately to develop more cost-effective regulations. The new generation of health risk information thus may serve the goals of two political trends that have crystallized in the past two decades. While many commentators have called for better risk prioritization and cost accounting in environmental regulation, others have advocated more explicit consideration of groups and individuals whose needs may diverge from those of the population at large. The debate over the place for genomics in the environmental regulatory system may reveal many areas of convergence in these perspectives, and may further the various normative goals embodied in our environmental regulatory scheme.

However, even if one were to concede that new genomic data might lend precision to the technical assessment of risk, the policy judgments involved in risk management will become far more complicated. Indeed, this information may challenge fundamental scientific assumptions that guide regulatory standard setting today. For example, the concept of a single “threshold” delineating safe from unsafe levels of noncarcinogens may become increasingly difficult to defend as genetics uncovers new susceptible groups and earlier evidence of chemically induced harm. If evolving science supports regulation at lower-dose levels, possibly approaching natural background levels of risk, regulatory standards that depart from the science may need to be justified on social policy grounds. Ironically, then, as science generates vast quantities of biological data pertinent to the assessment of environmental risk, risk-based regulatory decisions increasingly may need to be based on nonscientific criteria. Viewed from another perspective, technology may require us to unmask the value judgments inherent in environmental standard setting.

Part I of this Article suggests that a consequential, and perhaps paradigmatic, shift in the science underlying environmental law is taking place, and elucidates the implications of that shift for environmental regulation. In Part II, I employ the concept of “public health” as a framework for understanding the issues raised and argue that scientific advances are breaking down the distinction between public and individual health. In so doing, I show how future claims of genetically susceptible groups and individuals will challenge EPA’s definition of the relevant public to be protected under our environmental laws. The Clean Air Act’s health-based standards serve to illustrate these points, as they highlight the issues in the boldest relief. In Part III, I argue that new technological capabilities may

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10. See discussion infra Part IV.
11. Id.
redefine "health," and suggest that EPA may need to rethink its definition of health effects of "regulatory concern." This section highlights the problems inherent in drawing clear lines within increasingly continuous risk distributions and the difficulty of finding policy justifications for regulatory choices adopted. In addition to presenting conceptually new problems for environmental law, the proliferation of health risk information generated through genomics may so significantly expand the scope and complexity of existing problems that new solutions may be required.

Part IV examines issues at the intersection of science and law that may help inform the many choices ahead, and recommends ways in which the regulatory system can best accommodate the new science. In the short term, the influx of new and complex health risk information could erode support for risk-based regulation and build support for regulatory approaches that minimize the role of science. However, I suggest that wholesale de-emphasis of risk-based standard setting would be ill-advised. I recommend that we promote and safeguard regulatory instruments that provide incentives to generate and evaluate this new information, enabling us to make more informed choices in the future.

Despite the many challenges ahead, it would be ironic and counterintuitive to discourage risk regulation at a historic moment when increasingly refined risk information is made available in an entirely new dimension. Genomics—whether welcomed for lending precision to risk assessment and opening the door to new preventive measures, or feared for raising a new generation of daunting scientific problems and intractable policy choices—adds a new dimension to environmental law and regulation that is here to stay.

I
THE CHANGING SCIENTIFIC LANDSCAPE

Although only recently remarked upon in the world of environmental policymaking, a shift in the science underlying pollution control is underway. Our knowledge of molecular biology and genetics has undergone a meteoric rise since the discovery of the structure of DNA in 1953, and events of the past few decades are of particular consequence for environmental law and regulation. In this Part, I provide a historical perspective on the changing scientific landscape—a perspective that is essential to an informed understanding of the implications of the genomic revolution for environmental regulation. First, the import of contemporary advances in the science of toxic injury cannot be assessed properly without an understanding of earlier developments upon which these advances are based. For example, the "biomarker paradigm" of the late 1980s, which laid the groundwork for identifying various subcellular links in the causal pathway from chemical exposure to environmentally induced disease, has provided
an important conceptual foundation upon which to measure and interpret later scientific advances.\textsuperscript{13} Second, a historical perspective reveals important connections among disciplines and projects that otherwise may appear distinct; recent history thus may be a harbinger of future areas of convergence. History also informs our ability to distinguish paradigmatic shifts from incremental or evolutionary developments. Although distinguishing revolution from evolution may be largely subjective, a long-term view illuminates the value of recent scientific contributions while providing the perspective required for a realistic assessment of potential regulatory applications.

I endeavor to fill a gap in the literature by providing a portrait of relevant scientific and technological developments in their theoretical and temporal context. Not surprisingly, much of the scientific effort is compartmentalized with respect to discipline, research program, and literature. My goal in this Part is to synthesize the diverse elements of the emerging scientific landscape that may someday challenge the way we regulate to protect the environment and public health. At the same time, I highlight formidable scientific obstacles that will require regulators to differentiate between hypotheses and scientific facts, and to understand the limitations as well as the power of new genomic technologies capable of revealing early effects of toxic substances and varying susceptibilities thereto.

\textbf{A. Seeds of Change: Molecular Biology Enters the Science of Toxic Injury}

Essential to a contextual understanding of environmental genomics are developments born in the 1970s and maturing in the 1980s—the most salient being the application of the tools of molecular biology\textsuperscript{14} to the disciplines of toxicology and epidemiology, the linchpins of environmental risk assessment.\textsuperscript{15} The widespread application of molecular biology techniques to other disciplines during the 1980s provided new molecular-level insights into important biological processes, including cellular responses to drugs and toxic chemicals.\textsuperscript{16}

Specifically, scientists have gained the ability to “peer into cells” to observe the behavior and effects of toxic substances at the molecular level.

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\textsuperscript{13} See infra text accompanying notes 29-61.
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\textsuperscript{14} These tools include recombinant DNA technology, DNA amplification technology (polymerase chain reaction), and techniques for rapid sequencing of nucleic acids. Recombinant DNA technology has allowed individual genes to be isolated and replicated, and rapid sequencing techniques have made it possible to sequence thousands of base pairs efficiently. Robert E. Hurst \& Jian Yu Rao, \textit{Molecular Biology in Epidemiology}, in \textit{MOLECULAR EPIDEMIOLOGY: PRINCIPLES AND PRACTICES} 45, supra note 2.
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\textsuperscript{16} Hurst \& Rao, supra note 14.
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This capability also has revealed gene mutations and sequence variations that may confer differential human sensitivity to environmental agents. The key to detecting causal relationships and genetic susceptibilities is in the identification of biological markers, or "biomarkers."\textsuperscript{17} Formally, they are defined as "indicators signaling events in biological systems or samples"\textsuperscript{18} or "any measurement in or from biological material that defines an exposure or response to that exposure."\textsuperscript{19} Hence, biomarkers are indicators of exposure, effect, or susceptibility that are measured in biologic materials,\textsuperscript{20} such as tissues or bodily fluids, as opposed to estimates based on levels of foreign compounds in the ambient environment. The biomarker concept was not new in the 1980s. Traditional biomarkers include lead levels in blood and the presence of arsenic, lead, mercury, or the pesticide parathion in urine, indicating exposure to these substances.\textsuperscript{21} However, the new biomarkers reveal molecular interactions or events within biological systems, thereby providing much more information than the physical presence of foreign compounds or their immediate derivatives.

The identification of genetic and molecular-level biomarkers has allowed scientists to characterize a number of previously undetectable, intermediate events between chemical exposure and environmentally induced disease.\textsuperscript{22} Because classical techniques were insufficient to characterize these intermediate events, traditional toxicology and epidemiology...
generally were limited to studying the beginning and end of the process—initial toxic exposure and ultimate disease—viewing everything in between as a “black box.” The tools of molecular biology effectively opened this black box, revealing a “cascade” of events between exposure and clinical disease.

Those biomarkers that represent events along the causal pathway may give scientists insights into how diseases arise. Hence, certain biomarkers may allow assignment of clearer probabilities of disease risk based on early biological signs of chemical exposure. Specifically, “[b]iomarkers can be used to delineate more precisely how a given ambient toxic exposure causes disease by tracing the ‘molecular footprints’ as the toxin passes through the body, interacts with critical target molecules . . . and produces the molecular and cellular effects that eventually manifest as [disease].”

1. The Biomarker Paradigm: Opening the “Black Box”

A seminal paper published in 1987 by a scientific committee commissioned by the National Research Council (NRC) synthesized existing studies on the development and use of biomarkers in environmental health research. The paper identified three general types of molecular

25. Geoffrey Rose, Preventive Cardiology: What Lies Ahead?, 19 PREVENTIVE MED. 97, 100 (1990); see also Anthony P. DeCaprio, Biomarkers: Coming of Age for Environmental Health and Risk Assessment, 31 ENVTL. SCI. & TECH. 1837, 1838-40 (1997) (discussing the earlier “black box” model and new molecular techniques that identify multiple steps between exposure and disease); Perera, supra note 18, at 55 (distinguishing molecular epidemiology from the earlier “black box” model); Schulte, supra note 2, at 13 (discussing the “black box” approach and the new resolving powers of molecular epidemiology).


27. Epidemiological research frequently has been based on theories or speculation concerning the mechanism by which exposure causes disease. Schulte, supra note 2, at 7; see also Mark R. Fielden & Tim R. Zacharewski, Challenges and Limitations of Gene Expression Profiling in Mechanistic and Predictive Toxicology, 60 TOXICOLOGICAL SCI. 6, 7 (2001) (describing some of the complexities involved in defining a toxin’s mechanism of action).

28. Paul W. Brandt-Rauf & Sherry 1. Brandt-Rauf, Biomarkers—Scientific Advances and Societal Implications, in GENETIC SECRETS—PROTECTING PRIVACY AND CONFIDENTIALITY IN THE GENETIC ERA 184 (Mark A. Rothstein ed., 1997). Dr. Frederica Perera, a pioneer in the field of molecular epidemiology and an advocate of more widespread application of biomarker research, has explained the potential value of molecular-level biomarkers for cancer research:

[Molecular epidemiology] combines the tools of standard epidemiology . . . with the sensitive laboratory techniques of molecular biology . . . [The conventional approach] reveals nothing about the precise continuum of events leading from exposure to overt disease. Molecular epidemiology aims to uncover critical pre-cancerous events taking place inside the body and to identify measurable biologic flags signaling their occurrence . . . . [It] looks into the black box to uncover important steps leading from carcinogenic exposure to disease. It also identifies biological signs, or biomarkers that may indicate increased risk. Some markers reflect exposure or advancement along the pathway to cancer. Others reflect innate or acquired susceptibility to the effects of carcinogens.

Perera, supra note 18, at 54-55 (emphasis added).

29. National Research Council, supra note 20. Pursuant to a request from EPA and the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH), the National Academy of Sciences/National Research Council organized the Committee on Biological
biomarkers and provided a conceptual model illustrating relationships among them. The "biomarker paradigm," in which biomarkers identify various stages and interactions on the pathway from exposure to disease, provides the groundwork for understanding dramatic developments in environmental genomics since the 1990s. The three categories of biomarkers are those measuring susceptibility, exposure, and effect.

a. Biomarkers of Susceptibility

Broadly defined, susceptibility biomarkers are any identifiable genetic variations affecting absorption, metabolism, or response to environmental agents. These genetic variations, generally referred to as "polymorphisms" do not act alone to trigger disease, but confer differential sensitivity to the effects of drugs or chemicals. Such "environmental susceptibility genes" can be contrasted to highly penetrant "disease genes"—such as those for Huntington's disease, cystic fibrosis, and


31. For additional discussions of the development of molecular-level biomarkers and the biomarker paradigm, see Richard J. Albertini, Developing Sustainable Studies on Environmental Health, 480 MUTATION RES. 317, 317-31 (2000); Brandt-Rauf & Brandt-Rauf, supra note 28; DeCaprio, supra note 25; Perera, supra note 18; Schulte, supra note 2.  
32. National Research Council, supra note 20, at 4-6.  
33. Id. at 6. Genetic variations in response to toxic substances may result from the presence of alleles (alternate forms of the same gene) that promote adverse effects from exposures, or from the absence of alleles that provide protection (for example, resistance) from environmentally induced disease. The classic example of an allele is the gene that dictates flower color in a pea plant. The gene may be present in one form that dictates white color or in another form that dictates purple color. Both forms of the gene are referred to as alleles. CAMPBELL ET AL., supra note 6, at 158.  
34. Polymorphisms are common sequence variations within genes, which may include nucleotide substitutions, deletions, insertions, or gene duplications or deletions. Merrill C. Miller III et al., Genetic Variability in Susceptibility and Response to Toxics, 120 TOXICOLOGY LETTERS 269, 270 (2001); N. J. Schork et al., Single Nucleotide Polymorphisms and the Future of Genetic Epidemiology, 58 CLINICAL GENETICS 250, 251-52 (2000); see also Francis Collins et al., Variations on a Theme: Cataloging Human DNA Sequence Variation, 278 SCI. 1580 (1997).  
35. When there is a tight connection between possession of a gene variant and expression of a phenotypic trait, the gene is said to be highly "penetrant." The environment plays a limited role in the expression of highly penetrant genes, such as the so-called "disease genes." In contrast, one may possess an environmental susceptibility gene for a trait, but would not actually express the trait in the absence of an environmental exposure. Moreover, environmental susceptibility tends to be influenced by many genes working in concert. For discussion of the difference between environmental susceptibility genes and disease genes, see Neil Caporaso & Alisa Goldstein, Cancer Genes: Single and Susceptibility: Exposing the Difference, 5 PHARMACOGENETICS 59, 61-62 (1995); Kenneth Olden &
sickle cell anemia—in which a single mutation may be a predictor of disease even in the absence of an environmental exposure.  

Susceptibility genes are "neither necessary nor sufficient to cause disease. They modify risk." The relationship between genes and the environment has been compared to a loaded gun and its trigger: "A loaded gun by itself causes no harm; it is only when the trigger is pulled that the potential for harm is released or initiated. Likewise, one can inherit a predisposition for a devastating disease, yet never develop the disease unless exposed to the environmental trigger(s)."

Such genetic variations may increase the rate at which carcinogens or other harmful substances are activated, reduce an individual's ability to detoxify harmful compounds, or disable DNA repair mechanisms, tumor suppressor genes, or other protective functions. In this manner, one's genetic complement may affect the toxicity or potency of chemicals. For example, some studies indicate that people with an abnormally slow-acting form of an enzyme that deactivates carcinogens in tobacco smoke, air pollution, and certain cooked foods are at higher risk for bladder cancer. Likewise, smokers who harbor a variant of another gene that enhances the

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37. Olden & Guthrie, supra note 35, at 5.

38. Id. at 3-4.

39. Although certain genetic variations may reduce susceptibility to environmentally induced disease, this Article focuses on polymorphisms that enhance susceptibility, as the presence of genetically susceptible individuals and groups will likely raise questions about the adequacy of existing environmental standards. Even though genetic resilience could potentially affect estimates of risk in the general population, the issue of protecting more sensitive subpopulations remains distinct. See, e.g., Perera, supra note 18, at 60; Poulter, supra note 36, at 213-15.

40. Olden & Guthrie, supra note 35, at 5.

41. The enzyme associated with bladder cancer is N-acetyltransferase (NAT2), which has been shown to deactivate carcinogenic aromatic amines. See, e.g., R.A. Cartwright et al., *Role of N-acetyltransferase Phenotypes in Bladder Carcinogenesis: A Pharmacogenetic Epidemiological Approach to Bladder Cancer*, 2 Lancet 842-45 (1982); D.W. Hein et al., *Molecular Genetics and Epidemiology of the NAT Type 1 and NAT Type 2 Acetylation Polymorphisms*, 9 Cancer Epidemiol. Biomarkers Prev. 29-42 (2000); Perera, supra note 18, at 60. In another example, the absence of the gene coding for glutathione S-transferase M1 (GSTM1) has been associated with increased rates of bladder and lung cancer. This enzyme is believed to help detoxify several carcinogens including polycyclic aromatic hydrocarbons (PAHs), ethylene oxide, and styrene. Perera, supra note 18. But see Julian Peto, *Cancer Epidemiology in the Last Century and the Next Decade*, 411 Nature 390, 392 (2001) (discussing systematic meta-analyses revealing only modest increases in bladder cancer risk attributable to polymorphisms in the NAT2 gene and in lung cancer risk attributable to the GSTM1 deficiency).
activation of hydrocarbons have been shown to be at greater risk of acquiring lung cancer.\textsuperscript{42} Mutations in genes coding for enzymes that normally help break down certain classes of pesticides also have been identified.\textsuperscript{43} Studies involving occupational exposures have found a genetic marker of susceptibility in workers with berylliosis, a potentially fatal respiratory disease caused by exposure to beryllium.\textsuperscript{44} Polymorphisms believed to affect susceptibility to a palette of regulated chemicals have been identified.\textsuperscript{45}

\textit{b. Biomarkers of Exposure}

Biomarkers of exposure indicate the amount of a foreign compound that is absorbed into the body. Biological measurements performed on human tissues are vastly expanding the capabilities of classical epidemiology, which has relied primarily on indirect estimates of human exposure derived from chemical levels in the air, water, and other exposure routes.\textsuperscript{46} These indirect methods require modeling or monitoring of the ambient environment and significant guesswork as to actual human exposure levels.\textsuperscript{47} Moreover, these measurements have severe limitations, as individuals vary in their rates of absorption, metabolism, and excretion of toxic substances; hence, individuals subject to the same ambient exposure may

\textsuperscript{42} Individuals possessing variants of the CYP1A1 gene have been shown to have an increased chance of acquiring lung cancer. Perera, supra note 18, at 60. CYP1A1 is a member of the cytochrome P450 family, a related group of enzymes that act on numerous chemicals. \textit{Id.}

\textsuperscript{43} Variations of the gene coding for the enzyme paraoxonase, which helps break down toxic organophosphate compounds, including many insecticides, is one example. Jocelyn Kaiser, \textit{Environment Institute Lays Plans for Gene Hunt}, 278 Sci. 569 (1997); see also Olden & Guthrie, supra note 35, at 5.

\textsuperscript{44} Olden & Guthrie, supra note 35, at 5.

\textsuperscript{45} These chemicals include ozone, particulate matter, lead, benzene, vinyl chloride, asbestos, arsenic, ethylene oxide, beryllium, trichloroethylene, environmental tobacco smoke, aromatic amines, butadiene, and methylene chloride. See Gary E. Marchant, \textit{Genomics and Toxic Substances: Part II—Genetic Susceptibility to Environmental Agents}, 33 ENVT. L. REP. 10641, 10644 (2003). For animal and human studies suggesting linkages between genetic makeup and response to pervasive air pollutants, see, e.g., Enrico Bergamasci et al., \textit{Polymorphism of Quinone-metabolizing Enzymes and Susceptibility to Ozone-induced Acute Effects}, 163 AM J. RESPIRATORY CRITICAL CARE MED. 1426 (2001); Steven R. Kleeberger et al., \textit{Linkage Analysis of Susceptibility to Ozone-Induced Lung Inflammation in Inbred Mice}, 17 NATURE GENETICS 475 (1997); William F. McDonnell, \textit{Individual Variability in Human Lung Function Responses to Ozone Exposure}, 2 ENVT. TOXICOL. PHARMACOLOGY 171, 175 (1996); Yoshinori Ohtsuka et al., \textit{Genetic Linkage Analysis of Susceptibility to Particle Exposure in Mice}, 22 AM. J. RESPIRATORY CELL & MOLECULAR BIOLOGY 574 (2000).

\textsuperscript{46} Brandt-Rauf & Brandt-Rauf, supra note 28, at 186.

\textsuperscript{47} Exposure to environmental agents traditionally has been assessed by mathematical modeling based upon assumptions about emission levels, physical environmental influences, and the location of individuals relative to the source. Exposure also has been assessed by ambient monitoring through physical analyses of food, air, water, or soil, coupled with measurements or estimates of human intake of these media or by direct measurements of substances in body fluids or other tissues. Use of molecular-level markers to measure exposure or effect may be far preferable to modeling or ambient monitoring. National Research Council, supra note 20, at 4. The new approach does not supplant the tools of conventional epidemiology, but rather supplements them with the more sensitive laboratory techniques of molecular biology. Perera, supra note 18, at 54.
retain different amounts of toxins\textsuperscript{48} in their bodies.\textsuperscript{49} Exposure biomarkers detected in the human body may include the parent chemical, metabolic derivatives, or early interactive products of the chemical or drug and the biological system.\textsuperscript{50}

c. Biomarkers of Effect

Biomarkers of effect reflect changes in cells or tissues triggered by chemical exposure\textsuperscript{51} or changes that are qualitatively or quantitatively predictive of health impairment or potential impairment due to toxic exposure.\textsuperscript{52} Biomarkers of effect may measure early biochemical or cellular changes, structural or functional changes in affected cells or tissues, or changes formally recognized as health impairments or clinical disease.\textsuperscript{53}

The distinction between biomarkers of effect and biomarkers of exposure, however, is not clear-cut.\textsuperscript{54} These classifications may overlap, and may change as our knowledge increases.\textsuperscript{55} For example, scientists have classified DNA or protein "adducts"—complexes formed when carcinogenic substances bind to DNA or protein molecules in the body—as either markers of exposure or effect.\textsuperscript{56} While some have suggested that biomarkers of effect indicate the moment at which an environmental agent has brought about molecular change, others have limited the definition to

\textsuperscript{48} In the scientific literature, the term "toxin" generally refers to toxic substances that are produced in biological systems such as plants, animals, fungi, or bacteria. In contrast, "toxicant" refers to all toxic substances, including those that are produced by, or are byproducts of, human activities. See David L. Eaton & Curtis D. Klaassen, Principles of Toxicology, in CASARETT AND DOULL'S TOXICOLOGY, supra note 3, at 13. In this Article, "toxin" is occasionally used more broadly to incorporate both man-made and biologically-derived substances.

\textsuperscript{49} Brandt-Rauf & Brandt-Rauf, supra note 28, at 186; see also Marchant, supra note 45.

\textsuperscript{50} National Research Council, supra note 20, at 3.

\textsuperscript{51} Perera, supra note 18, at 54. Biomarkers of effect may represent responses to physical, chemical, or biological exposures. References to chemical exposure in this Article may be applied to hazardous exposures more generally.

\textsuperscript{52} National Research Council, supra note 20, at 5.

\textsuperscript{53} DeCaprio, supra note 25, at 1839. A biomarker of effect also may be an event peripheral to but correlated with any disease process and thus predictive of health impairment. National Research Council, supra note 20, at 4.

\textsuperscript{54} "These assignments are not mutually exclusive, and the distinctions between adjacent stages are frequently blurred." DeCaprio, supra note 25, at 1838.

\textsuperscript{55} Id.; see also National Research Council, supra note 20, at 3 ("[T]here is a continuum between markers of exposure and markers of health status, with certain events being relatable to both types of markers.").

\textsuperscript{56} Perera, supra note 18, at 58. For example, adducts formed when polycyclic aromatic hydrocarbons (PAHs) bind to DNA in the blood have been found to be early markers of an increased propensity for lung cancer. Id. Another example of the predictive role of adducts relates to aflatoxin, a naturally occurring carcinogen found in moldy corn and peanuts. Studies have indicated that individuals with liver cancer were more likely than control subjects to have aflatoxin-DNA complexes or aflatoxin derivatives in their urine. J.D. Groopman et al., Molecular Biomarkers for Aflatoxins and Their Application to Human Cancer Prevention, 54 CANCER RES. 1907S, 1909S (1994); Ronald K. Ross et al., Urinary Aflatoxin Biomarkers and Risk of Hepatocellular Carcinoma, 339 LANCET 943, 943-44 (1992). See also DeCaprio, supra note 25, at 1839-40.
changes that portend future disease. For legal purposes, the point at which a biomarker becomes predictive of disease may be a million dollar question (literally), and the process of "validation" aims to solidify the predictive power of early markers.

d. The Continuum Between Exposure and Disease

Perhaps the most important contribution of the biomarker paradigm is the concept of a continuum of effects between environmental exposure and disease. At one end of the continuum is exposure to a toxic substance. The other end represents a manifestation of overt disease, such as a cancerous tumor that may appear years after the initial exposure. The area between the two, once considered a "black box," now includes subcellular biomarkers of exposure and effect. When visualized as points along a horizontal bar, markers will proceed from left to right, with markers of exposure followed by markers of effect. Although these events are most clearly illustrated in the context of cancer, they also may be applied to neurological, immunological, reproductive, developmental, pulmonary, and other environmentally related health impairments.

Susceptibility biomarkers are conceptually distinct from markers on the horizontal bar, as they are present in individuals even in the absence of a chemical exposure. However, these sequence variations may influence the rate of progression from one class of marker to the next on the exposure-disease continuum. Markers of susceptibility therefore are indicators of increased risk of manifestation of effects at any stage along the continuum.

2. The Need for Validation

Before molecular and genetic biomarkers are used for legal or regulatory purposes, they must first be characterized and then "validated." Validation is essentially a quality control process whereby each biomarker is evaluated for its reliability as a measure of exposure, effect, or susceptibility. While some biomarkers have been deemed to be validated and

57. Id.
58. See discussion infra notes 63-74.
59. For helpful graphic representations of this continuum, see DeCaprio, supra note 25, at 1838, fig.2; National Research Council, infra note 20, at 4, fig.1; Schulte, supra note 2, at 7, fig.1.2.
60. DeCaprio, supra note 25, at 1838; Marchant, supra note 45, at 10644. For example, the process of carcinogenesis might be represented initially by the formation of adducts, followed by genetic mutations, then tumor formation. Perera, supra note 18, at 58-59.
61. DeCaprio, supra note 25, at 1840; National Research Council, supra note 20, at 4, fig.1.
63. See, e.g., Paul A. Schulte, Contribution of Biological Markers to Occupational Health, 20 AM. J. INDUS. MED. 435, 436 (1991). The term, "validation," can be taken to have different meanings. From an analytical perspective, validation refers to the process of establishing that a given test responds when a biomarker is present but not when it is absent. From a clinical perspective, validation refers to
ready for use in legal or regulatory settings,\textsuperscript{64} new high-speed, high-volume genomics technologies are identifying potential new biomarkers at a dramatic rate. Hence, the discovery of putative new biomarkers has far outpaced the validation process.\textsuperscript{65}

For biomarkers of effect, the goal of validation is to distinguish alterations that are predictive of clinical disease from changes that are benign, reversible, or represent adaptive or protective mechanisms.\textsuperscript{66} In other words, a key question is whether a putative biomarker represents a permanent, deleterious effect of a poison or a useful, adaptive response to fight the poison.\textsuperscript{67}

Validating markers of susceptibility is equally daunting. First, many DNA sequence variations have no known physiological or functional significance.\textsuperscript{68} There is no guarantee that a particular gene variant can be linked to any specific trait or disease.\textsuperscript{69} Second, susceptibility to disease may be influenced by many factors apart from genetic predisposition, including age, gender, nutrition, behavior, preexisting disease, and previous environmental exposure.\textsuperscript{70} Moreover, most environmentally induced diseases are not only multifactorial (caused by many factors, both genetic

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\textsuperscript{64} For discussions of the validation of biomarkers and their potential for use in scientific, legal, and regulatory settings, see, e.g., A. Aitio & A. Kallio, \textit{Exposure and Effect Monitoring: A Critical Appraisal of Their Practical Application}, 108 \textit{Toxicology Letters} 137, 142 (1999); Schulte, \textit{supra} note 63, at 436; see also DeCaprio, \textit{supra} note 25, at 1846 (discussing the lengthy process of translating into practical application research findings of a new scientific paradigm); Frederica P. Perera, \textit{The Potential Usefulness of Biological Markers in Risk Assessment}, 76 \textit{Envtl. Health Persp.} 141, 143-44 (1987).

\textsuperscript{65} As one commentator has noted, "The mere availability of biomarkers does not mean that they will be useful for human studies directed at public health issues. Although the current armamentarium is large, few of the biomarkers have been validated to the point where they are of known usefulness to epidemiological studies." Albertini, \textit{supra} note 31, at 323.

\textsuperscript{66} See, e.g., Smith, \textit{supra} note 3, at 283. The practical necessity of using surrogate markers in some cases may complicate the picture further. For example, for DNA adduct studies, samples from target organs are often unavailable. Therefore, surrogate markers (e.g., protein adducts) and surrogate tissues frequently serve as substitutes. The more removed a biomarker is from the causal pathway of disease, the less effective it will be as a predictor of disease risk. John D. Groopman & Thomas W. Kensler, \textit{The Light at the End of the Tunnel for Chemical-Specific Biomarkers: Daylight or Headlight?}, 20 \textit{Carcinogenesis} 1, 1 (1999).

\textsuperscript{67} See, e.g., Smith, \textit{supra} note 3, at 283.

\textsuperscript{68} Schork et al., \textit{supra} note 34, at 252.

\textsuperscript{69} Id.

\textsuperscript{70} Olden & Guthrie, \textit{supra} note 35, at 6. These factors may result in an increase in the internal dose, the biologically effective dose, or the target tissue response to an environmental agent. National Research Council, \textit{supra} note 20, at 6.
and environmental), but also polygenic (influenced by many genes).71 Thus, the effect of one susceptibility gene may be tempered by other genes or environmental influences.72 Finally, in contrast to highly penetrant disease genes, which are rare in the population but confer extremely high risk,73 susceptibility genes generally are believed to be of high frequency in the overall population but are assumed to increase individual risk by a lesser degree.74 However, this assumption may not apply uniformly, particularly when the combined effects of multiple genes are considered.

3. Implications

The biomarker paradigm has contributed to a growing realization that understanding the cause-effect relationships between exposure to toxins and development of disease will require not only an analysis of numerous intermediate events, but also knowledge of variations in individual susceptibility.75 In the future, interrelationships among biomarkers of exposure, effect, and susceptibility will need to be analyzed in order to develop more comprehensive and accurate estimates of environmental risk.76 Although it could be many years before particular biomarkers are understood sufficiently to affect environmental or occupational policies,77 the science is progressing quickly, backed by substantial public and private support. The validation and exploitation of biomarkers will contribute to the identification of vulnerable groups and individuals who may claim a right to protection under the environmental regulatory scheme. Likewise, the legal and regulatory significance of establishing a continuum of molecular-level markers between exposure and disease cannot be overstated. Advances in molecular biology and genetics may change the point at which we can determine that a disease or injury has occurred, thereby reducing the time period between exposure and remediable harm.78

71. Marilyn J. Aardema & James T. MacGregor, Toxicology and Genetic Toxicology in the New Era of “Toxicogenomics”: Impact of “-Omics” Technologies, 499 MUTATION RES. 13, 14 (2002). A variant of a single gene may not be detrimental but may become so in combination with other genes. For a discussion of the complexity of differentiating genetic from other risk factors, see Gary E. Marchant, Genetic Susceptibility and Biomarkers In Toxic Injury Litigation, 41 JURIMETRICS 67, 97-100 (2000).
72. Perera, supra note 18, at 61.
73. See supra notes 35-36.
74. Olden & Guthrie, supra note 35, at 4; Olden & Wilson, supra note 35, at 150; see also Kaiser, supra note 43, at 570.
75. See, e.g., Hoffmann et al., supra note 17, at 6-8; Frederica P. Perera, Molecular Epidemiology: Insights Into Cancer Susceptibility, Risk Assessment, and Prevention, 88 J. NAT’L CANCER INST. 496, 497-500 (1996); Ricarda Thier & Hermann M. Bolt, The New Era of Toxicology, 22 TRENDS IN PHARMACOLOGICAL SCI. 549, 549-50 (2001); see also Marchant, supra note 45, at 10646-47.
76. Brandt-Rauf & Brandt-Rauf, supra note 28, at 191.
77. As biomarkers must be validated independently, it is difficult to generalize about time frames for legal and regulatory application.
78. Poulter, supra note 36, at 237.
Because molecular and genetic changes are discernible at lower doses of toxic substances than are clinical symptoms,\textsuperscript{79} environmental regulators may need to decide whether to reduce permissible pollution levels accordingly.

\textbf{B. The Second Generation: Toxicogenetics and Toxicogenomics}

The entrance of molecular biology into the fields of toxicology and epidemiology represented a critical first step toward a more refined and comprehensive understanding of the interplay of genes and the environment. Substantial developments since the mid-1990s represent a quantum leap further. These include the sequencing of the human genome and the application of high-speed gene expression profiling technology to the study of gene-environment interactions.

Technological advances facilitating high-speed, high-volume analysis of gene expression patterns have identified a host of putative biomarkers since the 1990s. The miniaturization of semiconductor chips, developments in laser engineering and robotics, and DNA amplification techniques have enabled the development of DNA microarrays, also called “gene arrays” or “gene chips.”\textsuperscript{80} These technologies permit thousands of genes to be monitored simultaneously to determine whether they have been activated or deactivated as a result of chemical exposure.\textsuperscript{81} Such “high-throughput”

\textsuperscript{79} Schulte, supra note 2, at 4.

\textsuperscript{80} Microarray technology blends molecular biology techniques with advanced computer, robotics, and information technologies. In a DNA microarray, each chip is manufactured to contain thousands of target genes or pieces of genes. To assay gene expression in stimulated cells, one extracts RNA from the cells, reverse-transcribes the RNA to produce cDNA, labels the cDNA using a fluorescent or radioactive tag, and then incubates the labeled cDNA with the DNA chip. Each cDNA molecule should bind only to its complementary sequence on the chip, thereby indicating which genes were expressed in the original stimulated cells. One can also roughly quantify the relative level of gene expression in the stimulated cells by the intensity of the bound fluorescent or radioactive tag. Microarray technology also can be used to assay events downstream of the genome. For discussions of the capabilities of microarray technology, see generally Cynthia A. Afshari, Perspective: Microarray Technology, Seeing More Than Spots, 143 ENDOCRINOLOGY 1983 (2002); Herbert L. Frederickson et al., Toward Environmental Toxicogenomics—Development of a Flow-Through, High-Density DNA Hybridization Array and its Application to Ecotoxicity Assessment, 274 SCI. TOTAL ENV’T 137 (2001); Hisham K. Hamadeh & Cynthia A. Afshari, Gene Chips and Functional Genomics, 88 AM. SCI. 508 (2000); Hisham K. Hamadeh et al., Discovery in Toxicology: Mediation By Gene Expression Array Technology, in 15 J. BIOCHEMISTRY & MOLECULAR TOXICOLOGY 231 (2001); John F. Lauerman, Arrays Cast Toxicology in a New Light, 109 ENVTL. HEALTH PERSP. at A-20 (2001); Jennifer Medlin, Array of Hope for Gene Technology, 109 ENVTL. HEALTH PERSP. at A-34 (2001); Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 MOLECULAR CARCINOGENESIS 153 (1999); Bob Sinclair, Everything’s Great When It Sits on a Chip, 131 SCIENTIST 18 (May 24, 1999).

\textsuperscript{81} The technology permits expression patterns in normal cells to be compared to mutant cells, untreated cells to be compared to cells treated with drugs or chemicals, and normal tissues to be compared to diseased tissues. See Aardema & MacGregor, supra note 71, at 14; Hamadeh & Afshari, supra note 80, at 509-11; Hamadeh et al., supra note 80, at 231-32; Sandra Steiner & N. Leigh Anderson, Expression Profiling in Toxicology—Potentials and Limitations, 112 TOXICOLOGY LETTERS 467 (2000).
technologies allow for comprehensive analysis of gene expression at a speed and scale unknown in the past, and can potentially be used to scan the entire human genome to search for genetic responses to specific chemicals.\(^8\) Whereas scientists traditionally focused on one or a few genes at a time or on exposure to single environmental agents, microarrays and related technologies can reveal interactions among multiple gene pathways and may be used to document effects of multiple chemicals simultaneously.\(^8\)

The sequencing of the human genome signified another transformative moment in human genetics research and the development of tools for understanding the relationship between genes and the environment. The joint announcement by the Human Genome Project and Celera Genomics of a draft or “reference sequence” of the human genome in 2001\(^8\) is sometimes viewed as the watershed for a “second generation” in human genome research.\(^8\) The availability of a reference sequence, followed by announcement of the full sequence in 2003,\(^8\) has allowed the focus in the field of genomics to shift from mapping the genome to elucidating the function of individual genes.\(^8\) This expanded focus on “functional genomics” includes the study of the diversity of the human genome and its interaction with environmental factors.\(^8\) The emerging fields of toxicogenetics and toxicogenomics represent two important second-generation developments.

1. Toxicogenetics

Toxicogenetics is the study of the relationship between innate genetic makeup and susceptibility to the effects of toxic substances.\(^8\) To simplify, toxicogenetics might be viewed as a quest for specific genetic biomarkers of susceptibility and an understanding of their mechanisms of action.

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82. Afshari, supra note 80, at 1984; Hamadeh et al., supra note 80, at 231; Olden & Guthrie, supra note 35, at 7.
84. The Human Genome Project was conceived in the mid 1980s, coinciding with the development of high-throughput DNA sequencing technology. In 1988, the NIH and the Department of Energy agreed to coordinate research related to the sequencing of the human genome. The first complete draft of the genome was published in 2001.
85. See, e.g., Olden & Guthrie, supra note 35, at 6.
87. See, e.g., Olden & Guthrie, supra note 35, at 6.
88. Id.
89. See, e.g., Spencer Farr & Robert Dunn II, Gene Expression Applied to Toxicology, 50 TOXICOLOGICAL SCI. 1, 1-2 (1999); Nuwaysir et al., supra note 80, at 158.
Building on this foundation, microarrays and related technologies have enabled a genome-wide search for susceptibility genes and the mechanisms by which they predispose certain individuals to environmental harm. Estimates suggest that over 500,000 common genetic variations, or polymorphisms, occur in the coding region of human genes.\(^9\) The current focus is on polymorphisms in which a single nucleotide is varied (single nucleotide polymorphisms or SNPs), the most abundant form of polymorphism.\(^9\)

New technologies permit large-scale screening of SNPs in the human genome with the goal of developing a comprehensive collection of mapped SNPs.\(^9\) In 1997, the National Institute of Environmental Health Sciences (NIEHS) launched the Environmental Genome Project, the first large-scale, systematic study of human genetic variation in response to environmental agents.\(^9\) Other public, private, and joint efforts have since emerged.\(^4\)

2. Toxicogenomics

A major focus of toxicogenomics is the systematic investigation of patterns of gene expression in cells exposed to toxic substances.\(^5\) This investigation is based on the assumption that toxicity frequently evokes qualitative or quantitative changes in gene expression.\(^6\)

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91. See, e.g., Olden & Wilson, supra note 35, at 151; Schork, supra note 34, at 261; Craig Venter, Whole Genomes: The Foundation of New Biology and Medicine, 11 CURRENT OPINION BIOTECHNOLOGY 563, 581 (2000). SNPs, which may occur in the coding or regulatory regions of genes, can affect gene function or they can be neutral. Olden & Wilson, supra note 35, at 151; David G. Wang et al., Large-Scale Identification, Mapping, and Genotyping of Single-Nucleotide Polymorphisms in the Human Genome, 280 SCI. 1077, 1077 (1998).
92. Wang et al., supra note 91, at 1077. However, some scientists have cautioned against overreliance on SNPs. See, e.g., Elizabeth Pennisi, A Closer Look at SNPs Suggests Difficulties, 281 SCI. 1787 (1998) (suggesting that recombination can break down the correlation between SNPs and variants that inflate disease risk).
93. Olden & Wilson, supra note 35, at 151 box 1 (showing phases of the Environmental Genome Project).
94. In addition to the Environmental Genome Project of NIEHS, SNP discovery projects in the United States are sponsored by the National Human Genome Research Institute (NHGRI) of the National Institute of General Medical Sciences (NIGMS), the National Heart Lung Blood Institute, and the Lawrence Livermore National Laboratory. Private companies, academic institutions, and a large academic-industry consortium also are involved in toxicogenetic research. See, e.g., Miller et al., supra note 34, at 275 (summarizing the various SNP discovery projects).
96. See, e.g., Nuwaysir et al., supra note 80, at 154-55:

Fundamental to all of these methods is the fact that toxicity is often preceded by, and results in, alterations in gene expression. In many cases, these changes in gene expression are a far more sensitive, characteristic, and measurable endpoint than the toxicity itself. We therefore propose that a method based on measurements of the genome-wide gene expression pattern
may gain valuable insights into the mechanisms of toxicity by studying gene expression and downstream effects.\textsuperscript{97} Placed in the biomarker context, toxicogenomic studies of gene expression focus primarily on biomarkers of exposure and effect—early molecular precursors to toxin-induced disease.\textsuperscript{98} A stated goal is to survey the entire human genome to determine which genes are activated or deactivated by specific chemicals.\textsuperscript{99} The related disciplines of "proteomics" and "metabonomics" use new technologies to analyze events downstream of the genome, at the protein and cellular metabolism levels.\textsuperscript{100}

Gene expression research frequently is classified as either "mechanistic" or "predictive."\textsuperscript{101} Mechanistic research focuses on how chemicals may affect genes, proteins, and metabolic processes. Predictive studies seek to establish cause-effect relationships between events in the exposure-disease continuum. Indeed, these areas are complementary, as mechanistic studies often have substantial predictive value. The primary coordinating body for toxicogenomics research in the United States is the National Center for Toxicogenomics (NCT), which the NIEHS established in 2000.\textsuperscript{102} One goal is to develop a worldwide reference system of chemically induced gene expression patterns in order to provide a better understanding of the mechanisms by which environmentally induced injury occurs.\textsuperscript{103}

It may be helpful conceptually to understand the distinctions and similarities between toxicogenetic investigations of genetic susceptibility and the mechanistic and predictive aspects of toxicogenomics. To distinguish the two, I suggest that toxicogenetics focuses on individual genetic differences, while toxicogenomics tends to focus on general mechanisms of toxic response. Thus, while toxicogenetics focuses on the role of individual genes in moderating or accentuating the effects of environmental agents, of an organism after toxicant exposure is fundamentally informative and complements the established methods.

\textsuperscript{97} Aardema & MacGregor, supra note 71, at 16.
\textsuperscript{98} Olden et al., supra note 83, at 1965.
\textsuperscript{99} Id.
\textsuperscript{100} Aardema & MacGregor, supra note 71, at 14. Proteomics and metabonomics refer to technologies that allow rapid and global analysis of, respectively, proteins and chemical metabolites (that is, the small molecules involved in the pathways of intermediary metabolism). These technologies are complementary to nucleic acid microarrays and permit a more complete analysis of cellular constituents. Id. at 14-15; Raymond W. Tennant, The National Center for Toxicogenomics: Using New Technologies to Inform Mechanistic Toxicology, 110 ENVTL. HEALTH PERSP. A8, A9 (2002). Proteomics involves "the comprehensive functional annotation and validation of proteins in response to toxicant exposure." Hamadeh et al., supra note 95, at 47.
\textsuperscript{101} See, e.g., Fielden & Zacharewski, supra note 27, at 6-10; Hamadeh et al., supra note 95, at 47; William D. Pennie, Use of cDNA Microarrays to Probe and Understand the Toxicological Consequences of Altered Gene Expression, 112-13 TOXICOLOGY LETTERS 473, 474 (2000).
\textsuperscript{102} The National Center for Toxicogenomics consists of the NIEHS microarray center and university-based regional centers. See Tennant, supra note 100, at A8.
\textsuperscript{103} Id.
toxicogenomics measures thousands of genes and gene products to determine how environmental agents affect overall gene function.

On the other hand, the two pursuits overlap in ways not frequently discussed in the scientific literature. First, they may in some cases represent different applications of the same technology. For example, gene expression profiles analyzed in toxicogenomic research may be useful in discovering DNA sequence polymorphisms. Moreover, work on polymorphisms may uncover more general information about toxin-induced gene expression. Finally, because individual susceptibility influences the progression from exposure to disease, a comprehensive understanding of the causal relationships underlying disease progression necessarily will include consideration of variations in susceptibility.

3. Implications

It is axiomatic that the application of new genomic technologies represents a significant change from the past in terms of speed, volume, scale, and efficiency. The rate of change in this area is striking. Moreover, these new technical capabilities add to the arsenal of potential biomarkers of exposure, effect, and susceptibility, and can document gene and protein interactions and effects of chemical mixtures to a degree

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104. One commentator has noted that the primary mechanism for selecting new candidate genes likely will involve toxicogenomics or gene expression profiling. Olden & Guthrie, supra note 35, at 7.
105. Id.
107. See, e.g., Hoffmann et al., supra note 17, at 5-7; Thier & Bolt, supra note 75, at 549-50.
108. Underscoring the recency of these developments, the application of gene array technology to the science of toxic injury is widely attributed to a scientific paper published in 1995. Mark Schena et al., Quantitative Monitoring of Gene Expression With a Complementary DNA Microarray, 270 Sci. 467 (1995); see also Afshari, supra note 80, at 1983 (describing the Schena article as a "landmark paper initiating a new era"). But see Roger Ekins & Frederick W. Chu, Microarrays: Their Origins and Applications, 17 ThITeCH 217, 217-28 (June 1999) (suggesting that sensitive microarray-based assays had been developed in the mid-1980s). As noted, the term "genomics" first appeared in 1987 to mark the advent of a new scientific journal. See McKusick & Ruddle, supra note 6. The NIEHS coined the term "environmental genomics" with the announcement of the Environmental Genome Project in 1997. See F.P. Guengerich, The Environmental Genome Project: Functional Analysis of Polymorphisms, 106 ENVTL. HEALTH PERSP. 365, 365-68 (1998); Kaiser, supra note 43, at 569-70; Olden & Guthrie, supra note 35, at 6. "Toxicogenomics" entered our lexicon in the late 1990s, see, e.g., Nuwaysir et al., supra note 80, at 153, as did "toxicogenetics," see B. Kevin Park & Munir Pirmohamed, Toxicogenetics in Drug Development, 120 TOXICOLOGY LETTERS 281 (2001). "Proteome" was coined in a 1995 publication. See Marc R. Wilkins et al., Progress with Proteome Projects: Why All Proteins Expressed by a Genome Should Be Identified and How To Do It, 13 BIOTECHNOLOGY AND GENETIC ENGINEERING REV., 19, 20 (1995) (defining the proteome as the "entire protein complement expressed by a genome"). "Proteomics" followed shortly thereafter. See Peter James, Protein Identification in the Post-Genome Era: The Rapid Rise of Proteomics, 30 Q. REV. BIOPHYSICS 279, 284 (1997). "Metabonomics" was pioneered in the late 1990s. See J.K. Nicholson et al., "Metabonomics": Understanding the Metabolic Responses of Living Systems to Pathophysiological Stimuli via Multivariate Statistical Analysis of Biological Nuclear Magnetic Resonance Spectroscopic Data, 29 XENOBIOTICA 1181, 1182 (1999) (explaining that metabonomics provides a "history of time-related metabolic changes ... in [a] biological system").
impossible before. The systematic identification of potential biomarkers through microarrays and other new technologies underscores the need for validation before such data can be relied upon in legal or regulatory settings.\textsuperscript{109}

Despite the many hurdles ahead, two developments in toxicogenetics and toxicogenomics may be particularly significant for environmental law and regulation. First, research since the 1990s has provided further evidence suggesting a link between exposure to particular chemicals and unique genetic "signatures," potentially enhancing the predictive power of early markers. Second, new technology may lay the groundwork for more personalized assessments of environmental risk.

\textit{a. Telltale Patterns—Gene Signatures or "Fingerprints"}

One of the most important capabilities derived from microarray technology can be summed up in a single word—patterns.\textsuperscript{110} Ongoing research is based on the premise that the unique gene expression pattern that a particular class of chemicals induces—known as a "gene signature" or "gene fingerprint"—may establish exposure to that class of chemicals.\textsuperscript{111} The ability to correlate a signature response with exposure to a particular chemical or class of chemicals could suggest a relationship to subsequent disease: "The possibility that a specific group or class of compounds... may induce signature patterns of gene expression changes is the basis of the application of toxicogenomics to predictive toxicology."\textsuperscript{112} One goal of current scientific research is to develop "libraries" of distinctive cellular responses that particular classes of chemicals induce.

Gene expression patterns are not the exclusive form of genetic signature. Traditional biomarkers such as DNA adducts and signature mutations may in some cases reveal the identity of toxic substances through their

\textsuperscript{109} Gene expression profiling allows us to measure changes in the expression of many genes and proteins for which we do not understand the biological significance. Schwetz, supra note 15, at 5. As one scientist noted:

[T]he greatest obstacle to the spread of toxicogenomics may remain in interpreting the multitudes of data that pour out of each slide. At this point, it's difficult to say what the crests and valleys of gene expression mean—whether an increase in the expression of a particular gene indicates involvement in protection or vulnerability to a toxicant. Lauerman, supra note 80, at A21; see also William D. Pennie et al., The Principles and Practice of Toxicogenomics: Applications and Opportunities, 54 TOXICOLOGICAL SCI. 277, 282 (2000) (emphasizing the need for "sound judgment" and "toxicological skills and experience" in order to distinguish "toxicologically relevant changes in gene expression...from those that are of no concern"). For additional discussions of the strengths and limitations of gene expression profiling, see Fielden & Zacharewski, supra note 27, at 6-10; Schulte & Perera, supra note 63, at 81-104.

\textsuperscript{110} See, e.g., Medlin, supra note 80, at A35-A37; Nuwaysir et al., supra note 80, at 154-56.

\textsuperscript{111} See, e.g., Aardema & MacGregor, supra note 71, at 17; Hamadeh et al., supra note 80, at 231; Hisham Hamadeh et al., Gene Expression Reveals Chemical-Specific Profiles, 67 TOXICOLOGICAL SCI. 219-31 (2002).

\textsuperscript{112} Pennie et al., supra note 109, at 278.
effects on individual genes.\(^\text{113}\) However, microarray technology may reveal much more, exposing holistic effects on the entire genome. The capacity to monitor genes globally is critical to the identification of such patterns.\(^\text{114}\)

Admittedly, inherent biological complexity and the multi-factoral causation of human diseases pose potential limitations on practical application that must not be hidden in the rush to exploit gene signatures. Moreover, the validation process for chemical-specific biomarkers may prove to be particularly challenging and lengthy.\(^\text{115}\) However, once validated as reflective of particular exposures, signature gene expression patterns—at least for some chemicals or chemical classes—could be instrumental in establishing causal associations in tort and regulatory law.

b. Individualized Genetic Testing for Susceptibility, Exposure, and Effects

Another promise of toxicogenetics and toxicogenomics is personalized genetic screening for environmental susceptibility, exposure, and early evidence of injury. Information documenting individual susceptibilities, personal exposure levels, and disease precursors could have significant implications for environmental law and regulation.

Although it may be many years before microarray-based tests are accepted for routine screening for chemical exposure and susceptibility, scientists are laying the groundwork. Genotyping of an individual from a

\(^{113}\) Perera, supra note 18, at 58. For example, polycyclic aromatic hydrocarbons (PAHs), the class of carcinogens found in tobacco smoke, polluted air, and certain grilled foods, have been shown to leave a unique adduct "fingerprint" in human lung and blood cells. Id. The carcinogen aflatoxin B1, occurring naturally in moldy corn and peanuts, leaves fingerprints in the form of DNA adducts. Groopman et al., supra note 56, at 1907S–1908S; Ross, supra note 56, at 943. Lung tumors in smokers commonly reveal a mutation in the p53 tumor-suppressor gene that is characteristic of exposure to certain kinds of hydrocarbons and oxidants. Perera, supra note 18, at 58. Variations in p53 gene mutations have been shown to distinguish radon-induced cancers from cancers caused by cigarette smoking. Colin L. Soskolne, Ethical, Social, and Legal Issues Surrounding Studies of Susceptible Populations and Individuals, 105 ENVTL. HEALTH PERSP. 837, 839 (1997). A single "hot spot" mutation in the p53 gene appears in lung tumors of miners exposed to uranium. Perera, supra note 18, at 58. Other characteristic kinds of p53 gene mutations have been found in tumors induced by exposure to vinyl chloride. Id. at 59.

\(^{114}\) These possible signatures cannot be defined using classical methods where genes are investigated individually for potential association to chemical exposure. Given the universe of compounds available, signatures may only be attained using a higher number of variables (i.e., number of genes), where the collective state (expression) of these genes would define the profile associated with exposure to that compound. Hamadeh et al., supra note 111, at 219; see also Aardema & MacGregor, supra note 71, at 16 (discussing the implications of global monitoring of gene expression).

\(^{115}\) Noting the difficulty and importance of validating chemical-specific biomarkers, one scientist has cautioned: [M]ost validated risk markers may turn out to be composites of a group of biomarkers. . . . We will probably have to use multiple chemical-specific biomarkers to estimate risk. . . . If the light at the end of the tunnel is actually daylight rather than an on-rushing freight train, then we must make a long-term commitment to the rigorous validation of chemical-specific biomarkers so that their promise can be realized, or their limitations clearly defined.

Groopman & Kensler, supra note 66, at 4.
sample of DNA is already possible, and microarrays may permit large-scale, low-cost genotyping of individuals and populations in the future. The technology could permit individuals to discover their own genetic polymorphisms and susceptibilities to particular drugs or chemicals. Gene expression profiling of individuals and groups for chemical exposure also may become possible. This will be most relevant in occupational settings or for site-specific environmental problems (for example, hazardous waste contamination) in which samples from the same individuals can be taken over time. Importantly, relative gene expression levels may help reveal the dose as well as the nature of chemical exposures.

A growing body of legal scholarship focuses on threats to privacy and on the specter of employment and insurance discrimination from genetic testing. It is essential that current and future legal regimes ensure confidentiality by narrowly restricting the use of this information. Yet, little has been written about the potentially transformative effect of personalized assessments of environmental risk on the politics of environmental protection. If predictive value and reliability can be scientifically established, tests for genetic susceptibility combined with tests for exposure—if standardized and properly regulated—could provide individuals and groups.

117. David C. Christiani et al., Applying Genomic Technologies in Environmental Health Research: Challenges and Opportunities, 43 J. OCCUPATIONAL ENVTL. MED. 526, 527 (2001); see also Francis S. Collins, Microarray and Macroconsequences, 21 NATURE GENETICS 2, 2 (1999); Geoffrey S. Ginsburg & Jeanette J. McCarthy, Personalized Medicine: Revolutionizing Drug Discovery and Patient Care, 19 TRENDS IN BIOTECHNOLOGY 491, 495 (2001); Howard L. McLeod & William E. Evans, Pharmacogenomics: Unlocking the Human Genome for Better Drug Therapy, 41 ANN. REV. PHARMACOLOGY TOXICOLOGY 101, 103 (2001). Technologies are being developed to genotype large numbers of individuals for SNPs. Collins et al., supra note 34, at 1580-81. Some have suggested that in the future we will be able to screen a person’s entire genome for variant genes. Aardema & MacGregor, supra note 71, at 22.
118. DeCaprio, supra note 25, at 1841.
119. See Nuwaysir et al., supra note 80, at 157.
120. Id.
121. Although much of the literature on privacy and discrimination presumes genes that may influence disease in the absence of any chemical exposure, these issues are equally relevant to testing for environmental susceptibility. See generally GENETIC SECRETS, supra note 28; see also Robert A. Curley, Jr. & Lisa M. Caperna, The Brave New World is Here: Privacy Issues and the Human Genome Project, 70 DEF. COUNS. J. 22, 28 (2003) (reviewing federal and state laws preventing improper use of genetic information by insurers and employers, and discussing possible future development of privacy rights in DNA); Henry T. Greely, Genotype Discrimination: The Complex Case for Some Legislative Protection, 149 U. PA. L. REV. 1483, 1500 (2001) (arguing in favor of regulation of some kinds of genetic discrimination, partially “to allay public fears that could impede important genetic research”).
122. Extensive research is required before the predictive value and reliability of genetic tests can be scientifically established. See Michael Baram, Genetic Testing for Susceptibility to Disease from Exposure to Toxic Chemicals: Implications for Public and Worker Health Policies, 41 JURIMETRICS J. 165, 166 (2001); see also Richard R. Sharp, The Evolution of Predictive Genetic Testing: Deciphering Gene-Environment Interactions, 41 JURIMETRICS J. 145, 146-52 (2001) (discussing the wide ranges in predictive value of genetic tests, and danger of misinterpretation and misapplication of data).
with powerful environmental risk information unavailable in the past. Although these developments will be tempered by process and access barriers, the growing availability of biologically derived information relating to risk and exposure could help spawn the formation of new at-risk constituencies who will transform the politics of environmental protection—toward a politics in which groups and individuals exposed to toxic substances may have far more influence than in the past.

II
REDEFINING THE "PUBLIC" IN PUBLIC HEALTH: IMPLICATIONS OF GENETICS

Part I detailed important developments in molecular biology and genetics that will raise new challenges for environmental law and regulation. Parts II and III discuss regulatory implications of identifying a range of genetic susceptibilities to environmental agents and a continuum of subcellular biomarkers in the progression from chemical exposure to disease. This Part focuses on how advances in toxicogenetics may require regulators, reviewing courts, or Congress to clarify the "public" to be protected by our environmental laws. Part III illustrates how the definition of "health," and the regulatory delineation of threats to health, may need to change as new genomic information blurs traditional distinctions between health and disease, and between risk and injury.

The extent to which nationwide environmental standards should recognize and account for particularly sensitive subgroups—such as children, the elderly, and asthmatics—is already an important and challenging aspect of environmental regulatory policy. I use the example of EPA’s experience in setting national ambient air quality standards (NAAQS) under the Clean Air Act to illustrate the questions posed, and tensions inherent, in accounting for sensitive groups. Although the NAAQS legislative history and case law indicate that “particularly sensitive citizens” must be protected by air quality standards designed to protect the “public health,” the extent of such protection is far from clear. Regulatory and judicial precedent provides insufficient guidance for determining the types or sizes of subgroups to be protected or the degree of such protection.

As toxicogenetic research continues to identify genetic polymorphisms at an unprecedented rate, these problems will intensify and new issues will arise. I suggest that the often polygenic nature of environmental susceptibility may reveal a continuum of genetic susceptibilities to the adverse effects of particular chemicals. Such a continuum will create enormous difficulties in defining what constitutes a susceptible group.

124. See infra notes 138-50 and accompanying text.
entitled to governmental protection. Moreover, groups defined on the basis of genetic susceptibility may correspond with groups currently recognized or may transcend traditional group identity. The discovery of genetically sensitive subgroups will not only intensify EPA’s current struggle to define the relevant “public” to be protected, but will also raise new questions for environmental law and regulation.

A. The Concept of “Risk”

Defining the public to be protected and the health effects to be protected against are essential elements of the risk assessment process. The concept of risk involves the probabilistic anticipation of harm; however, the precise meaning may vary with the statutory context and the methodology used to assess the risk. “Risk” sometimes refers to the probability that a harm will occur. Alternatively, it may refer to the probability and the severity of the harm considered together as reflected in the D.C. Circuit’s often-cited language in *Ethyl Corp. v. EPA*:

Danger, the Administrator recognized, is not set by a fixed probability of harm, but rather is composed of reciprocal elements of risk and harm, or probability and severity. That is to say, the public health may properly be found endangered both by a lesser risk of greater harm and by a greater risk of lesser harm.126

Biomarkers of susceptibility, discussed here, and biomarkers of effect, discussed in Part III, inevitably will change estimates of probabilities. Whichever way risk is defined, new genetic information will affect future estimates of the type and size of sensitive populations, as well as the probability, severity, and nature of potential harms.

B. Risk and Health-Based Environmental Standards

The difficulty of defining the public to be protected will surface most prominently in the context of health-based and other risk-based environmental regulatory standards.128 In contrast to technology-based

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126. 541 F.2d 1, 18 (D.C. Cir. 1976) (en banc) (citations omitted).
127. Health-based standards require regulators to establish permissibly “safe” levels of pollutants in the ambient environment. The ambient environment might be the surrounding air, a water body, chemical waste cleanup site, or other route of exposure. The NAAQS are the clearest example of the health-based approach, as Congress has prevented countervailing considerations, such as cost or technical feasibility, to enter into the standard-setting process. See infra text accompanying notes 152-64. Section 112 of the Clean Air Act, 42 U.S.C. § 7412(d) (2000), which governs air pollutants listed as hazardous, calls for health-based standards if technology-based controls leave impermissible risks as specified by statute. See infra notes 134, 402.
128. The terms “health-based” and “risk-based” often are used interchangeably. Pure health-based standards do not permit considerations of cost or technical feasibility to enter into the standard-setting
standards, health-based standards require regulators to determine acceptably "safe" levels for individual pollutants in the ambient environment. Information on genetic susceptibility will add new dimensions to the monumental scientific and policy challenges inherent in setting standards based, in whole or in part, on estimates of public health risk. The issues raised in this context also are relevant for standards that balance the benefits of risk reduction with cost or feasibility considerations—as estimates of public health risk will affect the ultimate balance. These issues also are pertinent to hybrid standards involving the tiered application of technology-based and health-based controls. Moreover, all pollution

process. See infra text accompanying notes 153-56. Other kinds of risk-based standards may incorporate these other considerations at various stages and to varying degrees.

129. Technology-based standards focus on emissions levels that the regulated community can achieve practically using available technology.

130. Because people can never be absolutely safe, the concept of safety is not a purely scientific decision. See, e.g., Adam Babich, Too Much Science in Environmental Law, 28 COLUM. J. ENVTL. L. 119, 122 (2003) (noting that defining appropriate levels of safety may be more of a philosophical or political decision rather than a technical one); see also Wagner, supra note 12, at 127 (arguing that "scientific" decisions about appropriate levels of exposure to pollutants generally mask value choices).

131. Pollution control regulation has been characterized as a patchwork of risk-based and technology-based standards, and many regulatory standards combine the two approaches. Congress has vacillated between the two approaches over time, and the relative merits of each approach continue to stimulate debate. See infra notes 356-75 and accompanying text.

132. For discussions of scientific limitations inherent in setting risk-based environmental standards, see, e.g., NATIONAL RESEARCH COUNCIL, RISK ASSESSMENT IN THE FEDERAL GOVERNMENT: MANAGING THE PROCESS 29-33 (1983) (discussing the numerous uncertainties inherent in the risk assessment process). Some of the many uncertainties in risk assessment arise from: extrapolating experimental animal data to humans in dose-response studies, extrapolating data using high-dose experimental protocols to the lower doses more characteristic of human exposure, estimating exposure levels for human populations, understanding a toxicant's mechanism of action, and determining the shape of the dose-response curve. Id. Where no data are available, risk assessors often must rely on default assumptions that may or may not comport with reality. See, e.g., Mark Eliot Shere, The Myth of Meaningful Risk Assessment, 19 HARV. ENVTL. L. REV. 409 (1995).


134. See discussion infra Part IV. As noted, section 112 of the Clean Air Act, for example, employs a tiered regime of technology-based and health-based standards. Section 112 governs air pollutants that are considered to be hazardous but that are generally less pervasive than are pollutants regulated under the NAAQS. The statute first requires EPA to set technology-based pollution emission limits based on "maximum achievable control technology," 42 U.S.C. § 7412 (2000); see also Arnold Reitze Jr., Control of Hazardous Air Pollution, in AIR POLLUTION CONTROL LAW: COMPLIANCE AND ENFORCEMENT 123 (2001). It then specifies a process for developing health-based standards that "provide an ample margin of safety to protect public health" if the technology-based controls fail to do
control and food safety statutes include risk-based triggers that establish the evidentiary burden an agency must meet in order to regulate a toxic substance or other hazard. New genetic information could modify these initial risk estimates and dramatically increase the number of chemicals and pollutants subject to regulation.

C. The Clean Air Act's National Ambient Air Quality Standards

Future challenges posed by toxicogenetic data are best illustrated in the context of the health-based approach as exemplified by section 109 of the Clean Air Act, which directs EPA to promulgate and periodically revise national ambient air quality standards (NAAQS) for the most pervasive air pollutants. The NAAQS are the heart of the Clean Air Act as they establish pollution ceilings to be applied throughout the country and are the centerpiece of an intricate federal-state regulatory scheme affecting multiple sectors of the economy.

Section 109 requires the NAAQS to be set at levels “which in the judgment of the Administrator, based on [air quality] criteria and allowing an adequate margin of safety, are requisite to protect the public health.” The air quality criteria must “accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such pollutants in the ambient air.” The margin of safety is to protect against “hazards which research has not yet identified.” The Clean Air Act requires EPA to review the scientific criteria underlying the


135. See discussion infra Part IV.


137. Regulations specify daily and annual allowable concentrations of a given pollutant and apply to airsheds or “Air Quality Control Regions” nationwide. To implement these federal standards, states allocate emission limits among individual factories and other pollution sources in each Air Quality Control Region. The total area-wide emissions from these disparate sources must not exceed the concentration established in the national health-based standard. See, e.g., Percival, supra note 125, at 501-21.


139. Clean Air Act § 108(a)(2), 42 U.S.C. § 7408(a)(2) (2000). The air quality criteria are the scientific documents underlying the ambient air quality standards. Id. The NAAQS are set individually for the most pervasive air pollutants. These pollutants are often referred to as “criteria pollutants,” due to the statutory requirement for a comprehensive review of relevant scientific information in the criteria document.

standards every five years and to revise the criteria and standards “where appropriate.” The statute does not define “public health” or “adequate margin of safety”; nor does it direct when a revision of the NAAQS may be appropriate. The sole statutory reference to sensitive groups in the Clean Air Act is a general information-gathering requirement.

1. Legislative Intent to Protect Sensitive Groups

While the legislative history, rulemaking records, and case law shed some light on the definition of “public” in standards designed to protect the public health, they raise as many questions as they answer. EPA has struggled with how to protect sensitive subgroups under section 109’s general mandate to protect “public health” and the more specific language in the legislative history of the 1970 amendments, including the following comment by the Senate Committee on Public Works:

[T]he Committee emphasizes that included among those persons whose health should be protected by the ambient standards are particularly sensitive citizens such as bronchial asthmatics and emphysematics who in the normal course of daily activity are exposed to the ambient environment. In establishing an ambient standard necessary to protect the health of these persons, reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such group.

Ambient air quality is sufficient to protect public health of such persons whenever there is an absence of adverse effect on the health of a statistically related sample of persons in sensitive groups from exposure to the ambient air. An ambient air quality standard, therefore, should be the maximum permissible ambient air level of an air pollution agent... which will protect the health of any group of the population . . . .

For purposes of this description, a statistically related sample is the number of persons necessary to test in order to detect a deviation in the health of any person within such sensitive group which is attributable to the condition of the ambient air.

The identification of genetically susceptible subgroups will raise many interpretational questions. Of particular consequence in the genetic age is the extent to which the NAAQS are required to protect the most vulnerable individuals within a given subgroup. The 1970 Senate Report left open the question of what constitutes a “representative” or “statistically related sample” of sensitive individuals, and how many persons would

142. The 1977 amendments require EPA to publish and disseminate information to various agencies on “measures which may be employed to reduce the impact on public health or protect the health of sensitive or susceptible individuals and groups.” Clean Air Act § 108(f)(1)(C), 42 U.S.C. § 7408(0)(1)(C).
need to be tested to detect a "deviation in the health of any person within [the] sensitive group."144 The House Report on the 1977 amendments also left open the question of group size, noting that the Clean Air Act must "assure that the health of susceptible individuals, as well as healthy adults, will be encompassed in the term, "public health," regardless of the section of the act under which the Administrator proceeds."145

In litigation under the Clean Air Act, plaintiffs arguing for protection of the most vulnerable individuals have pointed to legislative and judicial references to "sensitive citizens" and "susceptible individuals" to show that "population size was rejected as a relevant factor by the drafters of both the 1970 and 1977 amendments."146 Conversely, EPA, distinguishing public from individual health, has focused on the reference to a "statistically related sample of persons in sensitive groups," arguing that "[t]he legislative history . . . confirms that in setting NAAQS to protect the health of sensitive groups, 'reference should be made to a representative sample of persons comprising the sensitive group, rather than a single person in such group."147

*Lead Industries Ass'n v. EPA,*148 a 1980 decision upholding EPA's standard for airborne lead, provided the first judicial interpretation of the agency's obligation to protect particularly sensitive groups. The Court of Appeals for the D.C. Circuit confirmed that the Clean Air Act's public health mandate encompasses sensitive groups, but failed to clarify whether the obligation to protect public health extends to the most sensitive individuals identified. Notably, the panel interpreted the legislative history to indicate that the NAAQS must protect "individuals who are particularly sensitive to the effects of pollution" and must be set at a level at which there is an "'absence of adverse effect' on these sensitive individuals."149 At the same time, the court agreed with EPA that an airborne lead standard that protected 99.5% of the target population (young children) was sufficient to protect high-risk subgroups and to provide an adequate margin of safety.150 Despite the court's emphasis on the precautionary nature of the Act and the need to protect "sensitive individuals," studies indicated that the standard for airborne lead upheld in *Lead Industries* would leave an estimated 25,000 inner-city children at risk.151 In practice, the debate about

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144. *Id.*
148. 647 F.2d 1130 (D.C. Cir. 1980).
149. *Id.* at 1153.
150. *Id.* at 1161-62.
151. The 1978 standard for airborne lead upheld in *Lead Industries* protected an estimated 99.5% of the sensitive population. *Id.* at 1161-62. Based on the 1970 census, the Administrator determined
individual and public health has been a debate about large and small groups.

2. Removal of Cost Constraints

The NAAQS are of particular interest in the context of susceptible groups because countervailing considerations, such as industry compliance costs and technical feasibility, have been removed from the regulatory calculus. As the D.C. Circuit emphasized in Lead Industries, "Congress made it abundantly clear that consideration of economic or technological feasibility are to be subordinated to the goal of protecting the public health." The Supreme Court affirmed that interpretation in 2001 when the question of compliance costs arose in conjunction with the landmark nondelegation challenge to EPA's construction of the NAAQS in Whitman v. American Trucking Ass'ns. Writing for a unanimous Court, Justice Scalia reiterated that "[t]he text of §109(b), interpreted in its statutory and historical context and with appreciation for its importance to the [Clean Air Act] as a whole, unambiguously bars cost considerations from the NAAQS-setting process, and thus ends the matter for us as well as the EPA." Under the NAAQS framework, cost and feasibility considerations may come into play later, during the implementation phase, when individual states allocate emissions among various polluting sources.

there were twenty million children under five years of age in the United States, twelve million in urban areas, and five million in inner cities where lead exposure may be especially high. Id. at 1144. Protecting 99.5% of the target population therefore would allow 25,000 inner-city children to remain at risk. Environmental groups did not challenge the standard for airborne lead. In its response to industry challenges, the Lead Industries court did not need to reach the issue of whether leaving a subpopulation unprotected was permissible under the statute.

152. Id. at 1153; see also Natural Res. Def. Council, Inc. v. EPA, 902 F.2d 962, 973 (D.C. Cir. 1990) (same, in reviewing particulate matter NAAQS); Am. Petroleum Inst. v. EPA, 665 F.2d 1176, 1185 (D.C. Cir. 1981) (same, in reviewing ozone NAAQS).
154. 531 U.S. at 471.

Perhaps the most important forum for consideration of claims of economic and technological infeasibility is before the state agency formulating the implementation plan. So long as the national standards are met, the State may select whatever mix of control devices it desires, and industries with particular economic or technological problems may seek special treatment in the plan itself. Moreover, if the industry is not exempted from, or accommodated by, the original plan, it may obtain a variance, as petitioner did in this case; and the variance, if granted after notice and a hearing, may be submitted to the EPA as a revision of the plan. Lastly, an industry denied an exemption from the implementation plan, or denied a subsequent variance, may be able to take its claims of economic or technological infeasibility to the state courts.

Id. at 266-67 (citations omitted). Total emissions of designated pollutants in each region, however, must fall within the federally established, health-based limits.
3. Racing Toward Zero

Where the legislature has indicated and the courts have confirmed that cost and feasibility are to be excluded from the standard-setting process, EPA faces a regulatory dilemma. The removal of economic and technical constraints from the regulatory calculus makes it difficult for the agency to find a credible rationale for failing to protect any identifiable group that may be vulnerable to harm from a regulated pollutant. As the marginal costs of protection presumably increase with each increment of control, the agency is forced either to confront the possibility of economic and social dislocation or to disobey the legislative intent.

The rapid discovery of susceptibility biomarkers through toxicogenetics will highlight these tensions and bring new dimensions to the problem. In the absence of new kinds of pragmatic solutions, the agency may face a quandary: continually revise the national standards to protect an expanding array of sensitive subgroups or leave vulnerable subgroups unprotected—an option that may not withstand judicial review.

Yet if EPA attempts to protect everyone, it may confront another premise underlying the current regulatory paradigm—that it is impractical and politically difficult to regulate to “zero-risk” levels, or, more appropriately, toward background levels of risk. The zero-risk regulatory dilemma traditionally surfaces in the context of “nonthreshold” pollutants, which are assumed to pose a human health risk at any exposure level above zero. Most carcinogens and radioactive substances are believed to be nonthreshold, and EPA has classified certain noncarcinogens, such as

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156. See, e.g., David D. Doniger, Federal Regulation of Vinyl Chloride: A Short Course in the Law and Policy of Toxic Substances Control, 7 ECOLOGY L.Q. 500, 515 (1978) (“As a general rule, as the degree of exposure control increases, the marginal costs of each additional increment of control increase.” Further, “as the degree of control increases, the cost of control grows more uncertain; the range of effects becomes more difficult even to identify, let alone quantify.”).


158. “Background levels of risk” is a more appropriate phrase than “zero-risk,” as it recognizes that many pollutants also originate, albeit usually at low levels, from natural and other sources not subject to regulatory control.

159. See infra text accompanying notes 223-31.

160. The traditional assumption regarding cancer risks is that there is no threshold below which exposure is considered safe. It has been assumed that exposure to even a single molecule of a carcinogen is associated with an increased risk of tumor induction. If a threshold exists for carcinogens,
ozone, as nonthreshold. Lead also exhibits properties similar to nonthreshold pollutants, due to the combined effects of airborne and non-airborne sources of lead. While Lead Industries underscored the irrelevance of cost considerations to health-based standard setting, it also quoted the legislative history of section 109 to discourage zero-risk decision making: "Obviously, this no-risk philosophy ignores all economic and social consequences and is impractical." As research now shows that the most highly susceptible individuals may respond to exposures that are at or approaching natural background levels, this dilemma may come into play for a growing number of chemicals.

4. Consequences of Failing to Protect an Identifiable Subgroup: American Lung Association v. EPA

The legal consequence of leaving certain subgroups unprotected—at least without a clear rationale—was illustrated more recently in American Lung Ass'n v. EPA, a 1998 case concerning protection of asthmatics under the primary NAAQS for sulfur dioxide (SO₂). The plaintiffs challenged EPA’s refusal to revise the existing SO₂ standard on the ground that it failed to protect a subset of the asthmatic population from short-term, high-level “bursts” of SO₂ periodically emitted by petroleum refineries, power plants, and other industrial facilities. Studies indicated that around it is so low that it cannot be identified. NATIONAL RESEARCH COUNCIL, supra note 4, at 65. However, this assumption has been challenged for certain carcinogens. See, e.g., Chlorine Chem. Council v. EPA, 206 F.3d 1286, 1290 (D.C. Cir. 2000) (overturning EPA’s reliance on a linear, nonthreshold dose-response curve in setting a zero maximum-contaminant-level goal for chloroform, a suspected carcinogen). See infra text accompanying notes 238-43.

161. See American Trucking Ass'ns v. EPA, 175 F.3d 1027, 1033 (“EPA regards ozone definitely, and [particulate matter] likely, as non-threshold pollutants, i.e., ones that have some possibility of some adverse health impact (however slight) at any exposure level above zero.”)

162. See American Trucking Ass'ns v. EPA, 175 F.3d 1027, 1033 (“EPA regards ozone definitely, and [particulate matter] likely, as non-threshold pollutants, i.e., ones that have some possibility of some adverse health impact (however slight) at any exposure level above zero.”)

163. Lead Indus. Ass’n v. EPA, 647 F.2d 1130, 1152 (D.C. Cir. 1980). “This is particularly true in light of the legal requirement for mandatory attainment of the national primary standards within 3 years.” Id. at 1151 n.41 (quoting H.R. REP. No. 95-294 (1977)). See also Natural Res. Def. Council, Inc. v. EPA, 824 F.2d 1146, 1154 (D.C. Cir. 1987) (acknowledging that attempting to deliver absolute safety could result in “massive economic and social dislocations by shutting down entire industries”). The rulemaking record accompanying the first ambient air quality standard for ozone similarly reflects this tension:

The Clean Air Act, as the Administrator interprets it, does not permit him to take factors such as cost or attainability into account in setting the standard . . . . He recognizes that controlling ozone to very low levels is a task that will have significant impact on economic and social activities. This recognition causes him to reject as an option the setting of a zero-level standard as an expedient way of protecting public health without having to decide among uncertainties.

Revisions to the National Ambient Air Quality Standards for Photochemical Oxidants, 44 Fed. Reg. 8,213 (Feb. 8, 1979).


165. 134 F.3d 388 (D.C. Cir. 1998).

25% of mild to moderate asthmatics, or 41,500 people, experienced substantial physical effects when exposed to these bursts during exercise. In deciding not to revise the existing standard, the EPA Administrator had concluded that the “likelihood that asthmatic individuals will be exposed... is very low when viewed from a national perspective” and that short-term peak concentrations of SO$_2$ did not constitute the type of “ubiquitous public health problem for which establishing a NAAQS would be appropriate.”

Remanding for further clarification, the D.C. Circuit questioned EPA’s failure to protect a subset of the asthmatic population:

In its effort to reduce air pollution, Congress defined public health broadly. NAAQS must protect not only average healthy individuals, but also ‘sensitive citizens’—children, for example, or people with asthma, emphysema, or other conditions rendering them particularly vulnerable to air pollution... If a pollutant

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167. At the time of the decision, estimates indicated that nine to ten million asthmatics resided in the United States,approximately 4% of the nation’s population. Brief for Respondents at 4, Am. Lung Ass’n v. EPA, 134 F.3d 388 (D.C. Cir. 1998) (Nos. 96-1251 & 96-1255). Studies in the rulemaking record estimated that from 180,000 to 395,000 “exposure events”—defined as a heavily breathing asthmatic exposed to an SO$_2$ burst—would occur annually, affecting 68,000 to 166,000 asthmatic individuals. National Ambient Air Quality Standards for Sulfur Oxides (Sulfur Dioxide)—Final Decision, 61 Fed. Reg. at 25,574. Of those, around 25% of 166,000, or 41,500 individuals, would experience “atypical effects.” Id. Such effects might cause disruption of ongoing activities, require use of medication or other medical attention. Id. at 25,566, 25,572. The Administrator “discerned in the medical debate a consensus, which she adopted, that ‘repeated occurrences of such effects should be regarded as significant from a public health standpoint.’” American Lung, 134 F.3d at 390 (quoting National Ambient Air Quality Standards for Sulfur Oxides (Sulfur Dioxide)—Final Decision, 61 Fed Reg. at 25,573).

168. National Ambient Air Quality Standards for Sulfur Oxides (Sulfur Dioxide)—Final Decision, 61 Fed. Reg. at 25,575. Although repeated exposures of exercising asthmatics to peak SO$_2$ levels above 0.6 ppm could pose a risk of significant health effects in some localized situations, the Administrator concluded that these localized health risks are most appropriately addressed at the state level. Id. at 25,576.

169. EPA initially agreed to respond to the remand by the end of 2000, see National Ambient Air Quality Standards for Sulfur Oxides (Sulfur Dioxide); Intervention Level Program, 63 Fed. Reg. 24,782 (May 5, 1998), but delayed response pending the Supreme Court’s decision in Whitman v. American Trucking Ass’ns, 531 U.S. 457 (2001), which involved revisions of the NAAQS for ozone and particulate matter. In 2001, the agency solicited comments on a proposal to undertake state-level actions in lieu of revising the NAAQS for SO$_2$. The proposed actions included development of an “intervention level program” (ILP) that would authorize states to take action when localized SO$_2$ concentrations reached a “concern level” above 0.6 parts per million, even if the national standard, measured on an area-wide basis, was met. The proposal also included data gathering on five-minute peak concentrations of SO$_2$, and evaluation of current placement of air monitors for SO$_2$. Under the proposal, states and tribes would be permitted to relocate existing SO$_2$ monitors to areas where five-minute peak concentrations might be of concern. National Ambient Air Quality Standards for Sulfur Dioxide, 66 Fed. Reg. 1665, 1666 (Jan. 9, 2001). EPA has not formally responded to the remand in American Lung.
adversely affects the health of these sensitive individuals, EPA must strengthen the entire national standard.\textsuperscript{170}

The court determined that EPA had not adequately explained its conclusion that the physical effects experienced by certain asthmatics from exposure to short-term, high-level SO$_2$ bursts did not amount to a public health problem: "Without answers to these questions, the Administrator cannot fulfill her responsibility under the Clean Air Act to establish NAAQS 'requisite to protect the public health.'"\textsuperscript{171} The panel’s remand instructions required EPA to articulate a standard for selecting one sensitive group over another:

The Administrator may well be within her authority to decide that 41,500 or some smaller number of exposed asthmatics do not amount to a public health problem warranting national protective regulation, or that three or six or twelve annual exposures present no cause for medical concern. But unless she describes the standard under which she has arrived at this conclusion, supported by a plausible explanation, we have no basis for determining whether her decision is arbitrary, capricious, or an abuse of discretion.\textsuperscript{172}

\textit{American Lung} highlighted the challenge of finding a defensible rationale for leaving any identifiable sensitive population unprotected. Although the case involved plaintiffs with manifest disease—asthma—rather than asymptomatic but genetically sensitive groups, the uncertain status of the 41,500 asthmatics in \textit{American Lung} may be shared in the future by genetically sensitive subgroups whose at-risk status is identified through the application of DNA technology to environmental health risk assessment.

\textbf{D. Defining the Relevant Public: Current Practice}

\textit{American Lung} revealed other tensions as well. Although there is a consensus among the three governmental branches that the national

\textsuperscript{170} Am. Lung Ass’n v. EPA, 134 F.3d 388, 389 (D.C. Cir. 1998) (citing S. Rep. No. 91-1196, at 10 (1970); Lead Indus. Ass’n, Inc. v. EPA, 647 F.2d 1130, 1152 (D.C. Cir. 1980)); see also id. (citing Lead Industries, 647 F.2d at 1153 (quoting S. Rep. No. 91-1196, at 10: NAAQS “must be set at a level at which there is ‘an absence of adverse effect’ on . . . sensitive individuals’)). Notably, the court did not embrace EPA’s explanation that SO$_2$ bursts were localized and site-specific and therefore should be handled at the state level: "'[L]ocalized,’ ‘site-specific’ or even ‘infrequent’ events might nevertheless create a public health problem, particularly since, in some sense, all pollution is local and site-specific, whether spewing from the tailpipes of millions of cars or a few offending smoke stacks." Id. at 392.

\textsuperscript{171} Id. The D.C. Circuit panel posed the following questions: Why is the fact that thousands of asthmatics can be expected to suffer atypical physical effects from repeated five-minute bursts of high-level sulfur dioxide not a public health problem? Why are from 180,000 to 395,000 annual “exposure events” (the range indicated by 1994 studies) or some fewer number (as suggested by the industry studies) so “infrequent” as to warrant no regulatory action? Why are disruptions of ongoing activities, use of medication, and hospitalization not “adverse health effects” for asthmatics? Answers to these questions appear nowhere in the administrative record.

\textsuperscript{172} Id. at 392-93.
ambient standards must be stringent enough to protect sensitive populations, there is no consensus as to what kinds of groups merit protection, the appropriate size of a relevant subgroup, or the proper method or degree of protection. To date, the selection of subgroups for consideration in environmental standards has been largely ad hoc.173 As the National Research Council noted in a comprehensive report on risk assessment:

Generally, the selection of the population segments is a matter of either a priori interest in the subgroup, in which case the risk assessor and risk manager can jointly agree on which subgroups to highlight, or a matter of discovery of a sensitive or highly exposed group during the assessment process.174

Apart from serendipity or political visibility, one rationale for EPA's attention to particular subgroups has been their "identifiability." As one commentator has suggested, "Congress, in talking of sensitive populations, meant identifiable groups within the population."175 Likewise, the National Research Council's report noted that when "persons of high risk or susceptibility are identifiable, society has tended to feel a responsibility to protect them."176 In addition, the consideration of particular subgroups is partly a function of the availability of scientific information on group-specific risks of pollutant-induced health effects.

1. The Focus on Readily Identifiable Groups

In general, when sensitive subpopulations have been acknowledged in environmental standard setting, they have been limited to large, readily identifiable groups defined on the basis of gender, life stage, or manifest disease (for example, children, the elderly, pregnant women, asthmatics, and people with cardiopulmonary disease). Standard setting for individual pollutants under the NAAQS illustrates this point. The rulemaking records generally reflect an effort to identify the "most sensitive" population with reference to the particular health effects considered.177 For example, children under age five served as EPA's sensitive reference population, or "target population," in setting the standard for airborne lead in 1978.178 Although the agency had studied effects of lead on other sensitive groups,179 it selected small children as the "most sensitive population that

173. FRIEDMAN, supra note 123, at 7.
174. NATIONAL RESEARCH COUNCIL, supra note 4, at 373.
175. FRIEDMAN, supra note 123, at 173.
176. NATIONAL RESEARCH COUNCIL, supra note 4, at 213.
177. See FRIEDMAN, supra note 123, at 4-5.
179. These groups included young children, pregnant women, fetuses, workers with occupational exposures to lead, and individuals suffering from dietary deficiencies or exhibiting genetic inability to produce certain blood enzymes. Lead: Proposed National Ambient Air Quality Standard, 42 Fed. Reg. 63,076, 63,077 (Dec. 14, 1977) (codified at 40 C.F.R. § 50.12 (2004)).
could be characterized." Asthmatics served as the target population for public health protection in setting the national ambient air quality standard for SO\textsubscript{2}. The 1994 rulemaking record for the NAAQS for carbon monoxide identified individuals with angina as the group "at greatest risk from low-level, ambient air exposures to [the pollutant]." The record acknowledged other potentially at-risk groups, but noted a lack of experimental evidence demonstrating an increased risk of carbon monoxide-induced health effects for those groups. Sensitive populations recognized in setting the NAAQS for nitrogen oxides in 1995 included children age five to twelve and persons with preexisting respiratory disease. The 1997 revision of the NAAQS for particulate matter acknowledged special sensitivities of children, the elderly, and individuals with respiratory and cardiopulmonary disease. The 1997 revision of the ozone standard recognized similar susceptible groups.

When other regulatory programs have considered sensitive groups—whether or not congressionally specified—these groups have roughly mirrored those considered under the Clean Air Act. For example, guidelines for the cleanup of hazardous wastes under CERCLA have recognized special sensitivities of pregnant women and children. The Food Quality Protection Act of 1996, which regulates pesticide residues in food, focuses on the special susceptibilities of children.

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80. National Primary and Secondary Ambient Air Quality Standards for Lead, 43 Fed. Reg. at 46,252. EPA indicated that there may be groups at higher risk, but the agency was unable to obtain sufficient information for estimating a threshold for adverse effects separate from that of young children. Id. Hence, the availability of scientific data was a factor in determining which subgroup should be considered.


83. Other potentially at-risk groups included persons with cerebrovascular disease, individuals with anemia or chronic obstructive lung disease, fetuses and young infants. Id. at 38,909.

84. Id.


88. Although the Superfund cleanup standards correlate to existing environmental standards, EPA's 1990 guidelines noted that "all preliminary remediation goals will be set so that they are protective for sensitive subpopulations, such as pregnant women and children." National Oil and Hazardous Substances Pollution Contingency Plan, 55 Fed. Reg. 8,666, 8,713 (March 8, 1990) (codified at 40 C.F.R. § 300.1 et seq. (2004)).

As the above examples illustrate, children are a favored group in environmental standard setting because they are readily identifiable, inherently susceptible to, and often—as in the case of pesticides and lead—differently exposed to environmental contaminants. Moreover, protecting children from environmental harm combines science and politics in a manner that is difficult to oppose. The focus on children has intensified as a result of the Clinton administration's Children's Health Initiative, which called for consideration of children's special susceptibilities when establishing environmental standards.\textsuperscript{190}

2. Growing Congressional Interest: Statutory Inclusion of Sensitive Groups

Two recently enacted environmental laws are noteworthy in that the statutes themselves contain detailed references to protection of sensitive populations. The Food Quality Protection Act of 1996 includes an explicit mandate to account for children's "special susceptibilities" in issuing pesticide "tolerances," or acceptable levels of pesticide residues on food.\textsuperscript{191} The Act requires a "reasonable certainty that no harm will result to infants and children" from aggregate exposure to the pesticide chemical residue, and directs EPA to "publish a specific determination regarding the safety of the pesticide chemical residue for infants and children."\textsuperscript{192} Most importantly, the statute requires EPA to apply an "additional tenfold margin of safety" for certain pesticide residues to account for toxicity to infants and children.\textsuperscript{193} EPA must also consider the sensitivities of "major identifiable subgroups" of the population in setting pesticide tolerances.\textsuperscript{194}

The Safe Drinking Water Act Amendments of 1996, which authorize federal standards for municipal drinking water supplies, direct EPA to conduct "a continuing program of studies" to identify groups at "greater risk than the general population of adverse health effects" from exposure to...
drinking water contaminants. The studies must evaluate "whether and to what degree infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that can be identified and characterized are likely to experience elevated health risks, including risks of cancer, from contaminants in drinking water."196

These two statutes may reflect a trend toward more serious congressional attention to vulnerable groups in environmental standard setting. The Food Quality Protection Act departs from reliance on a broad public health mandate—as in section 109 of the Clean Air Act—to an explicit statutory requirement to account for high-risk groups. Acknowledging a growing societal concern for sensitive populations, the American Thoracic Society noted that "since the early 1980s, societal perspectives had shifted . . . and a formal concern for the impact of air pollution on specific groups had been expressed through the environmental justice movement."197 Noting that the "heterogeneity of populations needs full acknowledgment," the society called for "additional research on subpopulations with increased baseline risks, including those based on genetics."198 Although there may be a considerable gap between rhetoric and effective protection,199 the statutory language in the Food Quality Protection Act and the Safe Drinking Water Act may represent a turning point, at least for some readily identifiable groups.

E. The Challenge of Defining Sensitive Groups Based on Genetics

1. Scientific Questions

If biomarkers of genetic susceptibility can be validated successfully as predictors of environmental health risk,200 groups possessing certain polymorphic genes will become identifiable as sensitive populations to be

196. Id. (emphasis added).
197. American Thoracic Society, supra note 22, at 666-67. The environmental justice movement generally has focused on disparities in risk based on differential exposure, but has begun to address differential susceptibility and its implications for regulatory standard setting.
198. Id.
199. Indeed, there may be a disconnect between avowed recognition and actual incorporation into the risk assessment process. Even where sensitive populations are acknowledged, they are not necessarily studied empirically in risk assessments. See, e.g., Edward J. Calabrese, Biochemical Individuality: The Next Generation, 24 REG. TOXICOLOGY & PHARMACOLOGY, at S58, S59-60 (1996). In general, estimates of safe levels of pollutants are derived for the average seventy-kilogram white male, and then safety factors are applied to account for more sensitive individuals. One commentator remarked that "risk assessors and risk managers . . . [have been] numbed . . . by risk assessment strategies aimed at finding the mean risks or central tendency responses posed by substances." Carl F. Cranor, Eggshell Skulls and Loss of Hair From Fright: Some Moral and Legal Principles that Protect Susceptible Populations, 4 ENVTL. TOXICOLOGY & PHARMACOLOGY 239, 239 (1997).
200. As noted, the scientific challenge of proving that a hypothetical "susceptibility polymorphism" does indeed increase risk for a particular disease is significant.
considered in environmental risk assessments. These groups would cut across the traditional categories used in standard setting, such as age, gender, and manifest disease. However, defining groups based on genetic sensitivity will prove to be far more complicated than traditional means of ascertaining the "most sensitive" groups for regulatory purposes. EPA’s first report to Congress pursuant to the amended Safe Drinking Water Act acknowledged this difficulty. Not surprisingly, the report focused on sensitive populations identifiable by gender, life stage (fetuses, infants, children, the elderly), manifest disease (groups with diabetes, liver impairments, cardiovascular disease, and AIDS), and high exposure levels. Emphasizing that genetic traits are "complex" and "poorly understood," the report noted that it was unclear whether subpopulations with heightened sensitivities based on genetic factors could meet the statutory criterion of "subpopulations that can be identified and characterized."

Several challenges will arise in identifying and characterizing genetically sensitive subpopulations. The most obvious is that these groups are asymptomatic and thus do not exhibit classical phenotypic traits generally used to identify subpopulations today. Second, because genetic predisposition is not absolute but probabilistic in nature, a major policy decision is whether and when the additional quantum of risk conferred by polymorphic genes is sufficient to merit regulatory attention. While some people may have polymorphisms that confer only moderate risk of disease, others may have genetic variants that make them substantially more sensitive than others to a pollutant. This may mean that certain relative risk thresholds should be established before these genetic traits are incorporated into environmental or occupational standards.

In some cases, a single susceptibility factor may increase disease risk after exposure to certain chemicals, while at the same time protecting against the effects of exposure to other chemicals. For example, impaired

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202. "Phenotype" is defined as "the observable properties of an individual as they have developed under the combined influences of the genetic constitution of the individual and the effects of environmental factors." Purves et al., Life: The Science of Biology (5th ed. 1997) (glossary). Phenotype is contrasted with "genotype," defined as "an exact description of the genetic constitution of an individual, either with respect to a single trait or with respect to a larger set of traits." Id.

203. For example, an expert in medical genetics has recommended relative risk thresholds before genetic screening is to be applied in occupational settings:

The relative risk for a significant adverse outcome must be at least three (the risk for those with the trait compared with those lacking the trait), based on experience with relative risks for histocompatibility phenotypes associated with various diseases. Preferably the relative risk should exceed 10, so as to enhance the likelihood that the particular tested predisposition is, indeed, putting those workers at a significantly higher risk than other workers with other, but nonidentifiable predispositions.


204. Id.
function of glutathione S-transferase has been shown to increase the risk of lung and bladder cancer among smokers, but may reduce the risk of stomach, colon, and liver cancer among individuals exposed to haloalkanes and haloalkenes. This suggests that genetic susceptibility does not necessarily create "at-risk" groups in general, but instead creates groups that are at higher risk of suffering certain adverse effects from particular chemical exposures. The implications of these differential susceptibilities may not be readily discernable in those environmental standard setting efforts that proceed pollutant by pollutant. However, the disparate effects of genetic polymorphisms may be highly relevant for cleanup standards for sites containing complex mixtures of hazardous wastes and for future standards that may take into account the combined effects of multiple pollutants.

The fact that genetic susceptibility is often polygenic—or influenced by many genes—intensifies the problem of defining genetically sensitive populations. For a particular chemical exposure, regulators must decide which combinations of polymorphic genes increase risk sufficiently to merit regulatory consideration. Illustrating the interactive effects of multiple polymorphisms, a study of individuals with squamous cell carcinoma of the lung documented the multiplicative risk ratios associated with the combined effects of two susceptibility genotypes compared to one. Complicating the regulatory decision further, the combined effect of multiple genes may lead scientists to find that there is a continuum of genetic susceptibilities to the adverse effects of a single contaminant, paralleling the concept of a continuum of health effects illustrated by the biomarker paradigm. Another confounding aspect of genetic susceptibility is that gene combinations may be either antagonistic or synergistic:

The different physiologic effects of two susceptibility factors can work synergistically, and, consequently, increase the risk for those individuals who carry both respective genes over the risk of those who carry only either one of the two. However, the presence of one factor can as well antagonize the effect of another. Even the simplest theoretical case of two factors would already lead to four

205. Id.
206. Marchant, supra note 45, at 10644; see also Hoffmann et al., supra note 17, at 12 ("Susceptibility is not a problem of a [single] genetically underprivileged minority but a general principle that likely concerns almost everybody and relates to almost any exposure situation." (citation omitted)).
207. Calabrese, supra note 199, at S62 (citing K. Nakachi et al., Polymorphisms of the CYP1A1 and Glutathione S-Transferase Genes Associated With Susceptibility to Lung Cancer in Relation to Cigarette Dose in a Japanese Population, 53 CANCER RES. 294-99 (1993)). The researchers found that, among light smokers, cancer risk was sevenfold higher in the susceptible genotype as compared with a less susceptible genotype. However, at low-level exposures, the combined effect of the two susceptibility genotypes resulted in substantially higher risk. Id.
groups of people who are either positive for only one of the two, positive for both, or negative for both.\textsuperscript{208}

Further demonstrating the complexity of identifying genetically sensitive groups, the handful of population-based studies focusing on the interactions among different susceptibility factors have found different risks for each of the possible genetic combinations.\textsuperscript{209}

2. Genetic Susceptibility Transcends Traditional Groups

The presence of susceptibility genes may correspond with, or cut across, traditional groups. This could mean that subgroups now recognized in environmental standard setting, such as asthmatics, will be stratified into a growing number of “sub-subgroups” with varying levels of relative risk. With regard to the NAAQS, \textit{American Lung} suggests that EPA will need to find a principled basis for excluding these identifiable subsets from regulatory standards.\textsuperscript{210} An open question is whether groups identified on the basis of genetic susceptibilities will garner the same level of cultural empathy (and political acceptance) that appears to influence the selection of sensitive groups recognized in environmental standard setting today—children, the elderly, pregnant women, and people with overt disease. Recall the NRC’s comment: “When persons of high risk or susceptibility are identifiable, society has tended to feel a responsibility to protect them.”\textsuperscript{211} Even accepting the truth of this statement, it is unclear, for example, whether individuals possessing a variant of the CYP1A1 gene\textsuperscript{212} will attract the same level of societal concern as would infants exposed to pesticide-laced peaches—or whether such cultural affinities should matter.

3. Group Size: How Small is Too Small?

Once genetically sensitive populations are identified, questions will arise concerning the appropriate size of populations to be considered for protection. EPA has announced that in deciding what is requisite to “protect public health” under the NAAQS, the agency is allowed to consider “the nature and severity of the health effects involved, the size of the sensitive population(s) at risk, the types of health information available, and the kind and degree of uncertainties that must be addressed.”\textsuperscript{213} The

\begin{enumerate}
  \item Hoffmann et al., \textit{supra} note 17, at 11 (citations omitted).
  \item \textit{Id.}
  \item 134 F.3d 388, 392-93 (D.C. Cir. 1998).
  \item \textit{National Research Council, supra} note 4, at 213.
  \item As noted, CYP1A1 is a member of the cytochrome P450 family, a related group of enzymes that act on numerous chemicals. Variations in genes that encode, or carry the instructions for manufacturing, the cytochrome p450 enzymes have been linked to a propensity for cancer. Perera, \textit{supra} note 18, at 60.
\end{enumerate}
agency has not established a minimum size for subpopulations to meet in order to receive protection.\textsuperscript{214} Illustrating the complexity of the line-drawing exercise, EPA’s selection of the initial primary standard for ozone in 1979 was based on the concentration the agency believed would protect “the least sensitive member of the most sensitive 1 percent of the most sensitive group.”\textsuperscript{215}

The multivariate nature of genetic susceptibility may call into question some of EPA’s traditional line-drawing approaches and thus undermine the agency’s distinction between public and individual health, at least as a practical matter. For pollutants regulated under the NAAQS, EPA has interpreted the statute and legislative history to require protection of sensitive groups, rather than the most sensitive individuals within these groups. The government’s brief in \textit{American Lung} noted that “nothing in the language of the statute requires EPA to protect every individual within the sensitive population . . . . The statutory mandate is to protect the ‘public health.’”\textsuperscript{216} Conversely, the plaintiffs in \textit{American Lung} highlighted the Senate report’s reference to “sensitive citizens” and “susceptible individuals” to show that the drafters of the Clean Air Act rejected population size as a relevant factor.\textsuperscript{217} The plaintiffs also pointed to alleged inconsistencies in EPA’s position.\textsuperscript{218}

Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information: Office of Air Quality Planning And Standards (OAQPS) Staff Paper 11-2 (July 1996)). The above criteria—severity of effect, certainty of effect, and size of the population—were approved in \textit{Lead Industries Ass’n v. EPA}, 647 F.2d 1130, 1161 (D.C. Cir. 1980).

\textsuperscript{214} A numerical cut-off point for group size would not necessarily be desirable given the number of factors relevant to defining a public health problem.

\textsuperscript{215} \textsc{Friedman}, supra note 123, at 8 (discussing U.S. Environmental Protection Agency, \textit{A Method for Assessing the Health Risks Associated with Alternative Air Quality Standards for Ozone}, at 4-5 (July, 1978)). Although decisionmaking in the face of scientific uncertainty involves case-by-case determinations and best estimates based on incomplete information, the agency’s explanation for this decision is a veritable brain teaser:

The selection of the 1 percent figure unavoidably involves some arbitrariness, but was selected for several reasons. To use the health effect threshold of the most sensitive group rather than the threshold of the least sensitive member of the most sensitive 1 percent of the most sensitive group would be impractical for at least one reason. For the types of effects contributed to by ozone, the most sensitive member of the most sensitive group is an unknown type of person who would be extremely difficult for the health expert to make judgments about. Subjective judgments grade from well-informed judgments to sheer guesses; judgments about the most sensitive member of the most sensitive group would be at the latter end of the scale.

\textit{Id.} at 9 (quoting U.S. Environmental Protection Agency, \textit{A Method for Assessing the Health Risks Associated with Alternative Air Quality Standards for Ozone}, at 2-25 to 2-26 (July, 1978)).

\textsuperscript{216} Brief for Respondents at 36, \textit{Am. Lung Ass’n v. EPA}, 134 F.3d 388 (D.C. Cir. 1998) (Nos. 96-1251 & 96-1255).

\textsuperscript{217} Brief for Petitioners at 53, \textit{Am. Lung Ass’n v. EPA}, 134 F.3d 388 (D.C. Cir. 1998) (Nos. 96-1251 & 96-1255).

\textsuperscript{218} For the proposition that the size of a sensitive subpopulation should not affect protection under the NAAQS, the plaintiff’s brief quoted EPA’s rulemaking record for the initial ozone standard, in which the agency noted that “[s]tandards must be based on a judgment of safe air quality level and not on an estimate of how many persons will intersect with given concentration levels.” \textit{Id.} at 19
EPA's distinction between public health and individual health surfaced again at oral argument in *American Trucking*. Industry plaintiffs had argued that EPA's construction of section 109—requiring air pollutants to be confined to levels requisite to "protect public health," with an "adequate margin of safety"—gave undue discretion to the agency, amounting to an unconstitutional delegation of legislative power. The issue of undue discretion was particularly problematic for pollutants such as ozone, which EPA treats as nonthreshold and thus capable of causing adverse health effects at any level above zero. Arguing on behalf of EPA, the United States Department of Justice (DOJ) noted that Congress had placed "multiple specific restrictions on EPA's discretion in setting and revising NAAQS that satisfy the constitutional requirements of the nondelegation doctrine." One such restriction was the public health mandate of section 109: "[P]ublic health is distinct from individual health; the standards must protect sensitive populations, such as asthmatics, but not the most sensitive individuals within those populations."

Deciding when a collection of individuals is an identifiable subgroup meriting regulatory protection will become more difficult as new genetic information challenges traditional notions about the interaction of toxic chemicals and the body. The potential presence of a range of genetic susceptibilities to the effects of particular chemicals suggests that, for a given substance, a range of sensitive populations of varying sizes will be identified.

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219. Am. Trucking Ass'n v. EPA, 175 F.3d 1027, 1034 (D.C. Cir. 1999); see supra note 172 and accompanying text.
221. *Id.* (citing S. REP. No. 91-1196, at 10 (1970)); see also *id.* at 10 ("[R]eference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group."). Citing to this and several other factors, the government argued successfully that the statutory language provided an "intelligible principle" which cabined agency discretion sufficiently to avoid a nondelegation claim. The Supreme Court found for the government principally on the ground that the language of section 109 of the Clean Air Act was no broader than that of numerous other statutes that had withstood nondelegation challenges. *American Trucking*, 531 U.S. at 272-76.
4. Continuum of Susceptibilities: New Challenges to the Threshold Concept

The identification of groups with varying susceptibilities leads to questions not only about which groups merit protection, but also about the concept of threshold levels of exposure below which no adverse health effects will occur. The threshold concept is essential to understanding how particularly sensitive subgroups are accounted for in regulatory standard setting today, and elucidates some of the changes that may occur as a result of new biological evidence of susceptibility.

Many harmful chemicals (including neurotoxins, immunotoxins, and chemicals that cause cardiopulmonary and developmental effects) are presumed to have a threshold level beneath which exposure is deemed “safe.” The language of section 109, which requires air quality standards to be set at levels “requisite to protect the public health” with an “adequate margin of safety,” appears to assume a discrete threshold of safety. Although the threshold concept has been debated from the outset, regulatory standards have treated most of the pollutants covered under section 109, with the exception of ozone and particulates, as threshold pollutants. The same is true for most noncarcinogens regulated under other sections of the Clean Air Act and other statutes.

In the language of risk assessment, threshold chemicals are presumed to have either a “no observable adverse effect level” (NOAEL) or “lowest observed adverse effect level” (LOAEL) at or below which exposure is deemed safe for an average person or experimental animal. The NOAEL is the highest exposure in available experimental studies at which no toxic effect is observed in average subjects.

To protect particularly sensitive subgroups and to extrapolate from experimental animal data to humans, arbitrary numerical defaults called “safety factors” or “uncertainty factors” generally are applied to the threshold concentration (NOAEL or LOAEL). A safety factor of ten frequently

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222. See Friedman, supra note 123, at 11. The legislative history of section 109 indicates that EPA would first identify a threshold below which there were no reported adverse health effects, adopt a margin of safety, and then set the standard. Id.
223. “[I]n no case is there evidence that the threshold levels have a clear physiological meaning. . . . [T]he ‘safe threshold’ concept is, at best, a necessary myth to permit the setting of some standards.” H.R. Rep. No. 95-294, at 127 (1977) (House Committee on Interstate and Foreign Commerce quoting National Academy of Sciences during consideration of 1977 amendments to the Clean Air Act).
224. EPA considers ozone to be a nonthreshold pollutant, and particulate matter likely to be a nonthreshold pollutant. See note 161 supra.
225. National Research Council, supra note 4, at 60-64. Much of the safety evaluation of drugs and chemicals involves administration of a large dose of a compound to experimental animals, followed by extrapolation to lower doses to predict risks experienced by humans. See, e.g., National Research Council, supra note 132, at 61-64.
226. National Research Council, supra note 4, at 61-64.
227. Id. at 39; Olden & Guthrie, supra note 4, at 61-64.
is applied for interspecies extrapolation, and an additional safety factor of ten customarily is applied to account for inter-individual variability in the population.\textsuperscript{228} Once safety factors are added to the threshold concentration, risk assessors arrive at a “reference concentration” (RfC), which represents the concentration of a pollutant that will not result in substantial risk of adverse effects to the exposed human population, including sensitive populations, after a lifetime of exposure. Thus, the RfC (the presumed “safe” level of exposure for the population) generally is based on arbitrary defaults that are not biologically determined.

As the definition of sensitive subpopulations becomes increasingly refined, and as the potentially adverse effects of chemicals can be discerned at lower levels of exposure, the threshold level of “safety” for many pollutants will become lower, possibly approaching natural background levels of risk. In some cases, the threshold may be so low that it can no longer be identified. The lack of a single, scientifically defensible threshold will accentuate the already formidable line-drawing problems inherent in setting risk-based environmental standards, and may further call into question whether EPA’s distinction between public and individual health—which I interpret as a distinction between large and small groups—will have any practical significance.

In addition, the further erosion of the threshold concept may undermine some of the current regulatory distinctions between noncarcinogens and carcinogens, which traditionally have been considered to have no safe threshold above zero. Carcinogen regulation has focused less on the identification of “safe” levels of exposure, and instead on what degree of protection is appropriate as a policy matter, assuming that any exposure carries a risk. Judicially imposed adoption of “significant risk” regulatory thresholds, regulatory standards of “acceptable risk,” exemptions for “de minimus risks,” and other regulatory conventions applied to carcinogens could potentially be considered for noncarcinogens in the future. However, such an approach would do little to resolve the line-drawing problems inherent in distinguishing “acceptable risks” that society should tolerate from “significant risks” that government should regulate.\textsuperscript{229} Whereas

\textsuperscript{228} National Research Council, \textit{supra} note 4, at 30; see also Smith, \textit{supra} note 3, at 281. Occasionally, toxic effects will be seen at the lowest dose available in a toxicology study, hence a NOAEL would not be available. In that case, risk assessors typically use the LOAEL and apply another safety factor of ten, resulting in an overall factor of 1000. E.M. Faustman & G.S. Omenn, \textit{Risk Assessment}, in \textit{Casarett and Doull's Toxicology}, \textit{supra} note 3, at 75.

significant risk thresholds traditionally have been applied to cancer risks, they may be even more problematic for noncarcinogens, where the health endpoints are less clear-cut.\textsuperscript{230} Moreover, for cancer and noncancer risks alike, toxicogenetic and toxicogenomic data may change the denominator of the risk threshold,\textsuperscript{231} calling into question whether any neutral, across the board, significant risk threshold can be established as a matter of policy.

F. Protecting Subgroups—From Arbitrary Defaults to Biological Data: Panacea or Pandora's Box?

Much of the scientific literature predicts that new, biologically derived data on the prevalence and characteristics of susceptibility genes will remove some of the guesswork from risk assessment, allowing for more tailored and precise estimates of environmental risks within populations.\textsuperscript{232} Several commentators have argued that the standard safety factors used for noncarcinogens are blunt instruments suffering from the shortcomings of any broadly applicable device—overprotective in some cases and under-protective in others.\textsuperscript{233} According to this view, substituting direct biological measurements for arbitrary defaults might permit protection of vulnerable

\textsuperscript{230} Cancer risks provide clearer health endpoints (e.g., mortality), than, for example, neurological deficits resulting from lead exposure.

\textsuperscript{231} A traditional cancer risk estimate—such as a 1-in-100,000 or 1-in-1,000,000 risk of cancer death after a lifetime of exposure—will vary depending upon the health effect considered. Attention to interindividual variability in susceptibility—generally overlooked in cancer risk estimates—would further affect the denominator. For example, a 1-in-100,000 risk for the general population might be a 2-in-100,000 risk for someone with a single genetic variant, or a 3-in-100,000 risk for individuals possessing two relevant polymorphisms.

\textsuperscript{232} Smith, supra note 3, at 281. One example is in the area of dose-response estimates. Dose response, or potency assessments, attempt to “characterize quantitatively the relationship between the dose of an agent and the incidence of an adverse health effect in exposed populations and [to estimate] the incidence of the effect as a function of human exposure to the agent.” \textit{Carl F. Cranor, Regulating Toxic Substances} 13 (1993). Dose-response estimates for humans customarily are derived from experimental animal data. The high doses used in these experiments must be extrapolated to lower doses more representative of actual human exposure. High to low-dose extrapolation currently is achieved by using default estimates, or uncertainty factors. Scientists hope that biomarkers of the biologically effective dose will allow for more direct interspecies comparisons and reduce the need to use uncertainty factors for the purpose of species-to-species extrapolation. DeCaprio, supra note 25, at 1841; see also Olden & Wilson, supra note 35, at 154; Olden & Guthrie, supra note 35, at 8-9.

\textsuperscript{233} See, e.g., Smith, supra note 3, at 281. Some argue that current default assumptions may overestimate risk by several orders of magnitude. Conversely, inter-individual variation in susceptibility may be far greater than the customary assumption of a ten-fold variation. See Carl F. Cranor, Risk Assessment, Susceptible Subpopulations, and Environmental Justice, in \textit{The Law of Environmental Justice} 307, 330-32 (Michael B. Gerrard ed., 1999).
groups while avoiding over- or under-regulation. Recognizing this, several experts have called for reduced reliance on arbitrary defaults and better incorporation of biological data on population heterogeneity into risk assessments.

On the other hand, the ability to identify susceptibility genes and the ability to discern new subcellular evidence of disease will introduce new levels of complexity into the risk assessment and risk management process. Even if one were to concede that the new biological data will lend precision to the technical assessment of risk—an assumption that is highly debatable—the policy judgments inherent in risk management will become far more complicated. I suggest that, until now, traditional science—which has enabled the selection of large, readily identifiable subgroups—has provided a relatively “comfortable fit” with regulatory justifications. As our ability to identify susceptible groups and health effects becomes ever more refined, however, we may witness a growing disjuncture between scientific data and regulatory choices. If new data support regulation at lower-dose levels, possibly approaching background levels of risk, regulatory standards that depart from scientific findings may need to be justified more explicitly on social policy grounds. Ironically, then, as scientific advances generate vast quantities of biological data pertinent to the assessment of environmental risk, risk-based regulatory decisions increasingly may find their basis in nonscientific criteria. At the same time, EPA will need to confront the fact that courts frequently will require the agency to support its decisions on the basis of the “best available science,” as specified by statute.

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234. See, e.g., National Research Council, supra note 4, at 6 (stating that better data and understanding of biological mechanisms should enable risk assessments that are less dependent on conservative default assumptions and are more accurate predictors of human risk); see also William E. Bishop et al., The Genomic Revolution: What Does It Mean for Risk Assessment?, 21 Risk Analysis 983, 986-87 (2001) (noting that toxicogenomic data could reduce the need to apply default uncertainty factors); Carol J. Henry et al., Use of Genomics in Toxicology and Epidemiology: Findings and Recommendations of a Workshop, 110 Envil. Health Persp. 1047, 1048 (2002) (same).

235. Bishop et al., supra note 234, at 987.

236. Risk assessments are performed by scientists in the technical and scientific divisions of federal agencies. However, as the title of the NRC’s seminal report on risk assessment makes clear, regulatory risk assessment is a blend of scientific inquiry and policy judgment. National Research Council, supra note 4. Risk management is concerned with evaluating regulatory alternatives and choosing among them, and hence is policy oriented by definition. National Research Council, supra note 132, at 1819, 38.

G. Future Proliferation of Science-Based Challenges and New Types of Claims

1. Science-Based Challenges

Indeed, science-based challenges to regulatory decisions are likely to proliferate. These may include challenges to default regulatory criteria and guidance values including NOAELs and LOAELs, reference concentrations, and cancer potency factors. Biomarkers of genetic susceptibility, as well as biomarkers signaling early health effects, could substantially change current dose-response assumptions for carcinogens and noncarcinogens alike.\(^{238}\) Most risk assessment approaches treat humans as identical in their responses to carcinogens,\(^{239}\) despite evidence to the contrary. Although courts traditionally defer to EPA's selection of risk assessment methodologies,\(^{240}\) the D.C. Circuit's decision in *Chlorine Chemistry Council v. EPA*\(^{241}\) may be a harbinger of more stringent review by the courts. Venturing into one of the most technical aspects of the risk assessment process, the court required EPA to abandon a customary default relating to the mechanism of action of chloroform, a suspected carcinogen, and set aside the agency's maximum contaminant level goal for the chemical pursuant to the Safe Drinking Water Act.\(^{242}\) On the ground that the agency had ignored the "best available, peer-reviewed science," the court challenged EPA's long-standing assumption that chloroform was a nonthreshold carcinogen.\(^{243}\) This decision may foreshadow new kinds of challenges to foundational assumptions and defaults used to control pollution and protect the public's health, particularly where the agency allegedly has failed to keep pace with available science.

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\(^{238}\) The result of a dose-response assessment for a carcinogen is a "potency factor," or a unit risk factor for cancer potency. National Research Council, *supra* note 4, at 143.

\(^{239}\) Perera, *supra* note 75, at 497. Carcinogen risk assessments generally specify either the total numbers of people likely to experience the adverse effect (population risk, e.g., 1,000 additional cases of cancer in the exposed population), or the likelihood that any one individual exposed to the hazard will suffer the adverse effect during a lifetime of exposure (individual risk, e.g., an exposed individual faces a 1-in-10,000 chance of developing cancer). Smith, *supra* note 3, at 282. One of the most controversial defaults used in air pollution exposure and risk assessment has been the maximally-exposed individual (MEI), who is assumed to be the person at greatest risk (e.g., the person assumed to be residing at a power plant boundary continuously for 70 years). As the name indicates, these so-called "high-end exposure estimates" are based on differential exposure, not susceptibility. National Research Council, *supra* note 4, at 204.

\(^{240}\) Although the "hard look" doctrine emerging in the 1980s resulted in more aggressive analysis of agency evidence in toxic substance cases, see, e.g., Gulf S. Insulation v. Consumer Prod. Safety Comm'n, 701 F.2d 1137 (5th Cir. 1983), EPA's choice of risk assessment methodologies and default assumptions generally were not questioned.

\(^{241}\) 206 F.3d 1286 (D.C. Cir. 2000).

\(^{242}\) Id. at 1290.

2. New Types of Claims

If regulatory decisions fail to accommodate newly identifiable subgroups, new claims are likely to arise. For example, as new technologies set the stage for personalized genetic screening and testing for environmental susceptibility, exposure, and early evidence of injury, newly identified sensitive groups and individuals may petition for enhanced regulatory protection or seek private law remedies to fill putative regulatory gaps.

A recent case of first impression involving children with asthma and cystic fibrosis is instructive. Although the case did not involve genetic data, Save Our Summers v. Washington Department of Ecology\textsuperscript{244} represents a novel claim by two vulnerable individuals allegedly left unprotected under the Clean Air Act's public health mandate. Notably, the plaintiffs reached beyond the contours of environmental law to address an acute air pollution problem.

The case arose in response to high concentrations of particulate matter generated by agricultural burning of wheat stubble in eastern Washington state, a region presumptively in compliance with the Clean Air Act.\textsuperscript{245} Save Our Summers, a public interest group working on the children's behalf, invoked Title II of the Americans with Disabilities Act (ADA)\textsuperscript{246} in an attempt to remedy the ill effects of localized heavy smoke. The plaintiffs alleged that the smoke prevented the two children from going outdoors, excluding them on the basis of their disabilities from using public facilities such as schools, parks, and roads.\textsuperscript{247} The plaintiffs sought a preliminary injunction in federal court against the issuance of wheat stubble burning permits by Washington state.\textsuperscript{248}

The essential question was whether the Clean Air Act, which establishes nationwide standards to protect public health, trumps the ADA regarding private claims of environmental harm.\textsuperscript{249} In an \textit{amicus curiae}

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\textsuperscript{244} 132 F. Supp. 2d 896 (E.D. Wash. 1999).
\textsuperscript{245} To measure compliance with the NAAQS, the nation is divided into Air Quality Control Regions. 42 U.S.C. § 7407(b) (2000). Compliance (or noncompliance) with the NAAQS is measured on a regionwide basis; therefore, localized peaks in pollution levels will not necessarily bring a region out of compliance.
\textsuperscript{246} 42 U.S.C. §§ 12131-12165 (2000). Title II states that “no qualified individual with a disability shall, by reason of such disability, be excluded from participation in or denied the benefits of the services, programs, or activities of a public entity, or be subjected to discrimination by any such entity.” 42 U.S.C. §12132 (2000). Intentional discrimination is not required to sustain a Title II claim. A public entity is required to make “reasonable modifications in policies, practices, or procedures” to accommodate individuals with disabilities, unless the entity can demonstrate that such modifications would “fundamentally alter” the nature of the service, program, or activity. 28 C.F.R. § 35.130(b)(7) (2003). Plaintiffs had also raised a claim under the Rehabilitation Act of 1973, 29 U.S.C. § 791 (2000).
\textsuperscript{247} Save Our Summers, 132 F. Supp. 2d at 905, 907-08.
\textsuperscript{248} The permit program was part of the state’s implementation plan under the federal Clean Air Act. \textit{Id.} at 900-01.
\textsuperscript{249} \textit{Id.} at 901. Washington state responded that the Clean Air Act’s comprehensive regulatory scheme foreclosed the ADA claims. After denying the motion for a preliminary injunction on
brief requested by the court, the DOJ argued that the Clean Air Act and the ADA could be read harmoniously. Without dismissing the case, which ultimately settled, the district court denied the injunction, concluding that the Clean Air Act and the ADA could not be reconciled.

Save Our Summers is noteworthy, less for its value for future claimants than for the broader themes it reveals. Whether the ADA may treat as "disabled" individuals who are genetically susceptible to toxic effects is a matter of ongoing debate. However, like American Lung, Save Our Summers brought to the fore the tension between the broad-based public jurisdictional grounds, plaintiffs moved for reconsideration, and the court sought counsel from the DOJ on these novel jurisdictional questions. The district court requested that the following issues be addressed in an amicus curiae brief from the DOJ:

(1) whether the comprehensive statutory and regulatory scheme of the Clean Air Act, including private remedies, foreclosed plaintiff’s claims under the ADA; and
(2) whether the objectives and remedies of the ADA and the Rehabilitation Act can be reconciled with the Clean Air Act’s standards that are the result of a compromise and consensus.


The DOJ argued that the ADA could require “reasonable accommodations” for disabled persons resulting from an air pollution problem, as long as such accommodations would not amount to a “fundamental modification” of the existing statutory scheme—in this case, the Clean Air Act’s cooperative federal-state program. Brief for Amicus Curiae of the United States at 15-16, Save Our Summers v. Wash. Dept. of Ecology, 132 F. Supp. 2d 896 (E.D. Wash. 1999) (No. CS-99-269-RHW).


Even if a future court were to conclude that the ADA and the Clean Air Act could be reconciled, a multiplicity of ADA claims likely would amount to a “fundamental modification” of the Clean Air Act’s regulatory program and thus would not pass muster under ADA precedent. The DOJ’s amicus curiae brief recognized the difficulty of accommodating many such ADA claims without undermining the federal-state air quality scheme:

The present case involves the claims of only two individuals; it is unclear to what extent other such claims might be asserted in the future. The United States believes that it would be important, however, to monitor the aggregate effect of remedies that might be awarded in such cases, and that remedies standing alone might be fundamental alterations when considered in the aggregate.


Genetically susceptible individuals are asymptomatic or presymptomatic and thus would not be considered to suffer a physical or mental “impairment” that “substantially limits one or more . . . major life activities,” 29 C.F.R. § 1630.2 (2003). The question is whether asymptomatic or presymptomatic individuals should be protected from employment discrimination under the “regarded as” prong of the ADA, which recognizes that disability discrimination may result from the perception of disability even when no actual disability exists. 42 U.S.C. § 12102(2) (1990). The Equal Employment Opportunity Commission (EEOC) has supported this position, interpreting the ADA to bar employment discrimination against “individuals who are subject to discrimination on the basis of genetic information relating to illness, disease, or other disorders.” 1 EEOC Compl. Man. (BNA) § 902-45 (Mar. 1995). However, subsequent Supreme Court decisions appear to undermine the EEOC position. In Murphy v. United Parcel Service, Inc., 527 U.S. 516 (1999), the Court held that, in order for employees to be disabled under the “regarded as” prong, an employer must regard them as substantially limited in a major life activity. In Sutton v. United Airlines, 527 U.S. 471 (1999), the Court determined that if employees have mitigated their potential disabilities, they must be considered in their mitigated state rather than a hypothetical disabled state. Id. at 483. This emphasis on the employee’s actual functionality would work against claims based on susceptibility alone.
health protections of the environmental regulatory framework and more particularized individual or small group claims. *Save Our Summers* highlights this tension in bold relief: the ADA is a quintessentially individualized statute, originally conceived and designed to accommodate individuals whose needs may differ from those of the public at large.254

The nuances of the government’s position may foreshadow future dilemmas for EPA. The DOJ brief echoed EPA’s position that “public health” does not necessarily mean “individual health,” and it listed as one of the most “important features” of the federal regulatory scheme “the [Clean Air Act’s] creation of distinctively national standards for air quality,” which “protect sensitive populations, but not the most sensitive individual within a population.”255 At the same time, the government’s attempt to harmonize the Clean Air Act with the ADA reflects discomfort with the notion that two vulnerable individuals might remain unprotected by the existing regulatory scheme.256 This aspect prompted a Heritage Foundation spokesperson to characterize the DOJ’s position as a “legal train wreck,” due to the impossibility of reconciling two complex statutes with fundamentally different goals: “The Clean Air Act’s mission is to protect the general public health, and the Americans With Disabilities Act’s intention is to focus on disabled populations.”257

Although *Save Our Summers*, like *American Lung*, involved individuals with manifest disease (asthma and cystic fibrosis) as opposed to genetic susceptibilities, the case may be another sign of things to come. The possible proliferation of individual or small group claims could potentially reshape the dynamics of environmental regulation. In some situations, this development could shift the current balance between tort and regulation in

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254. The ADA was enacted to “provide a national mandate ‘for the elimination of discrimination against individuals with disabilities.’” Komblau v. Dade County, 86 F.3d 193, 194 (11th Cir. 1996) (citing 42 U.S.C. § 12101(b)(1)); see also H.R. REP. No. 101-485, at 23 (1990) (“The purpose of the Americans With Disabilities Act (ADA) . . . is to provide a clear and comprehensive national mandate to end discrimination against individuals with disabilities and to bring those individuals into the economic and social mainstream of American life.”).

255. Brief for Amicus Curiae of the United States at 19, *Save Our Summers* v. Wash. Dept. of Ecology, 132 F. Supp. 2d 896 (E.D. Wash. 1999) (No. CS-99-269-RHW). The brief noted that “EPA must consider the effects to a representative sample of persons comprising the sensitive group rather than to a single person in such a group.” *Id.* at 20 (quoting Sen. REP. No. 91-1196, at 10 (1977)). The brief noted that “EPA’s standards thus establish the appropriate national level of ‘public health’ protection for sensitive subpopulations with regard to these pollutants, recognizing the possibility that some sensitive individuals may continue to experience ill effects as a result of exposure to particulate matter.” *Id.* at 20.

256. Thus, the significance of the federal government’s position in *Save Our Summers* may not only be its adherence to the limitations of EPA’s public health mandate in the NAAQS, but also its hesitancy to acknowledge that two vulnerable children might remain without a remedy for a clean air problem insufficiently addressed under that mandate.

protecting the public from environmental harms. Where an association between genetic susceptibility and membership in otherwise socially disadvantaged groups can be established, additional normative and legal claims may arise. The success of future claims will depend, in part, on the future reliability of genetic and other molecular biomarkers as indicators of susceptibility, correlates of risk, or warrantors of injury.

III

REDEFINING HEALTH AND HARM IN THE GENETIC AGE

In Part II, I argued that the growing understanding of genetic susceptibility and the proliferation of toxicogenetic data will call into question the relevant "public" to be protected under environmental standards designed to protect public health. In this Part, I argue that traditional conceptions of "health" will be challenged as new technologies reveal early effects of chemical exposure. The rapid influx of toxicogenomic data will require regulators to decide whether risk assessments underlying environmental standards should account for early subcellular effects of toxic substances. Thus, in addition to uncovering new kinds of susceptible subgroups, as discussed in Part II, new genomic techniques will reveal new kinds of identifiable risks and injuries that may justify a regulatory response.

The essential question is whether these preclinical changes are sufficiently reflective of injury or predictive of disease to warrant governmental intervention. Regulators and policymakers will need to decide, for example, whether to define these early markers as "adverse health effects" and whether to reduce permissible pollution levels accordingly. Of course, unless or until gene expression changes and other subclinical events can be validated as predictive or reflective of underlying toxic mechanisms, the strengthening of environmental standards would not be justified. If validated, however, the predictive power of new genomic data may argue for adjusting standards, particularly since the purpose of risk-based regulation is to prevent harm before it occurs.

258. See infra Part IV.
259. "The preventive, ex ante orientation toward environmental quality levels is a fundamental attribute of the environmental regulatory scheme." Christopher H. Schroeder, Lost in the Translation: What Environmental Regulation Does That Tort Cannot Duplicate, 41 WASHBURN L.J. 583, 593 (2002). "The goal of much modern environmental regulation is to prevent harm to the environment before it occurs, with an implementation structure that includes prior approvals, permits that embody standards to be met, and the monitoring of compliance." Id. at 589. The judiciary placed its imprimatur on the preventive function of environmental regulation in Ethyl Corp. v. EPA, 541 F.2d 1, 13 (D.C. Cir. 1976) (en banc): "A statute allowing for regulation in the face of danger is, necessarily, a precautionary statute. Regulatory action may be taken before the threatened harm occurs; indeed, the very existence of such precautionary legislation would seem to demand that regulatory action precede, and, optimally, prevent, the perceived threat."
A. Consequences of Opening the “Black Box”

1. Predicting Deleterious Effects

Traditionally, the science of toxic injury has focused on health effects near the end of the exposure-disease continuum, such as tumor formation, evidence of major organ and tissue dysfunction, and other clinical symptoms. Classical toxicological methods were insufficient to identify and characterize many intermediate events or to establish their relationship to ultimate disease, giving rise to the concept of a “black box.” New technologies have enabled the discovery of new biomarkers, particularly gene expression changes, that may allow scientists to focus on preclinical events as predictors of disease. A central goal of environmental genomics is to identify gene expression patterns that portend harmful health effects:

If toxicity manifested at the organismal level is preceded by altered expression of related genes, then detection of altered gene expression can serve as an early warning of subsequent deleterious outcomes. As some manifestations of toxicity occur only after chronic insult at the cellular level, altered gene expression may precede organismal outcomes by weeks, months, or even years. To the extent that a causal relationship can be demonstrated between early alterations in gene expression and delayed manifestations of frank toxicity, measuring the former may reduce reliance on the latter.

The identification and validation of unique gene expression patterns or “fingerprints” may enhance the predictive power of toxicogenomic data, as such changes may be linked to chemicals for which mechanisms of toxicity are known. Furthermore, molecular and genetic changes are discernible at lower levels of exposure than are traditional indicators of disease.

2. Blurring the Distinction Between Health and Disease

In essence, new biomarkers of effect may blur the boundaries between health and disease. As genetic testing becomes more widespread, it will be possible to diagnose people who have a disease before any clinical symptoms appear (presymptomatic) and to identify those who do not have a disease but who are merely at greater risk (asymptomatic). Even those

260. DeCaprio, supra note 25, at 1841.
261. Id. at 1838.
262. See, e.g., American Thoracic Society, supra note 22, at 669 (“A frequent goal of biomarker development is the ability to readily measure changes that precede and predict continued or progressive events leading to clinical effects and disease.”); Schulte, supra note 2, at 6.
263. Farr & Dunn, supra note 89, at 1.
264. See, e.g., Schulte, supra note 2, at 6.
265. See, e.g., Eric Churchill, Supplement: Genes and Society: Puzzles, Promises, and Policy, 549 ANNALS AM. ACAD. POL. & SOC. SCI. 173, 175 (1997). “Predisposition testing will also be the catalyst
individuals currently labeled "healthy" may be at some stage along the exposure-disease continuum.\textsuperscript{266} In the medical field, these individuals have been referred to as "at risk" or the "healthy ill," and scholars have begun to explore the implications of this status for employment, insurance, and disability law.\textsuperscript{267} If early biomarkers of effect can be validated as representative of toxic processes, the concept of when a disease becomes "manifest" may need to change.\textsuperscript{268} By reducing our reliance on traditional clinical symptoms, new genetic data ultimately may transform the way we define disease.\textsuperscript{269}

3. \textit{Complicating the Designation of Adverse Effects}

In addition to defining the relevant public to be protected, risk-based standard setting under several environmental statutes requires designation of the "adverse health effects" against which regulation seeks to protect. For example, the Clean Air Act requires air quality standards to protect the public—including particularly sensitive citizens—against "adverse effects" resulting from exposure to air pollutants.\textsuperscript{270} Therefore, before EPA can use epidemiological, toxicological, and clinical data to estimate risks of harm, it must distinguish adverse from nonadverse effects.\textsuperscript{271}

\footnotesize{for a new category of patient, the asymptomatic ill, who carry a gene that gives them a predisposition for a disease." Id. \textsuperscript{266} Id. at 175. \textsuperscript{267} Asymptomatic or presymptomatic status may carry major life consequences relating to job access, or eligibility for employment or insurance. Such status may also carry the real possibility of discrimination. See, e.g., Larry Gostin, \textit{Genetic Discrimination: The Use of Genetically Based Diagnostic and Prognostic Tests By Employers and Insurers}, 17 AM. J. L. & MED. 109, 124 (1991) (citing Human Genetics Committee of the Council for Responsible Genetics, \textit{Position Paper on Genetic Discrimination}, GENEWATCH, May 1990, at 3); see also Churchill, supra note 265, at 183-84. \textsuperscript{268} For a discussion of the status of genetic and other subcellular injuries in tort law, see generally Donald T. Ramsey, \textit{The Trigger of Coverage for Cancer: When Does Genctic Mutation Become "Bodily Injury, Sickness, or Disease"?}, 41 SANTA CLARA L. REV. 293 (2001). \textsuperscript{269} For an interesting discussion of the definition of disease in medicine and law, see Lars Noah, \textit{Pigeonholing Illness: Medical Diagnosis as a Legal Construct}, 50 HASTINGS L.J. 241 (1998-99). \textsuperscript{270} S. REP. NO. 91-1196, at 10 (1970). \textsuperscript{271} American Thoracic Society, supra note 22, at 665.}
a. Current Practice

The definition of an adverse health effect is not fixed, and the selection of adverse effects to be measured in risk assessments is determined on a case-by-case basis. There is a shortage of meaningful guidance for identifying which health effects merit regulatory concern. The American Thoracic Society, an authority on the adverse effects of air pollution, has noted that "[t]he term . . . [adverse effects] is often used indiscriminately and loosely." Similarly, an EPA guidance on risk assessment methodology has acknowledged that "the distinction between adverse effects and nonadverse effects has been and remains problematic . . . and usually contains an element of scientific judgment." Delineation of the boundary between adverse and nonadverse health effects is a matter of debate and appears to depend on the pollutant at issue, the availability of relevant scientific information (including clinical data), and professional judgment.


273. Lewis et al., supra note 272, at 72 ("[O]ften the distinction between adverse and nonadverse effects is not clearly defined and interpretation needs scientific judgment on a case-by-case basis.").


275. U.S. Environmental Protection Agency, Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry 4-13, 4-15, EPA/600/8-90/066F (Oct. 1994) (RIC Guidance). A leading casebook notes that it is unsettled whether a "health effect" could be any detectable change in blood chemistry, or only those changes shown to have an adverse effect on bodily functions. Percival, supra note 125, at 552.

276. Considerable controversy around the definition of "adverse effects" ensued during revisions of the Clean Air Act in 1990. The American Thoracic Society made recommendations on the matter in 1985 and 1999. American Thoracic Society, supra note 274; American Thoracic Society, supra note 22. These reports outline principles for weighing evidence and setting boundaries between adverse and nonadverse health effects. They recognize that even if technical tools were available to make an objective determination of an adverse effect, the placement of dividing lines is a societal judgment. The 1999 report was prompted by improved sensitivity of research approaches, including the identification of biomarkers representing subtle perturbations of biological systems by air pollutants. Id. at 665.

277. For example, risk assessments may include clinical studies of asthma patients, but neurotoxic effects must be assessed through epidemiological or animal studies. Only a limited number of health endpoints can be studied ethically in dose-response tests involving human subjects.
(1) Customary Reliance on Clinical Symptoms

With regard to new genomic information, the most relevant question is when should a molecular or other subclinical event be deemed an adverse effect of regulatory concern. In the case of the NAAQS, although judicial precedent establishes that subclinical effects may be designated adverse for regulatory purposes, risk assessments underlying most of the air quality standards have focused on clinical symptoms. For example, the standard for SO\textsubscript{2} is based on the measurement of health effects determined to be "[c]linically or physiologically significant," including reduced lung function and respiratory symptoms that "could cause disruption of ongoing activities," such as the use of bronchodilator medication or the seeking of medical attention. Likewise, the standard for nitrogen oxides is based on diagnosable changes in organ function, including changes in airway responsiveness and pulmonary function. The 1997 revision of the NAAQS for particulate matter considered, among other clinical symptoms, premature mortality, aggravation of respiratory and cardiovascular disease, and changes in lung tissue structure and function. The recent revision of the ozone standard similarly relied on clinical symptoms. The air quality standard for carbon monoxide is based on a hybrid approach. A subclinical biomarker—elevated levels of a hemoglobin/carbon monoxide combination, COHb—was deemed to be an adverse health effect. However, the decision was based on a correlation of the biomarker with traditional clinical symptoms, including cardiovascular system effects, central nervous system effects, and developmental toxicity effects.

278. See infra notes 289-97.
280. The EPA Administrator concluded that repeated occurrences of such effects should be regarded as significant from a public health standpoint. Id. Some scientists questioned the significance of such transitory effects, but others argued that bronchial constriction severe enough to limit activity or require medication was significant. Id.
282. These health effects were indicated by increased hospital admissions, emergency room visits, school absences, and lost work days. National Ambient Air Quality Standards for Particulate Matter, 62 Fed. Reg. 38,652, 38,656 (July 18, 1997).
283. These symptoms included decreased lung function, hospital admissions and emergency room visits due to respiratory causes, repeated inflammation of the lungs, and long-term damage to the lung. National Ambient Air Quality Standards for Ozone, Final Rule, 62 Fed. Reg. 38,856 (July 18, 1997).
284. The carbon monoxide (CO) standard is particularly interesting because a biomarker in the blood, COHb, was used as a surrogate for clinical effects. The rulemaking record noted that "cardiovascular effects of CO are directly related to a reduced oxygen [O\textsubscript{2}] content of the blood caused by a combination of CO with hemoglobin (Hb) to form COHb and resulting in tissue hypoxia." Based on findings in the Criteria Document, the Administrator concluded that "COHb levels provide the most useful estimate" of CO exposures and "serve as the best biomarker of CO toxicity for ambient-level exposures to CO." The dominant view in the scientific community was that COHb levels were linked to other health effects such as cardiovascular effects, central nervous system effects, and developmental
Interestingly, an exchange on the topic of clinical versus subclinical health effects emerged during oral argument in *American Trucking*. Industry groups argued that the broad statutory language of section 109 of the Clean Air Act, when applied to presumed nontreshold pollutants such as ozone, gave the agency unbridled discretion to choose among potential standards: "EPA’s formulation of its policy judgment leaves it free to pick any point between zero and a hair below the concentrations yielding London’s Killer Fog." The DOJ countered by highlighting, among other things, EPA’s distinction between clinical and subclinical health effects as evidence that the statutory scheme sufficiently confined agency discretion: "[T]he legislative history of the NAAQS indicates that the health effects justifying a NAAQS must be ‘adverse,’ in the sense that they are ‘medically significant and not merely detectable.’" At oral argument, the solicitor general emphasized that "anything that does not rise to the level of a medically significant health effect does not count."

Notably, EPA’s distinction between public health and individual health, as discussed in Part II, and the distinction between medically significant and merely detectable health effects, as discussed here, have both served as rationales for confining agency discretion in health-based standard setting. DNA microarrays and other new technologies ultimately may add shades of gray to both these distinctions. Although there will be many molecular signs that do not portend ill, DNA technology will expand considerably the number of signs of disease beyond those recognizable using conventional diagnostic techniques.

285. As noted, section 109 specifies that air quality standards must be set at levels that, "allowing an adequate margin of safety," are "requisite to protect the public health." 42 U.S.C. § 7409 (2000).
286. *American Trucking*, 175 F.3d at 1037.
288. Transcript at 18, *Am. Trucking Ass’ns*, Inc. v. EPA, 531 U.S. 457 (2001), *available at 2000 WL 1674207 at *18. This prompted a challenge from the bench: "That’s circular. What is a medically significant health effect? Is a transient cough a medically significant health effect?" The solicitor responded: "As I explained earlier and as the Agency has explained and the D.C. Circuit has explained, it is a health effect that rises to the level at which a medical professional would deem it to be a concern that should be treated." Id. at 18-19. In the revision of the ozone standard, EPA concluded that "transient and reversible" effects on lungs from ozone exposure were not to be treated as "adverse effects." National Ambient Air Quality Standards for Ozone, Final Rule, 62 Fed. Reg. 38,856, 38,868 (July 18, 1997); National Ambient Air Quality Standards for Ozone, Final Decision, 58 Fed. Reg. 13,008, 13,011 (Mar. 9, 1993).
(2) Legal Support for Relying on Subclinical Effects: Lead Industries Association v. EPA

Despite the focus on clinical events in standard setting for SO₂, nitrogen oxides, ozone, and particulates, the D.C. Circuit’s 1980 decision in Lead Industries clarified that subclinical events may be defined as adverse for regulatory purposes. In upholding EPA’s standard for airborne lead, the court questioned the logic of distinguishing between clinical and subclinical effects. Specifically, the court upheld EPA’s determination that a subclinical effect—lead-related elevation of the protein, erythrocyte protoporphyrin (EP)—amounted to an “impairment of human health.”

EPA had reasoned that EP elevation indicated impaired function of the mitochondria, the subcellular organelles that play a crucial role in cellular respiration and energy production. Elevation of EP also indicated that lead exposure had begun to affect a “basic biological function” of the body—the production of heme, a protein required for the transport of oxygen to every cell. The court agreed with EPA that:

While EP elevation may not be readily identifiable as a sign of disease, the Administrator properly concluded that it indicates a lead-related interference with basic biological functions. As with other subclinical manifestations of impaired function, it is a prudent public health practice to exercise corrective action prior to the appearance of clinical symptoms.

It is significant that EPA decided to protect only against certain subclinical effects. The agency did not consider EP elevations to be “adverse” unless above a certain level. Moreover, EPA did not count as a physiological impairment another subclinical effect—lead’s inhibition of the production of an enzyme that catalyzes the production of heme. Here, the agency reasoned that there was no functional impairment, in part because the reduced enzymatic activity did not correspond to observable changes in the rate of heme synthesis.

Thus, while Lead Industries clarified that subclinical effects may be considered “adverse effects” and that impairment of cellular functions was
sufficient to constitute an impairment of bodily functions, EPA made a
decision to protect against certain subclinical effects but not others. EPA's
experience in setting the lead standard illustrated the degree of scientific
judgment already involved in distinguishing among potential health effects
of regulatory concern. The Lead Industries decision provides an appropri-
ate prelude to the debate about the implications of genomic information,
whereby health effects may be discerned long before clinical symptoms
emerge, requiring regulators to select among an expanding array of
potential adverse effects along the exposure-disease continuum.

B. Implications of New Genomic Information

The above section illustrates that although subclinical effects may be
considered "adverse" for regulatory purposes, reliance on traditional clini-
cal symptoms is still the norm, and principles for distinguishing between
adverse and nonadverse effects are neither comprehensive nor clear. Just as
new genetic data will complicate the line-drawing problems involved in
defining which sensitive groups should be protected, equally difficult pol-
icy questions emerge as toxicogenomics challenges traditional definitions
of health: When is a change in gene expression sufficiently validated as
reflective of injury or predictive of disease to warrant regulatory action?
How should the law treat the new genetic biomarkers?

As with toxicogenetic information, gene expression data may lend
precision to certain technical aspects of risk assessment, helping to over-
come some of the current uncertainties in the risk assessment process.\textsuperscript{298}
Importantly, whereas clinical symptoms may take months or years to
develop, changes in gene expression may be detected immediately after ex-
posure. The discovery of signature gene expression patterns may provide
"a higher resolution tool with much greater specificity than simply
monitoring the toxicological endpoint."\textsuperscript{299} Moreover, chemically induced
changes in gene and protein expression are expected to occur at lower lev-
els of exposure than clinical alterations.\textsuperscript{300} As EPA noted in a preliminary

\textsuperscript{298} Current uncertainties include extrapolating from experimental animal data to humans,
extrapolating from high-dose experimental results to low-dose human exposures, determining the shape
of the dose-response curve, and estimating actual human exposures. \textit{See} \textbf{National Research
Council}, \textit{supra} note 132, at 22-28. For a discussion of the potential benefits of gene expression data
for risk assessment, see Gary E. Marchant, \textit{Genomics and Toxic Substances: Part I—Toxicogenomics},

\textsuperscript{299} \textit{Id.} at 10073. EPA's Genomics Task Force similarly noted that "[g]enomics tools provide the
observer with a means to examine changes in gene expression and protein and metabolite profiles
within the cells of any organism, in contrast to older methods of analyses which restrict observers to
looking at whole organism effects or changes in single biochemical pathways." Genomics Task Force
and Risk Assessment Applications at EPA}, at 5, at http://www.epa.gov/OSA/genomics-external-review-

\textsuperscript{300} Gene expression data may not only help identify the nature of an exposure, but also help
quantify the dose to which an individual was exposed. This would represent a substantial improvement
policy statement in 2002, "[G]enomics will have an enormous impact on our ability to assess the risk from exposure to stressors and ultimately to improve our risk assessments."\textsuperscript{301} The agency's recently convened Genomics Task Force has echoed this view.\textsuperscript{302}

However, as in the case of defining susceptible subpopulations, even if one were to concede that new genomic information will lend precision to the technical assessment of risk, the policy judgments inherent in deciding "how safe is safe enough" will become even more daunting. The entrance of molecular biology into the science of toxic injury may provide a vast array of potential health endpoints of concern, compounding the complexity of designating adverse effects of regulatory significance.

1. Barriers to Defining Gene Expression Changes as Adverse Effects

There are many barriers to treating gene expression changes as adverse effects, at least in the short term. One major obstacle is that not all changes in gene expression imply toxicity: "A major challenge... is to determine which molecular events that may change at low doses are necessary for pathological outcomes, versus those that are adaptive, beneficial, and/or unrelated to the development of pathologies."\textsuperscript{303} Furthermore, some gene expression changes may be transient and reversible\textsuperscript{304} or represent background fluctuations,\textsuperscript{305} while others may...
represent permanent changes.\textsuperscript{306} The American Thoracic Society has underscored this problem: "We do not know if elevations of biomarkers during short-term experimental exposures signal risk for ongoing injury and clinical effects or simply indicate transient responses that can provide insights into mechanisms of injury."\textsuperscript{307} Similarly, the National Research Council has observed that "it may be difficult to relate disease to an exposure distant in time unless the disease has characteristics or biological consequences specific to a certain type of exposure."\textsuperscript{308} A third obstacle is that changes in gene expression measured in skin or blood cells may or may not always be representative of changes in less accessible target tissue.\textsuperscript{309} Finally, even if a gene expression change is considered adverse, these effects might not be severe enough to warrant the application of safety factors, such as those used to establish acceptable exposure levels for noncarcinogens.\textsuperscript{310}

In any event, unless or until gene expression changes can be validated as true markers of toxic response,\textsuperscript{311} many have recommended a cautionary approach. For example, EPA's 2002 statement, while acknowledging the potential for genomic information to improve risk assessment, cautioned that "the relationships between changes in gene expression and adverse effects are unclear at this time and may likely be difficult to elucidate."\textsuperscript{312} Noting that genomic data alone are currently an "insufficient basis for

\begin{itemize}
\item \textsuperscript{305} Marjorie F. Oleksiak et al., \textit{Variation in Gene Expression Within and Among Natural Populations}, 32 \textit{Nature Genetics} 261, 263 (2002).
\item \textsuperscript{306} This could be a result of genetic mutations, gene amplifications, or changes in DNA methylation patterns.
\item \textsuperscript{307} American Thoracic Society, \textit{supra} note 22, at 669-70.
\item \textsuperscript{308} National Research Council, \textit{supra} note 20, at 5.
\item \textsuperscript{309} See Tennant, \textit{supra} note 100, at A8, A9. EPA's Genomics Task Force has recognized this problem: "[E]fforts are underway to establish if readily available cells in humans, such as peripheral lymphocytes or buccal cells, can be used as predictors of adverse responses in tissues that are targets for adverse outcomes such as cancer, and reproductive and developmental effects." EPA \textit{Draft Genomics Task Force White Paper}, \textit{supra} note 299, at 36.
\item \textsuperscript{310} Marchant, \textit{supra} note 298, at 10086. If a safety factor approach is used, something less than the customary ten-fold safety factor may be warranted in some cases:
\begin{itemize}
\item If EPA does determine that changes in gene expression is an 'adverse effect' in a particular case, the next question is whether EPA should adjust the traditional uncertainty factors it uses to calculate the RfC or RID. . . . The standard set of uncertainty factors that EPA applies to calculate an RfD or RfC do not take into account the severity of the adverse effect that defines the LOAEL. EPA has occasionally applied on a case-by-case basis a reduced overall uncertainty factor when the relevant 'adverse effect' is of low severity, such as minor irritation lesions in the nasal cavity after inhalation of a chemical, but there is no general requirement for such an adjustment in the IRIS methodology.
\end{itemize}
\textit{Id.}
\item \textsuperscript{311} A significant barrier to toxicogenomics is a lack of standardization in microarrays and related technologies, and techniques for data analysis. EPA \textit{Draft Genomics Task Force White Paper}, \textit{supra} note 299, at 4.
\item \textsuperscript{312} \textit{Science Policy Council}, \textit{supra} note 301, at 2.
\end{itemize}
decisions,” the agency indicated that “EPA will consider genomics information on a case-by-case basis.”313

2. Arguments for Defining Gene Expression Changes as Adverse Effects

Although there are many barriers to treating gene expression changes as adverse effects, there are several compelling reasons for doing so. First, as Lead Industries acknowledged, the distinction between clinical and subclinical effects may not have any basis in terms of human health consequences:

[T]he clinical/subclinical distinction has little to do with the question whether a particular effect is properly viewed as adverse to health. Rather, the distinction pertains to the means through which the particular effect may be detected: observation or physical examination in the case of clinical effects, and laboratory tests in the case of subclinical effects. Thus describing a particular effect as a ‘subclinical’ effect in no way implies that it is improper to consider it adverse to health.314

This point gains added currency given the potential predictive capacity of gene expression data.315 Moreover, accounting for the prognostic significance of early genetic responses is intuitively appropriate for environmental standards based on risk and thus precautionary in nature. As the Lead Industries opinion emphasized, “expert medical testimony in the record confirms that the modern trend in preventive medicine is to detect health problems in their ‘subclinical’ stages, and theretoon to take corrective action.”316 By the time overt physical signs are detectable, the problem may be beyond the point of remedy. As one commentator noted, “[I]dentifying the moment when disease is clinically detectable does not help in identifying the moment when the benefits of risk regulation begin . . . . From a preventive perspective, the moment when a disease becomes clinically detectable is beside the point.”317

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313. Id. EPA’s Genomics Task Force similarly has noted that “[l]inking genomics changes to adverse outcomes represents a significant research challenge that must be addressed before genomics data can provide information essential to the support of risk assessment and regulatory decision making.” EPA Draft Genomics Task Force White Paper, supra note 299, at 40.

314. Lead Indus. Ass’n, Inc. v. EPA, 647 F.2d 1130, 1158 (D.C. Cir. 1980).

315. According to one commentator, “[g]ene expression profiling using DNA microarrays . . . offers a tool of unprecedented power for understanding and predicting the body’s response to toxic exposures.” Marchant, supra note 298, at 10089.

316. Lead Indus. Ass’n, 647 F.2d at 1158. Lead Industries noted that in an age of rapidly evolving science, EPA is not required to show that an effect is “clearly harmful” to health but rather can follow the public health practice of acting prior to the appearance of clinical symptoms. Id. at 1153-55 & n.51.

317. Lisa Heinzerling, Environmental Law and the Present Future, 87 Geo. L.J. 2025, 2059 (1999). Although these observations were made outside the context of genetics, the availability of new genomic information will make these considerations more pressing: “[F]or many diseases, most prominently cancer, the moments of risk reduction and disease prevention long precede our ability to detect the disease itself.” Id. at 2055. “Where one’s purpose is preventive, as in environmental law, the
This preventive aspect will become increasingly important when gene therapies and other techniques for early intervention become available in the future.\textsuperscript{318} Moreover, as with the identification of new kinds of sensitive subgroups,\textsuperscript{319} it may be imprudent or contrary to law for regulators to ignore newly discovered health effects. For example, the Clean Air Act specifies that the NAAQS must be based upon scientific documents or air quality criteria that "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such pollutant in the ambient air."\textsuperscript{320} Thus, ignoring subclinical but identifiable health effects may be both unwise from a policy perspective and in conflict with statutory mandates.

3. Recognition of a New Scientific Era

The implications of the changing science are reflected in two American Thoracic Society statements on the adverse effects of air pollution. Despite precedent established by \textit{Lead Industries} in 1980, the Thoracic Society's 1985 statement reflected the customary approach and based the distinction between adverse and nonadverse health effects on medical considerations, or clinical symptoms.\textsuperscript{321} The statement defined adverse respiratory health effects as "medically significant" physiologic or pathologic changes generally evidenced by one or more of the following: (1) interference with the normal activity of the affected person or persons, (2) episodic respiratory illness, (3) incapacitating illness, (4) permanent respiratory injury, and/or (5) progressive respiratory dysfunction.\textsuperscript{322} However, the society revised its statement in 1999 as new endpoints of relevance are the increase in risk and the initiation of disease, not the presence of clinically detectable disease." \textit{Id.} at 2061. Heinzerling argues that traditional definitions of the latency period—defined as the interval between the first exposure to a harmful stimulus and the appearance of clinically diagnosable disease—are misplaced. She urges recognition of the "true latency period"—the interval following disease induction but preceding clinical symptoms—"the time during which a process of disease is underway but invisible." \textit{Id.} at 2053. While cancer is the most obvious example of a disease with a long latency period, many other slow-developing diseases, such as asbestos-related respiratory disease, share this characteristic.

\textsuperscript{318} Since the 1970s, there has been a trend toward preventive medicine. One commentator in the medical field has noted that new genetic techniques already are moving medicine closer to a "predict and prevent" strategy, as opposed to the classical reliance on treatment of clinical symptoms. Early intervention is not only preferable from the patient's perspective, but "the ability to diagnose diseases early is a powerful cost-containment tool as well." See Churchill, \textit{supra} note 265, at 175.

\textsuperscript{319} See discussion \textit{supra} Part I.


\textsuperscript{321} American Thoracic Society, \textit{supra} note 22, at 669-70.

\textsuperscript{322} American Thoracic Society, \textit{supra} note 274, at 666. Recognizing the difficulty of making these distinctions, the statement did note, however, that "[p]erceptions of 'medical significance' and 'normal activity' will differ among physicians and among patients or subjects and will depend greatly on individual circumstances . . . ." \textit{Id.} It also noted that "selection of a point on a dose-response curve that separates a medically significant from a medically insignificant effect may be difficult." \textit{Id.}
scientific findings “raised questions as to the boundary between adverse and nonadverse in considering health effects of air pollution”\textsuperscript{323}

These new findings reflect improved sensitivity of research approaches and the application of biomarkers that can detect even subtle perturbations of biologic systems by air pollutants.\ldots. Increasingly accurate methods for exposure assessment have increased the sensitivity of epidemiologic data for detecting evidence of effects\ldots. Toxicologic studies have also gained in sophistication through incorporation of more sensitive indicators of effect and the careful tracing of the relationship between exposure and biologically relevant doses to target sites, which may now be considered at a molecular level.\textsuperscript{324}

The 1999 statement emphasized that, since 1985, the concept of biomarkers had been formalized and that:

\textquote{[A] continuously increasing number of candidate indicators of exposure, effect, and susceptibility have been developed\ldots. It is now possible to detect very early, or initiating phases of responses at the molecular level\ldots. The progressive development of genetic assays and understanding of the human genome have provided numerous candidate markers of both effects and susceptibility.} \textsuperscript{325}

Although the focus on clinical symptoms is still the norm, as reflected in EPA’s argument in \textit{American Trucking}, the American Thoracic Society’s 1999 statement concluded that the continued development of biomarkers is important “because of their considerable potential not only for detecting the adverse effects of air pollution exposure, but also for aiding the determination of the types and levels of response that should be considered adverse.”\textsuperscript{326}

Once a growing number of genetically sensitive subpopulations are identified, as discussed in Part II, and science uncovers and validates a growing number of markers of effect, as discussed here, it may become more difficult to support scientifically the failure to protect newly identified groups against earlier evidence of harm. As with the identification of genetically sensitive subgroups, the identification of early genetic and other molecular events that could qualify as “adverse effects” may make the

\textsuperscript{323} American Thoracic Society, \textit{supra} note 22, at 665.
\textsuperscript{324} \textit{Id.}
\textsuperscript{325} \textit{Id.} at 669.
\textsuperscript{326} \textit{Id.} at 670. However, the committee cautioned that validation is essential before these biomarkers can be used in a regulatory setting:

\textquote{Few of the rapidly growing list of candidate biomarkers have been validated sufficiently that their responses can be used with confidence to define the point at which a response should be equated to an adverse effect warranting preventive measures. The committee cautions that not all changes in biomarkers related to air pollution should be considered as indicative of injury that represents an adverse effect.}

\textit{Id.} at 672.
concept of a single safe threshold even more difficult to justify. Notably, the definitions of "public" and "health" are interrelated: the identification of sensitive groups may vary depending upon the health effect considered. The classification of changes in gene expression as adverse effects could modify substantially the risk measures upon which regulators depend. As one scientist has noted, "The pressure will be on to ignore such data and their consequences or regulate at lower-dose levels." EPA will be required to struggle with this problem in the years to come.

IV
REDEFINING REGULATION?

In this Article, I have suggested that a transformation in the science underlying environmental law and regulation could challenge current approaches for protecting the public against environmental risks. Developments emerging in the 1980s and fueled by the introduction of new technologies in the 1990s are enabling progressively fine-tuned observations of the effects of toxic chemicals on the body, and the role of genetic makeup in modifying toxic effects.

Toxicogenetics and toxicogenomics are still in their infancy, but they are developing quickly. Many questions remain as to the future reliability of genetic and other molecular biomarkers as indicators of susceptibility, measures of exposure, and predictors of disease. Although it is premature to overstate the power of these new technologies, it is similarly premature to underestimate them. Only when these fields mature will we be positioned to fully appraise their capabilities and limitations. One indisputable fact is that research is identifying putative new biomarkers at a rate inconceivable in the past. The new generation of candidate biomarkers will call into question current estimates of individual and public health risk attributable to toxic exposure.

327. Recall that the legislative history of Clean Air Act section 109 notes that "ambient air quality is sufficient to protect the health of such persons [particularly sensitive citizens] whenever there is an absence of adverse effect on the health" of a representative sample of such persons. S. REP. No. 91-1196, at 10 (1970). As described by Robert Friedman in a report for the Conservation Foundation, an EPA study on the initial ozone standard showed experts choosing many different groups as the "most sensitive," depending on the health effects under consideration. FRIEDMAN, supra note 123, at 7. For example, when "reduced pulmonary function" was the health effect under consideration, patients with asthma and emphysema were among the most sensitive populations. Id. (quoting U.S. Environmental Protection Agency, A Method for Assessing the Health Risks Associated With Alternative Air Quality Standards for Ozone 4-5 (July, 1978)). For reduced resistance to bacterial infection, young children were considered the most susceptible. Id. at 7-8 (quoting U.S. Environmental Protection Agency, supra at 4-11 (July, 1978)). This interplay between sensitive populations and health effects suggests that recognition of gene expression changes or other molecular markers of effect could potentially reveal the presence of sensitive populations that otherwise might not be acknowledged, including groups defined on the basis of inherent genetic traits.

328. Telephone conversation with Dr. Dale Hattis, PhD, Research Professor, risk modeling, Clark University, Worcester, Mass. (July 15, 2004).
Part IV illustrates how new health risk data generated by genomic technologies may accentuate core controversies surrounding the treatment and use of risk information in regulatory standards. While it can be argued that incorporation of the new data will lead to regulatory delay and paralysis, there are compelling arguments for its inclusion. The genomic revolution is likely to invigorate ongoing debates about the relative merits of "science-based" and "science-blind" regulatory approaches. Importantly, this fundamental debate may help reveal the structural elements of new approaches that could be considered in the future. I emphasize the importance of promoting and safeguarding regulatory instruments that provide incentives to generate and evaluate the new information, allowing us to make the right choices down the road. At this point, we do not fully understand the nature of the roadblocks ahead, nor do we appreciate the solutions that the science may provide. This Part explores selected features of the major regulatory approaches, and it hints at ingredients for future models. Strategies tailored to vulnerable groups also are considered.

Regardless of whether the new information ultimately is incorporated into final rules, data that can be validated should be given appropriate consideration at some stage in the standard-setting process. It is already clear that the fundamental ethical and policy questions raised by the new science will extend beyond agency technical expertise. Congress and the public, along with regulators and new kinds of expert consultative bodies, will need to engage in an important societal dialogue on the definition of public health risk and the appropriate parameters of governmental protection in the genomic age.

A. Genomics, Risk, and the Science Paradox

The continuing proliferation of health risk information at the molecular and genetic level will bring to the fore one of the core dilemmas in environmental regulation. Experience has shown that the enormous informational demands imposed by science-dependent regulatory standards may overwhelm the rulemaking process to the extent that paralysis ensues, with the result that many harmful chemicals and pollutants are left unregulated. Simpaly stated, more science can lead to less regulation. The risk assessment enterprise is complicated by scientific and legal uncertainty, data gaps, assumptions, and policy choices that open the door to valid scientific challenges, as well as internal and external efforts to obfuscate and delay the regulatory effort. This "synergy of uncertainties"
may result in a system that focuses on relatively few substances with regulations that are “an inch wide and a mile deep,” regulating “both too little and too much at the same time.” These features of risk regulation have led some commentators to advocate regulatory standards that are “science-blind,” either as wholesale replacements of science-based standards or as first-generation strategies, under the theory that it is preferable to regulate more chemicals more quickly than to exhaust scarce resources on a targeted few.

Ironically, however, we may need more science, not less, to remedy some of the problems accompanying risk-based regulation. EPA suffers from a paucity of good health risk data—the number of chemicals for which basic toxicity and exposure data are unavailable is striking.

The market and private law disincentives against producing health risk information are well recognized, as are incentives to resist knowledge of toxic decision making relating to the management of toxic risks); see also Wendy Wagner, Commons Ignorance: How the Environmental Laws Have Failed Us, 53 DUKE L.J. (forthcoming 2004) (discussing recent “good science” reforms and data access laws that impede the federal government’s development of scientific information).

Federal programs to reduce risks from toxic substances have become paralyzed by a synergy of uncertainties. Scientific uncertainty about health effects heightens legal uncertainty about ambiguous statutes, perpetuated by political uncertainty about risk management goals. Formulas that lawyers think provide clear guidance—such as “protect the public health” or “acceptable risk”—instead highlight the importance of social context, and hence political values, in each unique risk situation.

Id. at 271.


Technology-based standards are sometimes referred to as “science-blind,” as risk information generally is not a factor in setting permissible emissions levels. These levels are calculated based instead on what pollution sources can achieve using available technology. See discussion infra.

Strong arguments have been made in support of this position. See, e.g., Babich, supra note 130. See also discussion accompanying notes 364-69 infra.

An EPA report concluded that approximately half of the chemicals produced in the highest volumes did not meet the standards of the Organization for Economic Cooperation and Development (OECD) for toxicity testing. U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, What Do We Really Know About the Safety of High Production Volume Chemicals?, 22 CHEM. REG. REP. (BNA) 261 (1998). See generally ENVIRONMENTAL DEFENSE FUND, TOXIC IGNORANCE (1997) (concluding that basic toxicity data meeting OECD requirements were unavailable for seventy-one percent of high production volume chemicals); NATIONAL SCIENCE BOARD, NATIONAL SCIENCE FOUNDATION, DRAFT REPORT OF THE NSB TASK FORCE ON THE ENVIRONMENT (1999) (recognizing the severe undersupply of environmental data relative to needs).
exposure and effects.\textsuperscript{337} This unfortunate state of affairs may be remedied, at least in part, by more scientific data, better targeted to the issues at hand.\textsuperscript{338} As one commentator has observed, “[t]he supply of this information [toxicity and exposure data] guides the course of research and chemical regulation and its scarcity shapes the entire system.”\textsuperscript{339} Hence, one element of the effort to reduce regulatory paralysis and better serve the environmental regulatory mission would be to generate more and better science.

In light of these competing considerations, I suggest that we restate the core dilemma: whether there is “too much science in environmental law”\textsuperscript{340} or, conversely, not enough. To limit the role of science, or to create incentives to produce it—which is ultimately better for the public’s health?\textsuperscript{341} Paradoxically, both goals may be desirable from the standpoint of enhancing regulatory credibility and reducing regulatory gridlock.

1. Toxicogenetics and Toxicogenomics: Amplifying the Science Paradox

Toxicogenetics, toxicogenomics, and related disciplines will accentuate this central paradox by sharpening both critiques. The enormous complexity of the new science and attendant policy questions could exacerbate existing problems of regulatory delay or paralysis. Unless molecular and genetic clues are validated as predictors of susceptibility or established to have cause-effect relationships in the disease process, they will present additional problems of scientific uncertainty that will further complicate regulatory choices. In addition to the policy questions discussed throughout this Article, the new science is producing a new generation of probabilistic data for which quantification may be difficult, controversial, and in some cases, impossible. Numerous methodological and interpretational issues—including those involving research protocols and validation procedures—will be subject to dispute. There is a danger that the inevitable procession


\textsuperscript{338} Lyndon, supra note 337, at 1801.

\textsuperscript{339} Id.

\textsuperscript{340} Babich, supra note 130.

\textsuperscript{341} As one commentator has noted, “[t]he basic problem of toxic substances is an information problem.” Applegate, supra note 333, at 311. “[S]carcity of information needs to be addressed, either by generating more or by requiring less information.” John S. Applegate, \textit{A Beginning and Not an End in Itself: The Role of Risk Assessment in Environmental Decision-Making}, 63 U. CIN. L. REV. 1643, 1649 (1995).
of science-contesting lobbying and litigation may lead to further ossification of the rulemaking process and greater regulatory paralysis.

However, the new information has the potential to resolve at least some of the uncertainties in risk assessment. \(^{342}\) Empirically derived information about how chemicals behave inside the body—and how differential susceptibility to disease affects those mechanisms—could in some cases supplant uncertainty factors or at least help generate more accurate default assumptions. \(^{343}\) A better understanding of the mechanisms by which chemicals influence disease could have strong implications for risk assessment. The new techniques could reduce reliance on experimental animal data or allow for better extrapolations from animal data to estimates of human chemical response. \(^{344}\) Direct biological measurements of exposure could reduce reliance on traditional indirect methods, which require modeling or monitoring of the ambient environment and significant guesswork as to actual human exposure levels. \(^{345}\) If molecular and genetic changes can reliably be associated with exposure to particular chemicals, they could help identify exposed persons and possibly measure the degree of exposure. \(^{346}\) Moreover, this fine-grained information about genetic disposition, biochemical reactions, and molecular mechanisms eventually may allow us to understand something about the synergistic effects of multiple pollutants—a vast topic about which our current regulatory scheme, which regulates largely on a pollutant-by-pollutant basis, is virtually ignorant. \(^{347}\)

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342. EPA's Draft Genomics Task Force White Paper has recognized the potential of genomics technologies to reduce some of the uncertainties in risk assessment:

Enhancing understanding of the molecular mechanisms of toxicity may greatly reduce the uncertainty of extrapolations used in the current risk assessment process. Further, genomics technologies may enhance the development of more sensitive and cost-effective methods for toxicity screens and tests and may ultimately lead to the reduction, refinement, or replacement of more complex and costly standard tests for human and wildlife species.


344. See, e.g., Smith, supra note 3, at 282.

345. See, e.g., DeCaprio, supra note 25, at 1839.

346. Id.

347. EPA's Genomics Task Force has identified the potential value of genomics techniques for assessing the health effects of chemical mixtures:

Exposures of human and wildlife populations to environmental contaminants generally involve complex mixtures of chemicals, rarely individual chemicals. Although there have been some efforts to address responses to both simple and complex mixtures, much of the past and current research of the Agency has addressed the risk from exposures to single chemicals. Clearly, addressing the overall toxicological responses to mixtures is a complex problem that may require approaches different from those used for single chemicals. Given the charge to the Agency to increase its focus on research into the effects of mixtures, it is important to assess how genomics techniques might aid in meeting this need.

2. Rationales for Considering New Genomic Information

Incorporation of the new data into the standard-setting process—at least as a consideration—could be justified under both entitlement and utilitarian rationales. Some scholars have argued on ethical grounds that all citizens have the right to protection against involuntary exposure to environmental hazards, and others have framed this as an equal protection right. The growing availability of more nuanced and individualized health risk data raises the question whether it is morally appropriate to leave vulnerable groups and individuals unprotected once science has identified them. As EPA’s experience in setting the NAAQS has illustrated, failure to protect vulnerable groups and individuals becomes more difficult when lives are no longer statistical.

Incorporation of this new data also may prove to be justified on utilitarian grounds. This information may save lives by stimulating development of preventive measures and treatments for diseases for which chemical exposure plays a significant role. As screening and testing become cheaper, monitoring programs and new pharmaceuticals could lead to targeted interventions to prevent or treat disease in more cost-effective ways. Disease prevention for average and vulnerable groups alike may result in considerable reductions in health care costs for the nation. Further, a point that is often overlooked is that susceptible groups may act as “canaries in the coal mine”—sentinels that reveal latent but incipient adverse effects in the population at large. Hence, protecting susceptible groups may be more integral to the traditional public health mission than is sometimes recognized.

It is perhaps easiest to visualize how the new scientific information may support claims for more stringent environmental protection. However, a better understanding of the mechanisms of toxicity at the genetic and molecular levels also may enable more finely calibrated risk assessments, allowing regulators to substitute hard data for overly protective risk assumptions and ultimately to develop more cost-effective regulations. The new generation of health risk information thus may serve the goals of two political trends that have crystallized in the past two decades. While many commentators have called for better risk prioritization and cost accounting

349. Cranor, supra note 199, at 245.
350. Moreover, these immutable genetic traits may be present in groups that may be susceptible for other reasons (for example, children, asthmatics, the elderly), substantially compounding their risk. Hence, emerging technologies may allow us to more precisely pinpoint the most susceptible or adversely affected members of the population.
351. For example, prevention of only 20% of cancers in the U.S. would result in an estimated 200,000 fewer cases diagnosed annually, at a savings of $21.4 billion. Perera, supra note 75, at 602 (1999 estimates).
in environmental regulation, others have advocated more explicit consideration of differently situated subgroups and individuals whose needs may diverge from those of the population at large. The debate over the place for genomics in environmental regulation may reveal many areas of convergence in these perspectives, and may further the various normative goals embodied in our environmental regulatory scheme.

As a practical matter, if the government fails to account for the new science, citizens are likely to demand its consideration. As the public gains a better understanding of the role of genetic traits in moderating toxic effects, it will likely insist that the new information be given appropriate consideration in a system designed to address risks ex ante. As the current

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352. See, e.g., Matthew D. Adler & Eric A. Posner, Rethinking Cost-Benefit Analysis, 109 Yale L.J. 165, 167-68 (1999) (providing "a qualified defense of the use of [cost-benefit analysis] by administrative agencies," including EPA, but recommending modifications that may be necessary under some circumstances to ensure compatibility with distributive justice and other moral values); Robert W. Hahn, Sheila M. Olmstead & Robert N. Stavins, Environmental Regulation in the 1990s: A Retrospective Analysis, 27 Harv. Envtl. L. Rev. 377, 381 (2003) ("An efficient policy enacts a level of pollution control or rate of resource extraction that maximizes the difference between social benefits and social costs. Assessing the efficiency of policies requires benefit-cost analysis.").


354. In Rights Against Risks, Chris Schroeder has described the two major traditions in American jurisprudence and political theory and has illustrated how these traditions dominate the risk regulation field. These traditions include the utilitarian tradition of Jeremy Bentham and John Stuart Mill, carried forward into modern policy discussions by welfare economics, cost-benefit analysis, and the law and economics movement, and the “rights” tradition of John Locke and Immanuel Kant, more recently articulated and augmented by scholars as diverse as John Rawls, Robert Nozick, and Ronald Dworkin. Christopher Schroeder, Rights Against Risks, 86 Colum. L. Rev. 495 (1986). Schroeder has suggested that health-based standards such as the NAAQS, which do not permit cost-benefit balancing, represent a vindication of rights and a refutation of utilitarian theory: “Congress has also often rejected cost-benefit balancing in enacting environmental laws. In substantial measure, the legislation that provides much of this country’s risk regulation refutes the view that environmental lawmaking is grounded in utilitarian theory. Instead, the legislation seems to vindicate ‘rights.’” Id. at 506. Others have pointed to the predominance of interest-balancing discourse and utilitarian principles in environmental law. See, e.g., Sheila Foster, Meeting the Environmental Justice Challenge, 30 Env’tl. L. Rep. 10992, 10997 (2000). In the environmental justice context, scholars have highlighted the conflicting premises of environmental law and civil rights law, and the consequent difficulty of incorporating civil rights principles into the majoritarian environmental regulatory paradigm:

The overarching strategy of environmental protection in this country has been based not on a standard of justice that assumes government regulation should be directed to improving the conditions of some particular members of society but on utilitarian principles—the greatest good for the greatest number of people. These utilitarian principles are incorporated into environmental policies through such tools as benefit-cost analysis and, more recently, comparative risk. The potential conflict between environmental justice and utilitarianism will not be easy to reconcile.

population-based public health paradigm confronts a new generation of technologies designed to measure environmental susceptibility, exposure, and effects on a more individualized basis. EPA's traditional distinction between public and individual health will face more frequent challenges.

B. Risk Information and Regulatory Design: Implications of Genomics

When considering whether there is too much or too little science in environmental law, one should recognize that the answer may be yes to both queries. This may call for closer attention to regulatory arrangements that recognize practical and resource constraints while providing the necessary incentives to gather, evaluate, and potentially incorporate this information in a meaningful way. A brief taxonomy of the basic regulatory approaches is helpful as a first step in thinking about how different regulatory structures might best accommodate the new genomic information.

1. Statutory Standards and Triggers

The U.S. system of public environmental law is an amalgam of normative aspirations and regulatory tools. Some statutes, including the Clean Air Act and the Clean Water Act, employ fundamentally different approaches in different statutory sections. Within the domain of conventional approaches to pollution control, the current universe of statutory standards can be divided roughly into five basic types: health-based standards, technology-based standards, tiered approaches, risk-benefit balancing standards, and health-based standards limited by feasibility considerations. With the partial exception of the pure technology-based standard, all these approaches incorporate public health risk information at some stage and to some degree, and hence will be affected by the new genomic information.

Moreover, all pollution control statutes include a statutory “trigger” or “predicate” that establishes the evidentiary burden an agency must meet in order to regulate a toxic substance or other hazard. For instance, before EPA can regulate a contaminant in public drinking water, the Safe Drinking Water Act requires the agency to make a finding that the substance “may have an adverse effect on the health of persons” and that it is likely to occur in drinking water systems “with a frequency and at levels of

355. As one scientist has noted, “a shift from population-based to an individual-based assessment of hazard is likely to evolve.” DeCaprio, supra note 25, at 1846.

356. “A most striking feature of modern governmental regulation is that statutes reflect our wide disagreement over what constitutes a regulable risk. Statutes employ standards for regulatory action ranging from prohibitions of actions that impose unreasonable risk to requirements that human health be protected with an ample margin of safety.” Schroeder, supra note 354, at 496.

357. See, e.g., Percival et al., supra note 125, at 344-45, fig.4.1; Sidney A. Shapiro & Robert L. Glicksman, Risk Regulation at Risk 31-45 (2003).
public health concern. 358 Prior to regulating the manufacture or use of a toxic chemical under the Toxic Substances Control Act, EPA must have a "reasonable basis to conclude" that the chemical presents or will present an "unreasonable risk of injury to human health or the environment." 359 Regardless of the type of statutory standard in question—technology-based, health-based, tiered, balancing, or feasibility-limited—new information on genetic susceptibility and early health effects could modify these initial risk estimates and dramatically increase the number of chemicals and pollutants subject to regulation. 360 This may suggest a role for the new data in priority setting, 361 and a possible role for Congress or new expert

358. Safe Drinking Water Act, § 300g-1(b)(1)(A)(i)-(ii), 42 U.S.C. § 1412(b)(1)(A)(i)-(ii) (2000). EPA may regulate each such contaminant if, in the agency's judgment, the regulation "presents a meaningful opportunity for health risk reductions for persons served by public water systems." Id.


360. The new genomic information also may have implications for alternative regulatory approaches based on information disclosure, or for burden-shifting approaches whereby producers of toxic substances may avoid regulatory obligations by showing that exposure to their products poses no significant risk. As an example of the former approach, the Emergency Planning and Community Right to Know Act, 42 U.S.C. §§ 11-1-11050 (2004), does not impose restrictions on pollutant releases but instead requires manufacturers to report publicly their release of toxic chemicals. This strategy is premised on the notion that public disclosure will lead to internal or public pressure to limit routine release of pollutants. EPA compiles annual reports of pollutant releases into a Toxic Release Inventory (TRI), see, e.g., Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, 2002 Toxic Release Inventory (TRI) Public Data Release Report, EPA 260-R-04-003 (June 2004). To add a chemical to the TRI list, EPA must find sufficient evidence that the pollutant causes or may cause "significant adverse human health effects" or environmental effects. 42 U.S.C. § 11023(d)(2) & (3) (2000). The new genomic information could affect this threshold finding.

Genomic data also may enter into the calculation of "safe harbors" under California's Proposition 65, Safe Drinking Water and Toxic Enforcement Act of 1986, CAL. HEALTH & SAFETY CODE §§ 25249.5-13 (West 2003). The program imposes warning requirements and discharge limitations on users and producers of toxic substances unless they can show that "the exposure poses no significant risk." Id. at § 25249.8(a); see also David Roe, Ready or Not: The Coming Wave of Toxic Chemicals, 29 ECOLOGY L.Q. 623, 631-33 (2002). An implementing regulation defines "significant risk" as a 1-in-100,000 risk of cancer based on a lifetime of exposure. This figure does not account for variations in susceptibility, CAL. CODE REGS. tit. 22, § 12721(b) (2000). New genomic information could affect this threshold finding.

361. EPA's Genomics Task Force has expressed interest in using genomics technologies to set priorities among chemicals for further testing:

There are over 80,000 chemicals currently listed in the Toxic Substances Control Act (TSCA) Inventory. . . . Most of these chemicals have not undergone extensive toxicological testing, and there is sufficient information to allow a thorough evaluation of risk for only a fraction of them. Nevertheless, EPA program and regional offices need to make a variety of decisions about these chemicals. These decisions may include prioritization of the chemical(s) for further evaluation or a decision that no further research is needed . . . . However, there currently is no rapid, comprehensive method for prioritizing which chemicals or microbes should be tested . . . . Genomics technologies hold the promise of providing more mechanistic, molecular-based data for risk-based prioritization of these stressors. In addition, these technologies are likely to offer more efficient and low-cost alternatives to the tests EPA currently relies on for prioritization.

bodies in deciding which chemicals and pollutants should be subjected to
the most information-intensive risk-based reviews.

2. Two Poles of a Debate: Technology-Based and Health-Based Standards

The accentuation of the science paradox brought about by genomics is
likely to invigorate the debate over the relative merits of risk-based and
technology-based standards. The influx of new genomic data will bring
into contrast the former approach’s reliance on health risk data, and the
latter approach’s constraints on the use of such data in establishing permissible pollution limits. Importantly, this elemental debate may help reveal
the building blocks for new hybrid approaches that could be considered in
the future.

One might characterize health-based and technology-based standards
as opposing philosophical poles in the domain of conventional approaches
to pollution control. Although in evaluating the pros and cons of different
regulatory strategies it is useful to work from these two poles, many
environmental standards combine the two approaches.

Health-based standards—the NAAQS being the prime example—highlight the issues presented by the new genomic information most vividly. By excluding countervailing considerations such as compliance costs and technological feasibility from the initial standard-setting process and focusing solely on risk to public health, the NAAQS are designed to be “technology-forcing,” potentially stimulating the development of technologies unimaginable at the standard-setting stage. Because the health-based approach presumably is limited to considerations of public health risk, the policy choices posed by the new genomic information will be the most challenging in this context.

Technology-based standards present the opposite proposition. Once
the trigger or predicate for regulation is met, these standards may be blind
to risk information. Instead of requiring regulators to establish “safe” levels
of exposure for pollutants in the ambient environment, technology-based
standards focus on emissions levels that pollution sources can practically
achieve using available technology. Because risk to public health is not a
requisite factor in selecting permissible emissions levels under technology-based standards, new genomic information may be least relevant for statutory schemes of this nature.

Supporters of technology-based standards point to the dearth of reli-
able risk information, the relative ease of implementation compared to


363. As noted above, however, health risk information may come into play in deciding which chemicals are to be regulated using technology-based controls.
risk-based approaches, the reduced potential to bring about untoward economic consequences, and, in some cases, the capacity to stimulate new technology considerably and even to surpass risk-based goals. Furthermore, the difficulty in dealing with information-intensive risk-based standards leads to long delays in implementation, with the aforementioned result that many harmful chemicals and pollutants remain unregulated.

EPA’s experience in setting standards for hazardous air pollutants under the original section 112 of the Clean Air Act, which specified a pure health-based approach, is an often-cited example.

Critics of technology-based standards argue that they are inefficient and insufficiently technology-forcing as compared to health-based

364. See, e.g., Wendy E. Wagner, The Triumph of Technology Based Standards, 2000 U. Ill. L. Rev. 83-94 (2000). While acknowledging that promulgation of technology-based standards is not easy, and that such standards routinely attract legal challenges, Wagner notes that the volume of technology-based standards promulgated in the last ten years reflects a practical advantage over risk-based controls. Moreover, technology-based standards may function well as base innovations that can be fine-tuned with a variety of secondary regulatory strategies. Id. at 105-07.


366. Some technology-based standards may encourage development of new technologies more than is commonly presumed. For example, section 112(d) of the Clean Air Act directs EPA to promulgate emissions standards for air toxins for existing sources that are at least as stringent as the “average emission limitation achieved by the best performing twelve percent of the existing sources” or, if there are fewer than thirty sources in an industrial category or subcategory, are based on the “average emission limitation achieved by the best performing five sources.” 42 U.S.C. § 7412(d)(3)(A) & (B) (2000). For new sources, the standards must be at least as stringent as the average emissions achieved by the best-controlled sources in the same category. Id. Moreover, most technology-based standards take the form of quantitative pollution emission limits and thus permit industry to choose how best to meet the standards. This choice may include developing new pollution control technologies that can meet the emission limits more effectively or less expensively than existing technologies.

367. Babich, supra note 130, at 130 (“For some chemicals, a pure technology-based standard might be more stringent than a risk-based standard—requiring pollution reduction to continue past a point at which all known risks had been abated.”).

368. See, e.g., Reitze, supra note 134, at 128; see also Bradley C. Karkainnen, Information as Environmental Regulation: TRI and Performance Benchmarking, Presursor to a New Paradigm, 89 Geo. L.J. 257, 263-70 (2001) (discussing the significant informational barriers to standard setting under both the technology-based and health-based approaches, and resultant dearth of regulatory standards for many harmful chemicals).

369. The 1990 Clean Air Act amendments replaced the previous risk-based approach for regulating hazardous air pollutants with a predominantly technology-based approach based on “maximum available control technology” or “MACT.” 42 U.S.C. § 7412(d). See Reitze, supra note 134, at 134-38. Prior to the 1990 amendments, section 112 mandated pure health-based standards that would “provide an ample margin of safety to protect public health,” without first establishing technology-based controls. Id. at 127. However, confronted with the task of setting risk-based standards for hazardous air pollutants, the agency “froze up—issuing standards for only seven pollutants, compared with the 189 that Congress listed for regulatory action in the 1990 Clean Air Act Amendments.” Babich, supra note 130, at 133. The congressional listing of 189 hazardous air pollutants was a direct response to agency inaction. It should be noted, however, that the experience of setting risk-based standards under the original section 112 may not be entirely generalizable. Some hazardous air pollutants are quite localized and thus epidemiological data may be more difficult to obtain than for more pervasive pollutants such as those regulated under the NAAQS. Also, lack of political will may have contributed to regulatory inaction prior to the 1990 amendments.
Failure to revise these standards may “freeze” prevailing technology and undermine incentives to innovate, and the routine application of facility-specific variances may further aggravate this problem. Even where technology-based standards reflect state-of-the-art controls, such standards may allow pollution to reach levels that would not meet a reasonable definition of acceptable risk. Finally, a point often overlooked is that technology-based standards are inapplicable in many settings, including pesticide registration, food quality protection, and regulation of the manufacture and commercial use of toxic chemicals.

At least in the short term, it is unclear whether the availability of new genomic data will help promote confidence in risk-based environmental regulation, or, perhaps counterintuitively, lead to increased reliance on technology-based controls. On the one hand, as noted, the availability of increasingly fine-tuned and biologically derived data could help reduce some of the major uncertainties in risk assessment. Enhanced accuracy could result from reduced reliance on animal data, increased reliance on direct biological measurements of exposure, more accurate measurement of low-dose effects, and a correlative reduction in the use of arbitrary defaults. However, the inundation of new and highly complex information may prove so overwhelming that Congress retreats to the relative clarity and simplicity of what is technically possible, that is, technology-based standards. Such a step may be particularly seductive in the short term, before the new genomic information is validated.

Despite the many challenges ahead, I suggest that wholesale de-emphasis of risk-based standard setting would be ill-advised: “[A]fter all it is an acceptable level of risk and not best technology per se that provides the most direct measure of what environmental regulation seeks to protect, i.e., human and environmental health.” It would be ironic to discourage risk regulation at a historic moment when increasingly refined risk information is made available in an entirely new dimension. The public health mission might not be fully served if regulators were encouraged to limit the role of science just as scientific information becomes more nuanced and


372. Babich, supra note 130, at 130.

373. Laws governing manufacturing and commercial use of chemicals and pesticides are not amenable to technology-based controls as they do not involve emission limits or cleanup standards. Limits on pesticide residues on food similarly are not amenable to technology-based controls.


375. Marchant, supra note 298, at 10082.
sophisticated. Although much empirical work needs to be done on how best to structure incentives, it would be inappropriate to discourage the production or assessment of this new information before these emerging scientific disciplines are given a chance to mature.

C. The Law's Information-Generating Role

In evaluating the ultimate goal of environmental regulation, it is important to consider the law's role in generating reliable information about heretofore unknown or underappreciated risks: "[T]he task of environmental law is not only to establish the substantive policy and regulatory structures for managing toxic substances, but also to provide the information that the regulatory structures need in order to operate." Thus, the environmental regulatory system can help compensate for a dearth of market and private law incentives to produce public health risk information. This important aspect of environmental law is likely to be promoted by certain regulatory models more than others.

Scholarly attention has focused on various aspects of the information problem in toxics regulation, and many have called for an expanded governmental role in producing much needed data. However, future

376. Applegate, supra note 337, at 298. See also Lyndon, supra note 337, at 1795 ("Just as laws may create entitlements to the use of information, they may also be written to distribute information and to encourage information production.")

377. Much of the literature has focused on market disincentives to information production, and the failure of existing environmental laws to require the production of basic information on the harms polluting activities and hazardous products cause. See infra notes 330, 337. A handful of scholars have focused more generally on the information-generating aspects of different regulatory structures. See, e.g., Applegate, supra note 337, at 308-32 (discussing certain informational advantages of licensing schemes); Lyndon, supra note 337, at 1819-25 (comparing licensing schemes with schemes imposing limitations on chemical use and exposure); Mary L. Lyndon, Risk Assessment, Risk Communication and Legitimacy: An Introduction to the Symposium, 14 COLUM. J. ENVTL. L. 289 (1989); Milton C. Weinstein, Decision Making for Toxic Substances Control: Cost Effective Information Development for the Control of Environmental Carcinogens, 27 PUB. POL'Y 333 (1979). Most of the recent information-related scholarship in the environmental law area has focused on a different topic: the use of information disclosure strategies as alternatives or supplements to conventional regulatory approaches. See, e.g., Karkainnen, supra note 368; William F. Pederson, Regulation and Information Disclosure: Parallel Universes and Beyond, 25 HARV. ENVTL. L. REV. 151 (2001); David Roe, Ready or Not: The Coming Wave of Toxic Chemicals, 29 ECOLOGY L.Q. 623 (2002); Christopher H. Schroeder, Third Way Environmentalism, 48 U. KAN. L. REV. 801 (2000); Cass R. Sunstein, Informational Regulation and Informational Standing: Akins and Beyond, 147 U. PA. L. REV. 613 (1999).

378. See, e.g., Applegate, supra note 337, at 300 ("If market and private law incentives do not produce the information needed to regulate toxic substances effectively, then the government must take a part in doing so."); Daniel C. Esty, Environmental Protection in the Information Age, 79 N.Y.U. L. REV. 115, 144 (2004) (calling for an expanded government role in producing and disseminating health risk information); Lyndon, supra note 337, at 1816 ("The market disincentives to production and obstacles to independent evaluation of private data make public intervention necessary to ensure that accurate data are produced and distributed optimally."); Wendy E. Wagner, The "Bad Science" Fiction: Reclaiming the Debate over the Role of Science in Public Health and Environmental Regulation, 66 LAW & CONTEMP. PROBS. 63, 67 (2003) ("[T]he regulatory system should not only make the most of available science, but should encourage its production.").
scholarship is needed to assess the comparative effectiveness of the information-generating attributes of different regulatory approaches and to understand how risk information is used once it is obtained—a topic of particular relevance in the new genomic era. Regulatory programs may vary dramatically in their ability to generate, obtain, incorporate, and manage health risk information. As the development of a new generation of nuanced—and often controversial—health risk information amplifies the science paradox in environmental law, the need to respond to the information problem becomes more compelling. In this new era, information strategies should be a principal concern.

Ultimately, policymakers may elect to incorporate the new data into environmental standards for some substances while legitimately disregarding it for others. Policymakers should not, however, limit a priori these emerging developments from their deliberations on the grounds that they are too complex or controversial. Regardless of whether the new information eventually shapes final rules, data that can be validated should at least be given a place in the deliberative process.

D. Moving Beyond the Polarized Debate: Integrating the New Science

Attention to the information-forcing attributes of different regulatory structures could allow us to move beyond the bipolar debate between risk-based and technology-based standards, and to focus instead on combinations of regulatory tools that might satisfy the dual goals of providing incentives to generate and evaluate new health risk information without overwhelming the regulatory enterprise. Because the standard-setting procedure is only one, admittedly crucial, element of a multifaceted regulatory program, it would be inappropriate to judge among statutes using this as the sole criterion. This section will briefly identify selected features of the major standard-setting approaches to illustrate how elements of the science paradox are reflected in regulatory design, and to help inform future deliberations on how the regulatory system might best accommodate the new science.

379. See, e.g., Applegate, supra note 337; Lyndon, supra note 337.
380. Various incentives for producing toxicity and exposure data are present in the fields of toxicogenetics and toxicogenomics—due, in part, to the close association with the Human Genome Project. Thus, data will continue to be generated. However, it is important to ensure that EPA is able to obtain relevant data, and to stimulate the development of information tailored to meet the agency’s needs.
381. Prior to the development of the new genomic technologies, Mary Lyndon emphasized the importance of designing laws with informational considerations in mind. See, e.g., Lyndon, supra note 337, at 1795-97.
I. Functional Role of Aspirational Goals: The Safe Drinking Water Act

The standard-setting process of the Safe Drinking Water Act may serve as a partial model of how information on newly identified or under-appreciated health risks—such as those identified by genomics—might inform the regulatory process. An unusual hybrid employing a variety of tools in discrete steps, the Safe Drinking Water Act is an example of the "health-based, feasibility-limited" approach, where health risk information presumptively is considered first, followed by economic and technical feasibility considerations.

The Safe Drinking Water Act creates a two-stage process whereby EPA is first required to specify maximum contaminant level goals (MCLGs) for public drinking water systems based exclusively on public health considerations. The MCLG is to be set "at the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety." The statute then requires the agency to set the enforceable standards, or maximum contaminant levels (MCLs), "as close to the maximum contaminant level goal as is feasible." Notably, the health-based goal is nonlitigable, but EPA's selection of the goal may be questioned by litigants indirectly, as part of a challenge to the final, feasibility-based MCL.

The statutory mandate to set health-based goals as a first step may be important from both a practical and a normative standpoint. As a practical matter, such a requirement may ensure that data about sensitive groups or the full range of potential health effects will receive at least some consideration during the risk assessment process. At the same time, the clear separation of the various steps may promote transparency and fidelity to statutory requirements.

As a normative matter, the hybrid structure of the statute highlights a point generally overlooked: the potential functional importance of aspirational goals in regulatory standards. Aspirational goals frequently are vili- fied in the scholarly literature, especially where they occur as sweeping and unobtainable congressional declarations of policy. However, such goals can play an important functional role, particularly when coupled with more practical constraints in two-stage standard-setting procedures. Because discrepancies between the selected goals and final standards will be evident,
regulators will be called upon to explain the basis for broad departures, thereby promoting transparency and accountability in the standard-setting process. In the future, hybrid statutes could be structured so that significant gaps between the stated goal and the proposed rule would trigger default conditions, such as a shift to a more stringent feasibility standard.\footnote{387}

The Safe Drinking Water Act's mandate to establish pure health-based goals represents an advantage over risk-benefit balancing standards, where the incentive to identify new health risks may be diminished: “Protective goals force inclusion of provision for susceptible populations in risk assessments, an advance over much current practice.”\footnote{388} Moreover, determination of the marginal feasibility of different control options during the second stage of the standard-setting process may be contingent upon the prior analysis of health risks, including risks to sensitive populations:

[T]he question of what is feasible is not a hard and fast concept. To some extent, the limits of feasibility . . . depend on an evaluation of the health risk involved. At some point in the standard-setting process, an incrementally insignificant health benefit, however measured, might not be considered ‘feasible’ in light of the costs to be imposed; similarly, a very significant hazard might justify more costs or technology before the limit of feasibility is reached.\footnote{389}

\footnote{387. For example, feasibility currently is defined in the statute as “feasible with the use of the best technology, treatment techniques and other means which the Administrator finds, after examination for efficacy under field conditions and not solely under laboratory conditions, are available (taking cost into consideration).” 42 U.S.C. § 300g-1(b)(4)(D) (2000). A more stringent feasibility standard might require development of technologies using criteria based on theoretical extrapolations from laboratory results alone. Alternatively, new kinds of monitoring obligations could attach where identifiable populations remained unprotected under the selected standard. This may be particularly relevant in the genomic era, when real-time, high-throughput methods for screening potentially exposed individuals for incipient effects are under development. The idea of requiring obligations to attach in the event of a significant gap between the aspirational and operational standard was suggested to me in conversation with Dan Farber.

388. Cranor, supra note 199, at 241. EPA specifically refers to sensitive populations in a publication discussing the process of setting MCLGs:

These goals take into account the risks of exposure for certain sensitive populations, such as infants, the elderly, and persons with compromised immune systems. These goals are not enforceable levels because they do not take available technology into consideration, and therefore are sometimes set at levels at which public water systems cannot meet.


389. Friedman, supra note 123, at 34. The Occupational Safety and Health Administration's rulemaking record accompanying the standard for workplace exposure to lead provides an interesting parallel in a different statutory setting. The record noted that the selected exposure level of fifty micrograms of lead per cubic meter “is the level which properly balances the questions of feasibility and health effects of lead exposure and most adequately assures, to the extent feasible, the protection of workers exposed to lead. . . . [T]he [chosen level] represents the best intersection between maximization of health benefits and feasibility.” 43 Fed. Reg. 52,963 (1978) (discussed in Friedman, supra note 123, at 34). In issuing a standard for the male sterilant and carcinogen DBCP, OSHA suggested that given the extremely serious nature of the hazard, it would be in the bounds of feasibility}
Notably, the health-based goal may be set at zero for presumed nonthreshold contaminants, while allowing for pragmatic adjustments in the final, enforceable rule. The advantage of such a structure is that it could avoid some aspects of the zero-risk problem encountered in other statutory contexts where the health-based standard is independently litigable. The challenge under this hybrid model, however, is to prevent the process from becoming purely technology driven. Because feasibility constraints have the last say sequentially, they may "swallow" the health-based starting point. Such a consequence would render the more demanding health-based goals functionally irrelevant, thereby diminishing incentives to consider health risk information in a meaningful way.

This problem underscores the importance of structuring the regulatory process in a manner that preserves incentives to gather health risk information, such that the final enforceable standard may indeed be set "as close as is feasible" to the health-based goal. The 1996 Amendments to the Safe Drinking Water Act provided certain incentives by requiring EPA to conduct ongoing studies of sensitive subpopulations "that may be at greater risk than the general population of adverse health effects from exposure to contaminants in drinking water." When issuing rules under the statute, EPA must document, where possible, "each population addressed by any estimate of public health effects" and "the expected risk . . . for the specific populations." Once identified, these populations arguably will become more difficult to ignore during the risk assessment process.

\[390 \text{ EPA may place the MCLG for carcinogens and other presumed nonthreshold contaminants at zero on the ground that there is no threshold level of safety based on health concerns alone. The nonzero enforcement level (MCL) incorporates cost and technology considerations. National Primary and Secondary Drinking Water Regulations, Synthetic Organic Chemicals and Inorganic Chemicals, 55 Fed. Reg. 30,370, 30,373-75 (1990). The improvement of treatment technologies can permit MCLs to approach closer and closer to MCLGs, and for some contaminants these levels can be the same. However, for contaminants with MCLGs set at zero, such as carcinogens, the MCL cannot be set at the same level. This is because it is recognized as impossible for a water supplier to demonstrate the achievement of a zero level of a contaminant; in practice, the technical capacity to detect the presence of any contaminant is limited.}\]

\[391 \text{ This also avoids the additional delay that would result if the MCLG and the MCL were independently litigable.}\]

\[392 \text{ Indeed, statutory implementation may already reflect this phenomenon. Some critics have argued that the Office of Drinking Water's emphasis on detection technology has already eroded the functional significance of the more demanding MCLGs. Alon Rosenthal et al., Legislating Acceptable Cancer Risk From Exposure to Toxic Chemicals, 19 ECOLOGY L.Q. 269, 312 (1992).}\]

\[393 \text{ 42 U.S.C. § 300j-18 (2000). The statute requires the Administrator to report to Congress the results of the studies no later than four years after enactment of the statute, and "periodically thereafter as new and significant information becomes available." 42 U.S.C. § 300j-18(a)(2). This is part of a larger program providing substantial funding for top priority health effects research. Id.}\]

To be sure, other aspects of the statute make it a questionable model for standard setting. For example, additional provisions in the 1996 reauthorizing legislation—described by one commentator as "an ambitious, if at times garbled, effort to reach a compromise between the Safe Drinking Water Act's constituencies"—permit departures from the feasibility-based risk management standard based upon comparative risk assessment and cost-benefit analysis. Critics have cautioned that if these authorized departures prevent EPA from erring on the side of safety, the

In carrying out this section, the Administrator shall ensure that the presentation of information on public health is comprehensive, informative, and understandable. The Administrator shall, in a document made available to the public in support of a regulation promulgated under this section, specify, to the extent practicable—
(i) each population addressed by any estimate of public health effects;
(ii) the expected risk or central estimate of risk for the specific populations;
(iii) each appropriate upper-bound or lower-bound estimate of risk;
(iv) each significant uncertainty identified in the process of the assessment of public health effects and studies that would assist in resolving the uncertainty; and
(v) peer-reviewed studies known to the Administrator that support, are directly relevant to, or fail to support any estimate of public health effects and the methodology used to reconcile inconsistencies in the scientific data.


396. The comparative risk provision authorizes EPA to choose an alternative MCL if use of the technology and treatment techniques for obtaining the initial level would interfere with other treatment techniques or increase the concentration of other contaminants in drinking water. 42 U.S.C. § 300g-1(b)(5)(A) (2000).

397. The statute requires EPA to evaluate the "quantifiable and nonquantifiable health risk reduction benefits" and the "quantifiable and nonquantifiable costs" of standards under consideration, 42 U.S.C. § 300g-1(b)(3)(C)(i)(I)-(VII) (2000). This published analysis of costs and benefits must include the aforementioned analysis of "[t]he effects of the contaminant on the general population and on groups within the general population such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population." Id. § (C)(i)(V). The statute then permits (but does not require) EPA to set the final standard at a level other than the feasible level if it determines that the benefits of that level "would not justify the costs of complying with the level." 42 U.S.C. § 300g-1(b)(6)(A) (2000). On that basis, EPA may set the final standard at a less stringent level that "maximizes health risk reduction benefits at a cost that is justified by the benefits." Id.

398. The cost-benefit provisions in the Safe Drinking Water Act go further than most statutes in permitting EPA to select a level of regulation that is cost justified. Although some statutes, such as the Toxic Substance Control Act and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), permit an hoc, open-ended balancing of costs and benefits, Congress generally has rejected strict cost-benefit standards that would require EPA to adopt the level of regulation that equates regulatory benefits with costs. Shapiro & Glicksman, supra note 357, at 40. Many commentators have cautioned against proposals to subject regulatory decisions to strict cost-benefit criteria, due to the difficulty of quantifying environmental benefits and the tendency to overestimate compliance costs. See, e.g., Frank Ackerman & Lisa Heinzerling, Pricing the Priceless: Cost-Benefit Analysis of Environmental Protection, 150 U. PA. L. REV. 1553 (2002) (emphasizing the difficulty of monetizing environmental values); Victor B. Flatt, Saving the Lost Sheep: Bringing Environmental Values Back Into the Fold with
statute could require further amendment in the future. Whether these measures were prompted by structural aspects of the statute or whether they were a function of the Act’s unique constellation of local constituencies is a matter of debate. Nonetheless, certain features of the Act’s

a New EPA Decisionmaking Paradigm, 74 WASH L. REV. 1, 4-5, 13 (1999) (detailing the inadequacy of cost-benefit analysis as a tool for considering the full range of values that environmental decisions implicate); Percival, supra note 329, at 172 (discussing reasons for the overstatement of compliance costs and underestimation of regulatory benefits); Wagner, supra note 330 (manuscript at 46) (finding that inflation of compliance costs results, in part, from fact that privately held data upon which government estimates are made are not subject to critical review); see also DANIEL A. FARBER, ECOPRAGMATISM: MAKING SENSIBLE ENVIRONMENTAL DECISIONS IN AN UNCERTAIN WORLD 120 (1999) (“One of the risks of cost-benefit analysis is that it may obscure policy choices behind seemingly technical decisions.”). Cf. CASS SUNSTEIN, FREE MARKETS AND SOCIAL JUSTICE 139, 369-70 (1997) (advocating a modified form of cost-benefit analysis that would allow departures from purely economic criteria).


If, as Professor Sunstein suggests, the cost-benefit limit that Congress has placed on standard setting under the SDWA prevents the agency from erring on the side of safety in the assumptions that it adopts, then it will join section 6 of TSCA and section 6 of the pre-1996 FIFRA in the garbage heap of environmental statutes that are so difficult to implement and accomplish so little when implemented that they have been effectively discarded. I am persuaded that the 1996 amendments do not go that far, but if they do, then the statute may again require amendment in the future.

Id. at 2376. Cf. CASS R. SUNSTEIN, THE ARITHMETIC OF ARSENIC, 90 GEO. L.J. 2255, 2302 (2002) (arguing that even if efforts to weigh costs and benefits are imprecise and produce wide ranges of reasonable options requiring “a judgment of value and not of fact” in the final decision, the effort to trace costs and benefits may help inform the decision-making process).

400. Some authors have attributed the push for the cost-benefit provision to the stringency of the statute’s health-based goal. See, e.g., SHAPIRO & GLICKSMAN, supra note 357, at 192-93. Others have suggested that a more important cause was a statutory schedule in the pre-1996 Act that required EPA to regulate twenty-five new contaminants every three years. See, e.g., Steinzor, supra note 395, at 197-98. This schedule allegedly placed onerous implementation burdens on local drinking water systems. Id. The unique problems encountered in regulating lead in drinking water also played a role in the addition of the cost-benefit provision. Lead contamination is a byproduct of pervasive pipe corrosion. Hence, while it would be technically feasible to reduce levels of lead in drinking water to “safe” levels, it would cost billions of dollars, and would require public water systems to be responsible for elements of the distribution system beyond their control. EPA decided not to promulgate an MCL for lead under the prevailing standard. PERCIVAL ET AL., supra note 125, at 429.

401. Cost containment issues are particularly salient for the Safe Drinking Water Act due to chronic underfunding and underenforcement problems related to the statute’s unique constituencies. In contrast to other major environmental programs, such as the Clean Air Act, the Clean Water Act, RCRA, and CERCLA, the “regulated community” for the Safe Drinking Water Act is highly diverse, consisting of small, local water systems and small private entities in addition to the major municipal drinking water systems. Tarlock, supra note 395, at 253-54. Of the approximately 200,000 public water systems regulated under the federal drinking water program, about 60,000 are “Community Water Systems” that serve their populations throughout the year. Steinzor, supra note 395, at 192 (1996 estimates). Schools, hospitals, factories, campgrounds, or motels operate other systems that may serve transient populations or serve people for just parts of the day. Id. Hence, a persistent question is whether these entities can afford to implement the federal requirements. Id. at 202. Because many of the federal obligations imposed by the Safe Drinking Water Act are placed upon local systems with limited budgets, the Congressional Budget Office used the statute as a case study of the unfunded mandates problem, id. at 185 & n.281, and members of Congress highlighted the program during floor
The two-stage standard-setting process merit closer attention and could be improved upon in the future.

2. **The Elusive Stage Two: The Clean Water Act and Section 112 of the Clean Air Act**

For programs involving the tiered application of technology-based and health-based controls, as in the Clean Water Act and section 112 of the Clean Air Act, the sequence is reversed. These programs address the science quandary by applying technology-based controls at the outset, with health or ambient quality-based standards available as backstops should additional protections become necessary. However, the stages may be separated by many years, and procedures for moving to the second stage may be burdensome. Under these statutes then, the consequences of the new genomic data will depend upon the facility or enforceability of implementing the risk- or quality-based standards.

EPA’s experience in implementing the Clean Water Act is instructive. A major element of the water quality program, as specified in section 303(d), remained largely dormant for twenty years until a series of lawsuits beginning in the late 1980s and early 1990s forced EPA and the states to proceed to stage two. Although EPA’s responsibilities initially were...
viewed as discretionary and unreviewable,406 courts applying a little-used theory ultimately imposed a duty to act.407 Oliver Houck has described this forced progression beyond technology-based controls as the “remarkable resurrection of § 303(d), which has returned to the [Clean Water Act] and its players like Banquo’s ghost.”408

Many proponents of technology-based controls acknowledge their role as a first-generation strategy, meriting upward or downward adjustment should reliable risk data become available.409 New genomic

406. See Oliver A. Houck, TMDLs Are We There Yet?: The Long Road Toward Water Quality-Based Regulation Under the Clean Water Act, 27 ENVTL. L. REP. 10391 (1997). The obligations of section 303(d) were to be triggered by EPA’s formal identification of pollutants appropriate for water quality analysis and pollutant load allocations (TMDLs). Once these pollutants were identified, states had 180 days to submit lists of water bodies in need of ambient standards and TMDLs. EPA was required by statute to approve or disapprove state submissions. However, if EPA failed to identify the requisite pollutants, the clock would not begin. Early suits in the 1970s had failed “for want of a predicate: EPA hadn’t started the clock” and hence states were not required to submit lists of water bodies in need of cleanup. Id. at 10392.

407. By the 1980s, another round of citizen suits established EPA’s duty to act. In Scott v. City of Hammond, 741 F.2d 992 (1984), the Seventh Circuit held that the “prolonged failure” of a state to submit a list of water bodies in need of ambient standards and TMDLs could amount to a “constructive submission” to EPA of no TMDLs, hence triggering EPA’s duty to act: “[w]e think it unlikely that an important aspect of the federal scheme of water pollution control could be frustrated by the refusal of the states to act.” Houck, supra note 406, at 10394. Hence, EPA’s inaction was “tantamount to approval of state decisions that TMDLs are unneeded.” Id. The constructive submission theory took hold in a series of subsequent suits. Further litigation tightened requirements for the quality of state submissions under section 303(d), as well as the adequacy of EPA’s response. Id. at 10395. “How adequate they were, what kinds of TMDLs would follow, and in what time frame remained an open question. But at last, 25 years after the passage of § 303(d), the TMDL process had actually begun.” Id. at 10397.

408. Houck, supra note 405, at 5. Houck subsequently has examined the enormous difficulties encountered in setting resource-intensive ambient quality-based standards under the Clean Water Act. See generally Oliver A. Houck, The Clean Water Act TMDL Program: Aftershock and Prelude, 32 ENVTL. L. REP. 10385 (2002); Oliver A. Houck, TMDLs IV: The Final Frontier, 29 ENVTL. L. REP. 10469 (1999). However, he acknowledges that “TMDLs hold the best prospect of those now available for coming to grips with the last major unregulated sources of water pollution in this country [nonpoint source pollution].” Id. at 10486.

409. See, e.g., Babich, supra note 130, at 179.

It would be unnecessarily pessimistic to argue that scientists will never develop risk data reliable enough to form a basis for anti-pollution standards. Accordingly, when the purpose of a technology-based standard is to avoid risks to health or the environment, that standard should be subject to an adjustment that can be justified using reliable risk data. In fact, refusing to allow such adjustments in the face of convincing evidence of safety or continuing danger could damage the system’s credibility.

See also Bradford C. Mank, What Comes After Technology: Using an “Exceptions Process” to Improve Residual Risk Regulation of Hazardous Air Pollutants, 13 STAN. ENVTL. L.J. 263, 313 (1994) (emphasizing the potential for downward as well as upward adjustments based on risk estimates); Wagner, supra note 364, at n.116 (“In cases where reductions beyond best technology are needed or presumed to be needed to adequately protect public health or the environment, these and still other types of secondary regulatory programs likely will prove essential.”) Regarding section 112 of the Clean Air Act, Babich noted that “if at some point the young sciences of toxicology and epidemiology advance to the point that reliable assessments of risk are practical, section 112(f) provides a mechanism for that science to inform the regulatory effort.” Babich, supra note 130, at n.250. He suggested, however, that risk-based approaches only make sense if thresholds for safety can be found. Id. at 181.
information could enable such fine-tuned adjustments, or conversely, could amplify the uncertainties encountered at stage two. However, the tiered approach could potentially result in "too little science" if technology-based standards are frozen in place and residual risks are left unattended.

3. Lost in the Balance: TSCA and FIFRA

For standards that permit a balancing of risk reduction benefits with compliance costs under general commands to eliminate "unreasonable risks," estimates of costs and benefits may be conflated to such an extent that incentives for identifying new health risks are undermined: "Since no neutral equation or analytical tool can determine whether a risk is 'reasonable' or 'unreasonable,' the delegation of its resolution to an expert agency both avoids and obscures the real policy decision being made." Both the Toxic Substances Control Act (TSCA) and FIFRA, the pesticide law, provide EPA with broad discretion to arrive at an undefined, nonzero level of risk determined by an ad hoc balancing of health and nonhealth factors, including technological feasibility and cost. Unless Congress further constrains the manner or sequence in which EPA is to consider risks and costs, or identifies risks to be considered—as in the Food Quality Protection Act’s reference to children’s special susceptibilities—identifiable health risks will be lost in the balance. Such explicit statutory references could help ensure that sensitive groups are included in the risk assessment process. As one commentator noted, "[r]isk assessment is the step in a regulatory process where higher risks to sensitive subpopulations should be recognized regardless of the statute authorizing agency action."


411. Applegate, supra note 333, at 300.

412. Applegate, supra note 337, at 268. For example, under FIFRA, pesticide registrations and cancellations are conditioned upon a determination of whether the pesticide will have "unreasonable adverse effects on the environment," defined as an "unreasonable risk... taking into account the economic, social, and environmental costs and benefits of the use of any pesticide." 7 U.S.C. § 136a(c)(5)(C) & (D) (2000) (registration); 7 U.S.C. § 136d(b) (cancellation). Rules limiting production or use of chemical substances under TSCA require a balancing of health and environmental effects, beneficial uses of the substance, availability of substitutes, and "reasonably ascertainable economic consequences of the rule, after consideration of the effect on the national economy, small business, technological innovation, the environment, and public health." 42 U.S.C. § 2605(c)(1) (C)-(D) (2000).

413. As noted earlier in this Article, the Food Quality Protection Act, although not characterized as a balancing statute per se, targets one susceptible group for special protection. In applying a test of "reasonable certainty that no harm will result" from pesticide residues on food, Congress has required that the health risks of infants and children must be evaluated independently, and that an additional tenfold safety factor must be applied where evidence of developmental toxicity is found or where exposure or toxicity data are incomplete. Food Quality Protection Act of 1996, 21 U.S.C. § 346a(b)(2)(A)(ii) (2000).
including those which aim to prevent ‘unreasonable risks of harm.’\textsuperscript{414} Statutory reference to groups of concern—if accompanied by transparent processes to promote statutory fidelity\textsuperscript{415}—may come to be a common and important supplement to more general statutory commands.

4. The NAAQS

The new generation of genomic information is certain to have a place in the NAAQS standard-setting process, and deliberations over these standards will continue to highlight the science paradox most prominently. As the enforceable standards presumptively are based solely on public health considerations—and the meaning of “public” and “health” will be subject to rethinking in the genetic age—the task of delineating “safe” levels of air pollutants will be complicated considerably. However, certain features of the existing statutory scheme may help mitigate untoward results. Notably, the NAAQS are not self-implementing, but allow for pragmatic adjustments later in time, when states implement the standards.\textsuperscript{416} Since costs and feasibility may be considered at this later stage, the statutory scheme arguably helps buffer draconian consequences.\textsuperscript{417} As

\textsuperscript{414} Cranor, supra note 199, at 245.

\textsuperscript{415} Implementation of the Food Quality Protection Act has fallen short of its promise. See, e.g., Thomas O. McGarity, Politics by Other Means: Law, Science and Policy in EPA’s Implementation of the Food Quality Protection Act, 53 ADMIN. L. REV. 103, 198-202 (2001) (attributing EPA’s failure to apply the additional ten-fold safety factor in several recent cases to staff level failures promoted by EPA’s transparency-lacking, customary “closed door” approach to setting pesticide tolerances); Valerie Watnick, Risk Assessment: Obfuscation of Policy Decisions in Pesticide Regulation and the EPA’s Dismantling of the Food Quality Protection Act’s Safeguards For Children, 31 ARIZ. ST. L.J. 1315, 1341-58 (1999) (attributing failure to apply the additional ten-fold safety factor in several cases to EPA’s shortage of toxicity data for pesticides, and over-reliance on the regulated community’s data).

\textsuperscript{416} See Union Elec. Co. v. EPA, 427 U.S. 246 (1976) (discussing variances and other means for accommodating claims of economic and technological infeasibility at the state level). After states allocate pollution limits among the various polluting sources, total emissions loadings for designated pollutants in each air quality control region must fall within the federally-established health-based limit. 427 U.S. at 267. For discussions of the potential merits of back-end adjustments, see, for example, Shapiro & Glickman, supra note 357, at 158-77 (illustrating the role of localized, back-end adjustments in the NAAQS program and other regulatory schemes). “Instead of watering down the standards, policy makers make case-by-case adjustments pursuant to a process that entails a fine-tuned balancing that would amount to a difficult if not impossible task on a larger scale.” Id. at 171. See also Jim Rossi, Making Policy Through the Waiver of Regulations at the Federal Energy Regulatory Commission, 47 ADMIN. L. REV. 255, 277 (1995) (“[E]quitable adjustments in the implementation of regulations promulgated by rule provide an important ‘safety valve’ in the administrative process.”). As Dan Farber has noted, regulatory standards sometimes function merely as “starting points in the lengthy interactions between agencies and regulated parties, rather than as end points of compliance . . . . In effect, the standards may merely be the government’s opening demand in negotiations, and the final bargain is likely to be more favorable to the other side.” Daniel A. Farber, Taking Slippage Seriously: Noncompliance and Creative Compliance in Environmental Law, 23 HARV. ENVT'L. L. REV. 297, 315-16 (1999). However, Farber also has acknowledged the dangers of back-end adjustments, as they may take place “in the shadow of the law” instead of “in the light of public deliberation.” Id. at 319.

\textsuperscript{417} “The statute permits costs to be taken into account in a variety of contexts: in excusing individual sources from compliance where their continued operation is economically critical, in setting standards for new factories and for automobiles, and in setting certain other emissions reductions.”
Daniel Farber has noted, "[s]etting goals without regard to cost, while attending to costs in the implementation process...is responsive to the strong value our society places on public health and safety.... The current scheme, then, allows us to reaffirm our commitment to the value of human life, while allowing us to respect the limits of feasible regulation."418

The NAAQS regulatory scheme may be further complicated—but I believe not undone—by the new genomic data. For example, as scientific data document the presence of groups particularly susceptible to one or more pollutants, the assumption of a single “safe” threshold for most non-carcinogens may be harder to justify. In some cases, such data will support regulating to progressively lower levels of exposure. Thus, for health-based standards such as the NAAQS, an open question is whether future genomic research will provide appropriate “stopping points” (that is, specific new thresholds) that will help regulators avoid the zero-risk dilemma. We do not yet know the magnitude of the problem—for instance, how many different genetically sensitive groups will be identified for individual chemicals. In a similar vein, the discovery of new subclinical changes resulting from pollutant exposure may support a decrease in the acceptable level of exposure to certain chemicals. But again, the recency and preliminary nature of most such data prevents us from truly understanding the magnitude of the problem in a regulatory sense. We do not yet know when genomic or other data will be sufficiently indicative of functional disturbance or predictive of clinical disease to be deemed “adverse health effects.” With time, science will provide answers to at least some of the technical scientific questions.

Inevitably, for some substances, the entry of genomics will underscore and aggravate the existing problem of finding a principled basis for selecting nonzero standards for nonthreshold pollutants.419 This may prompt calls for statutory amendments that would permit cost or other countervailing considerations to enter into the standard-setting process. However, balancing health and cost considerations at the outset, while intuitively appealing to some, would introduce a host of new and often incommensurable

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418. Farber, supra note 417, at 77. Indeed, Farber has suggested that the American tradition of philosophical pragmatism has been the governing paradigm for environmental regulation, Farber, supra note 398, and advocates its continued application as a means of reconciling environmental and economic values. Id. See generally Shapiro & Glickman, supra note 357 (illustrating how contemporary environmental regulation reflects this pragmatic approach, and countering arguments for formal cost-benefit standards that would require EPA to adopt the level of regulation that equates monetized regulatory benefits with compliance costs).

419. See discussion infra accompanying notes 156-64.
variables that could compound the uncertainties already present in risk assessment.\textsuperscript{420} Other possible responses, such as incorporating "acceptable risk" or "significant risk" thresholds into the statute, similarly could provide the appearance of consistency while masking the discretion with which such terms may be applied.\textsuperscript{421} Although the NAAQS program has no shortage of critics, its successes must also be emphasized: emissions of nearly all of the most pervasive air pollutants in the United States have decreased dramatically since the 1970s, despite substantial growth in population, vehicle use, and economic activity.\textsuperscript{422} Notwithstanding the many challenges ahead, the "health-first" approach of the NAAQS program, when evaluated in its entirety, ultimately may prove preferable to other imperfect options. The responsibility of Congress and regulators at this time is to provide sufficient flexibility to ensure that new scientific developments are considered and given a place within the crucial public policy debates that are certain to follow.

\textbf{E. Tailored Strategies: Circumventing the Science Paradox?}

A remaining question is whether alternative approaches could help circumvent the science paradox, while at the same time accounting for health risks identified through genomics. Specifically, the new generation of molecular and genetic health risk information opens the door to an important dialogue about warnings and targeted remedies, two strategies employed to tailor environmental regulations to vulnerable individuals and groups. Environmental regulators intermittently use these remedies to supplement broader regulatory protections. These approaches are limited in their reach and are relevant only in specialized situations. Nevertheless, they may provide alternative models for responding to discrete health risks without requiring across-the-board pollution reductions that are more stringent than necessary to protect the majority of the population.

\begin{itemize}
\item \textsuperscript{420} See infra note 398 (discussing problems of overestimating compliance costs, underestimating regulatory benefits, and weighing incommensurables in standard setting under cost-benefit decision rules). Similar problems present themselves in statutory standards that permit open-ended balancing of the costs and benefits of environmental regulation. See infra discussion accompanying notes 411-15.
\item \textsuperscript{421} See infra discussion accompanying notes 229-31.
\item \textsuperscript{422} According to EPA data, emissions of the most pervasive air pollutants have declined dramatically between 1970 and 1995, with the exception of nitrogen oxides, which increased by 6\%. Lead emissions declined by 98\%, particulate matter emissions from industrial activity and fuel combustion by 79\%, \textit{SO}_2 emissions by 41\%, carbon monoxide emissions by 28\% (even though total vehicle miles traveled more than doubled between 1970 and 1995), and volatile organic compounds by 25\%. \textsc{J. Clarence Davies} \& \textsc{Jan Mazurek}, \textit{Pollution Control in the United States: Evaluating the System} 58 (1998). During this period, national ambient concentrations of all criteria pollutants subject to the NAAQS regime declined. \textit{Id.}
\end{itemize}
1. *Warnings*

The premise of warnings or labeling strategies is to allow exposed or particularly susceptible groups to take avoidance measures where possible. For example, EPA and the FDA recently issued a joint advisory for children, pregnant women, and nursing mothers, recommending restricted intake of fish species shown to contain high levels of mercury. 423 Similarly, for air pollutants regulated under the NAAQS, EPA’s Air Quality Index notifies members of the general population to limit heavy exertion when local pollution levels rise significantly above national standards and designates separate pollution levels of concern for “sensitive groups.”

Warnings may represent a low-cost alternative to regulatory protection in situations where exposure is at least partly a matter of personal choice, as in the use of food, drugs, cosmetics, and other products. 424 In these settings, shifting the burden of protection from risk creators and government regulators to individuals may be theoretically acceptable, assuming the availability of comparable substitutes and practical options for avoidance. The fairness and effectiveness of this strategy is far less apparent, however, in the context of air pollution, water pollution, and other diffuse environmental harms where risk avoidance may be costly, unduly burdensome, or even impossible.

Moreover, genetic susceptibility presents problems beyond those that animate warnings directed at readily identifiable groups. Because genetic susceptibility is identifiable only through testing, any warning strategy would depend on testing that is equitably available and uniformly selected. Admittedly, “[a]s the potential health benefits of preventive actions based on genotype become better validated and known, the demand for such

423. The kind of mercury found in fish, methyl mercury, is a toxin that has been shown to be particularly harmful to fetuses and young children. See U.S. Food and Drug Administration, U.S. Environmental Protection Agency, *FDA and EPA Development of a Joint Advisory for Methyl Mercury-Containing-Fish Consumption for Women of Childbearing Age and Children* (July 2003), available at http://vm.cfsan.fda.gov/~dms/mehg703.html (last visited Mar. 2004); see also Michael Janofsky, *Study Finds Mercury Levels in Fish Exceed U.S. Standards*, N.Y. TIMES, Aug. 4, 2004, at A15.


425. EPA’s Genomics Task Force already is considering the possibility of labeling pesticides for genetically sensitive groups:

If genomics technologies are successful in identifying populations susceptible to specific pesticides or industrial chemicals, product labeling will probably be necessary. For example, labels might include warnings for particular populations known to exhibit higher frequencies of an at-risk genetic polymorphism. The pharmaceutical industry already includes warnings to susceptible populations on drug labels. The Agency has the ability to follow similar practices for pesticides . . . .

testing is likely to be significant.\textsuperscript{426} However, a protective strategy premised on the universality of a demand for testing or the pervasiveness of testing opportunities will not be sufficiently comprehensive. Ultimately, warnings are unlikely to become generally useful strategies for dealing with the issues raised by variations in genetic susceptibility to common pollutants. The resources required to perform the ubiquitous genetic screening necessary to implement an effective warning program would, in the majority of situations, be better spent on programs to reduce the environmental concentration of the relevant pollutant.

2. Targeted Remedies

Targeted remedies, traditionally reserved for environmental emergencies or acute, site-specific harms, could become more commonplace in the future as a way of responding to small group claims and furthering preventive goals. In the past, such remedies have been employed where populations face heightened exposure to harmful substances due to their proximity to the source. For example, EPA has purchased bottled water for residents exposed to groundwater contamination at Superfund sites, and has required responsible parties to do so.\textsuperscript{427} Similarly, the Nuclear Regulatory Commission has approved the distribution of potassium iodide tablets to residents living within ten miles of nuclear power plants to counteract the effects of an emergency release of radioactive iodine.\textsuperscript{428} New genetic technologies might prompt regulators to take a similar approach as a way of responding to claims from other exposed groups, including those who are particularly susceptible.

Moreover, research could lead to new therapeutic interventions to counteract some of the deleterious effects of environmental pollutants, allowing regulators to “custom-design individual strategies to reduce or avoid a person’s exposure to environmental threats at a molecular level.”\textsuperscript{429}

\textsuperscript{426} Marchant, supra note 45, at 10659. However, unless adequate protections are implemented, this demand will be tempered by privacy and confidentiality concerns.


\textsuperscript{428} Nuclear Regulatory Commission, Potassium Iodide and Emergency Preparedness, 66 Fed. Reg. 5427 (Jan. 19, 2001). Potassium iodide has been shown to counteract certain effects of radiation exposure. If taken before or shortly after radiological exposure, potassium iodide blocks the thyroid gland’s ability to absorb radioactive iodine.

\textsuperscript{429} Wendy Yap & David Rejeski, \textit{Environmental Policy in the Age of Genetics}, 15 ISSUES IN SCI. & TECH 33, 34-35 (1998); see also A. Dan Tarlock, \textit{Genetic Susceptibility and Environmental Risk
One recent example suggests that such targeted measures may be cost-effective and nonintrusive. In a study of asthmatic children with genetic variants that made them particularly susceptible to lung damage from ozone, researchers found that a treatment involving vitamins C and E helped prevent lung damage and thus compensate for the genetic susceptibility. Similarly, new treatment options may permit targeted medical monitoring remedies designed to detect adverse health effects early in the disease process.

A major problem with the targeted approach, however, is that targeted remedies for selected populations do not reduce the environmental hazard and thus may divert resources from broader public health goals:

[M]olecular techniques might cause us to redirect our focus from identifying risks in the exogenous environment to identifying high-risk individuals and then making personalized risk assessments. . . . This would direct our focus to a form of clinical evaluation rather than one of public health epidemiology. Focusing on individuals could distract us from the important public health goal of creating a less hazardous environment. Clearly, there are both potential benefits and harms from the use of biomarker technology.

Moreover, these strategies raise important privacy and confidentiality questions, as individuals could not benefit from a targeted remedy without providing personal health information to third parties. The specter of discrimination by employers, insurers, and other third parties has received substantial scholarly attention and would become a critical element of any discussion of targeted remedies. However, if information policies can ensure confidentiality, these remedies may in certain cases prove useful, particularly in confined exposure scenarios or where most of the remaining societal risk for a particular toxic hazard is borne by a particular group.

Tailored strategies such as warnings and targeted remedies hold some promise for circumventing the science paradox by making judicious use of genomic information, limiting the information to the populations for which

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430. I. Romieu et al., Genetic Polymorphism of GSTM1 and Antioxidant Supplementation Influence Lung Function in Relation to Ozone Exposure in Asthmatic Children in Mexico City, 59 THORAX 8-10 (2004).


432. See infra note 121.

433. See Marchant, supra note 45, at 10062. If the societal risk is not confined to a limited population, it would be more appropriate to address the risk more generally: “[O]therwise even a small risk to the ‘non-susceptible’ majority of the population may produce more disease cases than a high risk to a small number of susceptible individuals.” Id; see also Harri Vainio & Kirsti Husgafvel-Pursiainen, Elimination of Environmental Factors or Elimination of Individuals: Biomarkers and Prevention, 37 J. OCCUPATIONAL & EnvTL. MED. 12, 13 (1995).
it has the most value. However, that advantage comes at the expense of unanchoring environmental regulation from its longstanding focus on protecting public health by reducing environmental hazards.

F. Circle of Risk: Private Law Implications

A final legal reality deserves serious consideration: if the regulatory system does not account for newly identified health risks, a rise in tort claims may be expected. Tort law may function, at least in certain circumstances, as a supplemental option for addressing residual risks that the existing regulatory regime leaves unattended. Given the possibility that the new science will prompt a shift toward technology-based controls, subpopulations that allegedly remain unprotected could potentially seek a remedy in court.

The incrementalist, technology-based approach may leave residual risks that regulatory measures do not cover; frequently, these may take the form of localized "hot spots" of risk. Viewed in a broader context, the daunting task of setting health-based standards may trigger a shift to technology-based controls, which in turn may leave residual risks. I will refer to this broader phenomenon as the "circle of risk."

The additional data yielded by new scientific capabilities might bolster the claims of populations affected by such risk. Information concerning environmental susceptibilities, exposure, and subclinical biological effects may serve as the ingredients for a new generation of tort claims.

434. While certain targeted strategies might focus on both genetically susceptible and other at-risk groups, other programs that provide genetically susceptible groups with superior protection could raise concerns about genetic exceptionalism. See generally Lainie Friedman Ross, Genetic Exceptionalism vs. Paradigm Shift: Lessons from HIV, 29 J. L. MED. & ETHICS 141, 141 (2001); Sonia M. Sutter, The Allure and Peril of Genetics Exceptionalism: Do We Need Special Genetics Legislation?, 79 WASH. U. L.Q. 669, 671 (2001). Genetic exceptionalism implies that genetic information is so different from other types of medical information that it raises unique issues and concerns that justify special treatment relative to other types of information. Sutter, supra, at 671. Critics of genetic exceptionalism argue that treating genetic information as unique fosters the public belief that genetic makeup commands special control over an individual's life. This concept frequently is referred to as genetic essentialism. See, e.g., Rochelle Cooper Dreyfus & Dorothy Nelkin, The Jurisprudence of Genetics, 45 VAND. L. REV. 313, 320-21 (1992). Much of the scholarly discussion in this area has focused on legislative proposals dealing with genetic privacy and discrimination. See, e.g., George J. Annas, Genetic Privacy: There Ought To Be a Law, 4 TEX. REV. L. & POL. 9, 11 (1999). While a discussion of these topics is beyond the scope of this Article, toxicogenetics, which is premised on the interaction of genetic and non-genetic (environmental) influences, may add a new twist to this debate.


436. Troyen Brennan has discussed the on-the-ground consequences of the incrementalist, technology-based approach: in contemplating risk assessments necessary to undertake health-based rules, regulators "either move very slowly or opt for incrementalist, technology-based controls that allow postponement of health assessments." Id. at 37. "Once technology standards are in place, one still is faced with toxic hot spots, and then the need to set media standards that focus on health. An incremental, technology-based approach leads to manageable costs, but it does not provide 'an ample margin of safety.' Some discrete communities will continue to be exposed to hazardous pollutants." Id. at 35.
based on injuries from chemical exposure, as well as increased risk in the absence of manifest injury.\textsuperscript{437} Even if decision makers view private law remedies as a desirable supplement to regulatory protections, the question becomes whether it is possible to manage these claims. It is too soon to predict when the science will be sufficiently developed to support or rebut tort claims based on genomic information, or for that matter how the tort system would respond if these enormously complex scientific questions migrate to the private law. Most fundamentally, however, pushing genomic information to other points along this "circle of risk" prompts questions about whether a potential growth in private law actions would be socially desirable from the standpoint of protecting the public's health.

\textbf{G. Transitional Measures}

Not only does the new science raise difficult technical questions, but it also raises fundamental ethical and policy issues that extend well beyond EPA's technical expertise. Perhaps at the outset, Congress should authorize new and existing expert consultative bodies to address the multifaceted problem of how to protect the public's health in the genetic age. Deciding which groups to protect raises questions of fairness and justice that cannot be explored fully in the risk assessment labs of EPA. In addition to geneticists and other scientists, the diverse body of stakeholders warrants broad representation. Questions concerning prevention, treatment, testing protocols for environmental susceptibility, and the point at which an adverse effect merits regulatory attention suggest an expanded role for medical experts in future deliberations. Moreover, standardized research protocols and validation techniques are essential if toxicogenetics, toxicogenomics, and related fields are to become reliable and credible in legal and regulatory settings. Finally, public input must be sought and respected. Even if protecting certain groups proves to be beyond the bounds of feasible regulation, their vulnerabilities should at least be acknowledged and considered in the regulatory process:

\begin{quote}
[B]oth the particularly susceptible and the healthy have equal moral standing to be protected.... [S]ome provision has to be made for the most vulnerable members of the moral community.... Their claim is not non-existent or extinguished or eliminated merely because it may turn out to be too expensive to protect them. If we do not even acknowledge their risks... by concluding that they have no standing to be protected, we would be suggesting that their claim was non-existent.\textsuperscript{438}
\end{quote}

The genetic revolution discussed in this Article will require us to assess the effectiveness of current mechanisms for responding to human

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\textsuperscript{437} See generally Poulter, supra note 36; Marchant, supra note 71.
\textsuperscript{438} Cranor, supra note 199, at 240.
\end{flushright}
health risks. There is unlikely to be one "right" answer that can be applied to all questions of protection of newly identified susceptible groups or inclusion of newly identified subclinical health effects. It seems more likely that each situation must be debated and decided on its own—chemical by chemical, biomarker by biomarker—within a responsive regulatory framework.

CONCLUSION

In this Article, I have argued that a shift in the science underlying environmental law is underway. Although this shift could profoundly affect the way we regulate to protect the public from environmental risks, policymakers have only begun to perceive the transformation. The new science has the potential both to measure individual genetic susceptibilities to the effects of toxic substances and to provide evidence of toxin-induced injuries long before clinical symptoms emerge. Moreover, new technologies are setting the stage for personalized assessments of susceptibility, toxic exposure, and early evidence of injury—a development that could change fundamentally the relationship between public and private law.

I have argued that advances in molecular biology and genetics will call into question the conception of "public" and "health" in environmental regulation. The growing technical ability to assess risk on an individualized basis suggests that the classic population-based, public health paradigm will be challenged as new kinds of sensitive groups and individuals petition for enhanced regulatory protection. Likewise, the definition of "health," and the regulatory delineation of threats to health, will be called into question as new technology uncovers earlier evidence of toxic harm. EPA will be required to decide whether these early, possibly predictive events should qualify as "adverse health effects" of regulatory concern. These developments all speak to the question of whether existing standards establishing "safe" levels of air and water pollutants, industrial chemicals, and pesticides are sufficiently protective of the public's health.

Moreover, new genetic data may challenge fundamental scientific assumptions that guide regulatory standard setting today. The concept of a single "threshold" delineating safe from unsafe levels of noncarcinogens may become increasingly difficult to defend as genetics uncovers new susceptible groups and earlier evidence of chemically induced harm. For carcinogens, regulatory distinctions between "acceptable risks" and "significant risks" may become even more opaque as the new science challenges the numbers upon which these determinations are based.

I have suggested that, in the short term, the influx of new genetic information and the resulting complexity of regulatory decisions could erode support for risk-based environmental regulation and trigger a shift to regulatory approaches that minimize the role of science. However, wholesale
de-emphasis of risk-based standard setting would be ill-advised. Until the new information is validated, we will not fully understand the parameters of the problems posed or the solutions that the science may provide. Hence, we should promote and safeguard regulatory instruments that provide incentives to generate and evaluate this new information, allowing us to make the right choices in the future. The challenge is to develop regulatory arrangements that will allow us to understand and make use of the new science without overwhelming the regulatory venture.