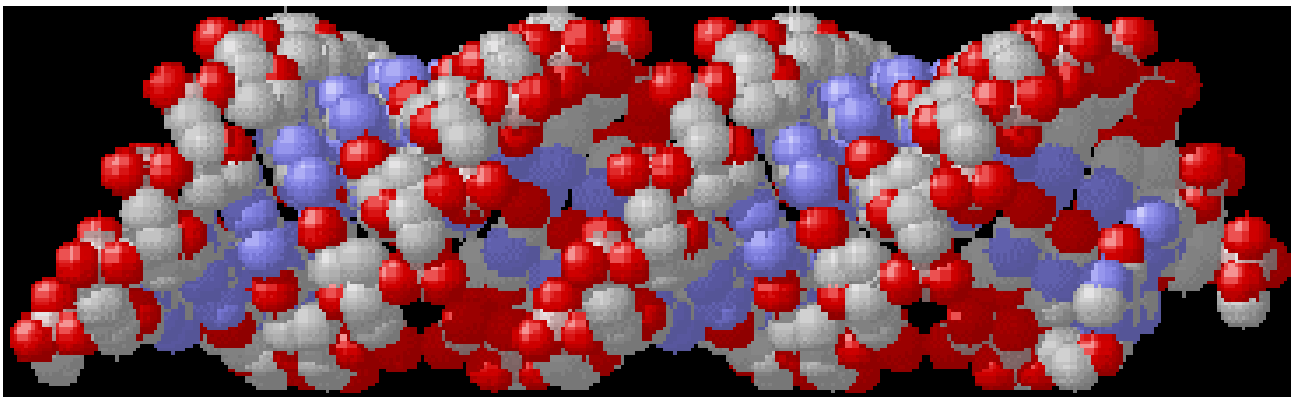

Genomics and Environmental Regulation

Scenarios and Implications

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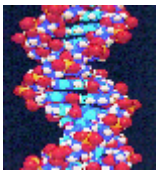

FOUR SCENARIOS

1. If DNA microarrays can provide a quick, inexpensive and accurate characterization of the extent and mechanism of a chemical's toxicity, there are a number of regulatory programs where such assays could be used and perhaps required. Should the U.S. consider requiring manufacturers to conduct a short gene expression assay using microarrays? Could such a test be required under the current provisions of the Toxic Substance and Control Act (TSCA)?

2. EPA has received anecdotal reports that a commonly used household pesticide has been linked with a variety of health effects including dizziness, headaches, and nausea. If tests indicated that residents exposed to the pesticide produced a gene expression profile that is characteristic of a known toxicological mechanism, would this result be sufficient to trigger more regulatory attention by EPA? If the tests showed no toxicologically significant changes in gene expression in the exposed residents, would EPA be reassured that the pesticide would not require more extensive investigation or regulation?

3. A citizen's group files a petition under EPA's Environmental Justice guidelines claiming that a State's approval of an air pollution permit for a new facility will have a substantial and adverse disparate impact on individuals in the local community carrying a genetic polymorphism that makes them particularly sensitive to one of the pollutants emitted by the new facility. There is no evidence that persons with such susceptibility receive higher exposures than any other segment of the population. How would EPA address this complaint? Is it necessary for environmental justice considerations to apply if the susceptible genetic polymorphism is primarily found in a disadvantaged racial group?

4. EPA has permitting authority under the Clean Air Act in Maryland. A permitted facility in that state requests a two-year variance from a certain regulatory requirement based on feasibility. A family residing near the facility objects to the proposed variance on the ground that several members of the family carry a genetic susceptibility to pollutants emitted by the facility, and that the variance would result in increased emissions that would unnecessarily limit their activities in violation of the Americans with Disabilities Act (ADA). How should EPA respond to this argument? Would a requirement under the ADA to deny an otherwise discretionary waiver constitute a fundamental alteration of the Clean Air Act?

EXECUTIVE SUMMARY

The sequencing of the human genome and associated efforts to identify and characterize the genes of humans and other organisms will have many scientific, medical, ethical, and legal consequences. The new genomic technologies and data from these efforts will also have many potential applications for environmental policy and regulation. Some of these applications will be available in the short-term, others will occur further into the future. Genomic information has the potential to make environmental regulation more effective, precise, efficient, and fair. At the same time, these new data will confront regulatory agencies such as the U.S. Environmental Protection Agency ("EPA") with some fundamental and difficult policy, legal, and ethical decisions.

This White Paper attempts to identify potential applications of genomic data for environmental regulation. It focuses on two specific types of genomic data – (i) gene expression data from toxicogenomic studies; and (ii) the identification of genetic polymorphisms that increase (or decrease) susceptibility to environmental toxicants. For both these types of data, the scientific basis of the data is summarized, followed by a discussion of potential applications to environmental regulation. A series of hypothetical scenarios are provided to identify specific questions and problems that may confront EPA from the application of genomic data in the near future.

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I. Toxicogenomics: Gene Expression Data

A. Scientific Summary

Toxicogenomics is defined as the scientific study of "how genomes respond to environmental stressors/toxicants."[1] A central focus of toxicogenomics is to identify and profile gene expression in a cell or tissue by collecting and characterizing messenger RNA ("mRNA") on a DNA microarray.[2] A DNA microarray (sometimes also referred to as a "gene chip") consists of a set of genetic markers fixed to a substrate such as a glass slide or fabric. The genetic markers can consist of short (500 to 2000 base pair) complementary DNA ("cDNA") sequences that bind to genes of potential interest. Ten thousand or more cDNA specific sequences can be spotted onto a glass slide in known positions. Alternatively, short DNA sequences, called oligonucleotides, that are complementary to known genes can be manufactured directly onto the substrate using a process called photolithography.

These DNA microarrays can be used to identify and characterize the response of a cell or tissue to perturbation, such as exposure to a toxic substance. Cells respond to external stimuli by changing the expression pattern of genes, which are transcribed to form messenger RNAs ("mRNAs"). The mRNAs migrate from the nucleus into the cell cytoplasm and bind to ribosomes where they are translated into proteins, the functional products of genes. Messenger RNA from treated and/or control cells, labeled with flourescent or radioactive markers, can be isolated and hybridized to the DNA microarray, and the pattern and intensity of DNA binding will indicate the genes that have been expressed in the treated cells. DNA microarrays thus permit the simultaneous genome-wide measurement of the expression of thousands of genes.

This microarray approach to studying gene expression provides "a tool of unprecedented power for use in toxicology studies."[3] Because toxicity usually involves the induction (up regulation) and repression (down regulation) of many different genes, only the genome-wide assays made possible by DNA microarrays can evaluate the entire cascade of gene responses to toxic exposure.[4] These gene expression changes measured by microarrays have the potential to

provide a more sensitive, characteristic and earlier endpoint than typical toxicological endpoints such as morphological changes, carcinogenicty, or reproductive toxicity.

DNA microarray data have several potential applications for understanding environmental toxicants. First, toxicogenomics will enhance understanding of the molecular mechanisms of toxicity. For example, at least some gene expression changes appear to be characteristic of specific mechanisms of toxicity.[5] Thus, when a chemical causes a tumor or some other toxicological endpoint, it may be possible using gene expression profiling to determine the mechanism causing the health endpoint. This technology thus offers the promise of being able for the first time to directly evaluate the etiology of a specific tumor or health effect. Second, toxicogenomics can be used for predictive toxicology. Whereas functional or morphological evidence of chronic toxicity may take weeks to years to appear, characteristic gene expression changes can be detected within hours or days of exposure. This permits much earlier, effective, and inexpensive opportunities for toxicity screening.

B. Potential Regulatory Applications

1. Risk Assessment

The traditional approach to risk assessment employed by EPA and other regulatory agencies has been based primarily on the two-year rodent bioassay. The limitations of this traditional model are well-known – and they include: the lack of information provided on the mechanism of disease, the inability to study low-dose effects with adequate sensitivity, the uncertainties in extrapolating results from animals to humans, and the high costs and lengthy duration of such tests. Gene expression data may help to overcome some of these limitations. First, to the extent that the mRNA profile in exposed cells can be classified into characteristic toxicity "fingerprints," then the chemically-induced changes in gene expression can be used to characterize the mode of action for toxicity. Second, a finding that gene expression changes characteristic of, for example, the carcinogenic response at high doses are also observed in low-dose groups, even though those low-dose animals may not develop tumors, may indicate that

low-dose exposures present a carcinogenic risk in large populations. Alternatively, the absence of any characteristic gene expression response in low-dose animals may suggest that the carcinogenic response only occurs at high doses. Third, comparing gene expression changes in rodent and human cells after a similar exposure may provide information on the relevance of rodent tumor response for human health risk. Finally, gene expression profiling may be particularly useful for evaluating the toxicity of chemical mixtures, which represent the most typical human exposure scenarios, but which are hard to evaluate using traditional toxicological methods.

Scenario 1: Carcinogen Classification

EPA has classified an important commercial chemical as a probable human carcinogen based on the results of a chronic rodent bioassay. The study found a clear increase in liver tumors at the highest dose levels in both male and female mice, but no increase in tumors at lower dose levels in mice or at any dose level in rats. A trade association representing the manufacturers of the chemical sponsored a series of studies intended to elucidate the mechanism of the observed cancer effect in mice. These studies found that the high and mid-level doses in mice induced a significant change in gene expression in the liver that is characteristic of other agents that induce tumors by a peroxisome proliferation mechanism. No similar responses in gene expression were seen in rats at any dose-level, or in cultured human cells exposed to a wide range of doses. Based on these results, the trade association argues that the chemical appears to be acting by a non-genotoxic mechanism that only applies at high doses in mice and not at all in rats or humans. The trade association therefore requests EPA to revise the cancer classification of the chemical to a non-carcinogen. How should EPA respond to these data?

Gene expression assays may also provide a more sensitive methodology for examining other risk assessment issues such as the differential sensitivity of children versus adults to specific environmental exposures.

Scenario 2: Additional Uncertainty Factor for Children

The Food Quality Protection Act of 1996 requires EPA to apply an additional tenfold margin of safety for the protection of infants and children in regulating pesticides exhibiting a health threshold, except that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." Assume that animal tests show that a particular pesticide produces a similar gene expression response in adult and neonatal rodents, both with respect to the magnitude and type of response. If there is no reason to believe that children will receive greater exposure than adults, would these gene expression results provide the "reliable data" needed to exempt application of the additional tenfold safety factor for differential susceptibility in children?

2. Definition of "Adverse Effect"

Changes in expression of genes that are characteristic of a toxic response can provide a more sensitive and early indicator of toxicity than traditional toxicity endpoints such as carcinogenicity, teratogenicity, reproductive toxicity, or systemic toxicity. The availability of gene expression data using DNA microarrays in cells or organisms treated with potentially toxic chemicals raises the issue of whether gene expression changes should be considered "adverse" effects for regulatory purposes. For any particular observed change in gene expression, a critical question will be whether such a change is an early marker of a significant toxicological response, or merely an adaptive response of the cell or organism to exposures that would not normally progress to toxicity. As one set of authors recently commented, this issue will require expert judgment to address:

> "Toxicogenomics is not a promise for the future; it is a tool that is available to us now, and which, if used correctly and within the guiding principles of good experimental biology, will bring huge dividends. Concern has been voiced already that a potential problem is the misinterpretation, or over-interpretation, of genomic analyses, particularly in the context of determining product safety. It must be recognized that the interaction of xenobiotics with biological systems will in many instances result in some changes in gene expression, even under circumstances where such interactions are benign with respect to adverse effects. The challenge again is to ensure that sound judgment and the appropriate toxicological skills and experience are brought to bear on the data generated, so that toxicologically relevant changes in gene expression are distinguished from those that are of no concern."[6]

Scenario 3: **"Adverse Effects" and NAAQS**

Section 109 of the Clean Air Act requires EPA to establish national ambient air quality standards that protect the public health "with an adequate margin of safety." The legislative history of the statute indicates Congress' intent that EPA protect the public from "adverse effects" from exposure to air pollutants, and one of the key issues EPA addresses in setting such standards is determining whether a particular response is an "adverse effect." For example, in setting the ozone standard, EPA has concluded that "transient and reversible" effects on lungs from ozone exposure are not "adverse effects." However, the courts have held that an "adverse effect" need not have clinical symptoms. For example, in *Lead Industries Ass'n v. EPA*, 647 F.2d 1130 (D.C. Cir. 1980), the DC Circuit held that EPA need not show that an effect caused by exposure to an air pollutant was "clearly harmful to health." The court therefore held that EPA could base its air quality standard for lead on the "subclinical" effect of elevated erythrocyte protoporphyrin levels, which although having no direct health impact, indicates that "lead has already begun to affect basic biological functions in the body." If data showed that a criteria pollutant induced gene expression changes that were characteristic of a known toxicological profile at levels below the existing NAAQS, would this finding constitute an adequate "adverse effect" to require tightening of the NAAQS?

If at least some gene expression changes are indeed considered "adverse effects," the regulatory consequence may be more stringent standards. Some may argue that the more sensitive test for adverse toxic effects should not necessarily result in more stringent standards, instead, these test should only be used to provide a more precise and certain assay for characterizing whether a toxicant does indeed cause a toxic response in humans. Under this view, EPA should compensate for the more sensitive test in setting regulatory standards.

Scenario 4: Identification of NOAEL or LOAEL

EPA traditionally bases regulatory decisions on non-carcinogens using Reference Doses ("RfDs") or Reference Concentrations ("RfCs") listed in the Agency's IRIS database. RfCs are used for respiratory inhalation, and RfDs for other routes of exposure (e.g., drinking water). An RfD or RfC is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of daily exposure to the human population that is likely to be without appreciable risk of deleterious effects during a lifetime." RfDs and RfCs are calculated by applying a series of uncertainty factors to the known observed adverse effect level ("NOAEL"), or in the absence of a NOAEL, the lowest observed adverse effect level ("LOAEL"). As these terms indicate, the effect must be "adverse" to be counted. If studies show that a chemical induces gene expression changes at levels below the existing NOAEL or LOAEL, should these changes be considered "adverse" and used to specify a lower NOAEL or LOAEL? The standard set of uncertainty factors that EPA applies to calculate an RfD or RfC does not take into account the severity of the adverse effect used to calculate the NOAEL or the LOAEL. However, EPA has occasionally applied on a case-by-case basis a reduced overall uncertainty factor when the relative "adverse effect" is of low severity, such as minor irritation lesions in the nasal cavity after inhalation of a chemical. If EPA uses changes in gene expression as the "adverse" effect for purposes of establishing the NOAEL or LOAEL, should it also reduce the uncertainty factors applied to calculate the RfD or RfC to compensate for the low severity of this "adverse" effect?

3. Product Screening

The majority of high-volume chemicals in commercial use in the United States have not been adequately tested for human toxicity and carcinogenicity potential.[7] Other than pharmaceuticals and pesticides, there is no legal duty imposed on manufacturers to pre-market test their products for toxicity. EPA and the chemical industry have begun to address this data gap for chemical risk assessment with the High-Production Volume (HPV) chemical testing initiative. However, given the large number of chemicals in commerce, it is not feasible to conduct traditional toxicological testing, including a chronic rodent bioassay, for all or even most chemicals in commerce. For example, the largest chemical testing program in the United States, conducted by the National Toxicology Program, has just recently completed its 500th carcinogenicity evaluation after thirty years of testing. The high costs ($1-5 million dollars), lengthy duration (2-4 years), and limited laboratory capacity to conduct chronic bioassays

necessarily restrict such testing to only a small percentage of the overall chemicals in commerce.

For the vast majority of chemicals, a rapid and cheap screening test for toxicity is needed. Genotoxicity assays and structure-activity relationship ("SAR") analyses are currently used to screen many chemicals, but these assays are limited in their utility. Gene expression assays that may allow for rapid, inexpensive and high throughput screening of chemicals for a wide range of genotoxic and non-genotoxic toxic responses could provide a promising methodology for systematically screening new and existing chemicals for toxicity. Dr. Kenneth Olden, Director of the National Institute of Environmental Health Sciences ("NIEHS"), stated that with new toxicogenomic technologies "[w]e'll be able to reduce the time it takes to test potential carcinogens from two to three years to a few days. And we'll reduce the cost of such studies from $2-3 million to less than $500 dollars."[8] DNA microarrays can be used to interrogate the gene expression of cells treated with chemical candidates and then to classify those chemicals to specific toxicological classes based on their gene expression profiles.[9] Potential toxicity mechanisms that may induce characteristic gene expression "fingerprints" include DNA alkylation, inflammation, oxidative stress, peroxisome proliferators, estrogenic action, and many others.

Scenario 5: Screening Requirements for New Chemicals

If DNA microarrays can provide a quick, inexpensive and accurate characterization of the extent and mechanism of a chemical's toxicity, there are a number of regulatory programs where such assays could be used and perhaps required. For example, before manufacturing a new chemical, a manufacturer must submit a pre-manufacturing notice ("PMN") to EPA under section 5 of TSCA. The data EPA requires in such submissions are relatively minimal, and EPA generally bases its assessment of toxicity on structure-activity relationships ("SARs"). The European Union has recently published a White Paper that would require manufacturers to produce much more data for new (and existing) chemicals in order to better evaluate their potential risks. The European chemical companies are concerned that these new testing requirements will be unduly burdensome. Should the U.S. consider a less burdensome, but perhaps even more informative data requirement, by requiring manufacturing to conduct a short gene expression assay using microarrays? Could such a test be required under the current provisions of TSCA?

In addition to potential regulatory applications in the screening of new chemicals under the Toxic Substances Control Act, screening of chemicals using DNA microarrays have a number of other potential regulatory applications. For example, the identification of hazardous wastes based on the characteristic of toxicity could be based on a quick and inexpensive microarray assay that could evaluate whether the waste induces a gene expression profile that is characteristic of a known toxicity mechanism. Similarly, the designation of listed hazardous wastes or chemicals on the Toxic Release Inventory ("TRI") list of reportable substances could be based on the results of DNA microarray analyses.

4. Environmental Clean-Up Standards

Many abandoned waste disposal sites contain large quantities of soils and sediments with moderate or low levels of contamination which present uncertain risks but very large clean-up costs. In many cases, the primary potential hazard is to local ecosystems and species rather than to human health. Assessment of these ecological risks is highly uncertain due to factors such as: incomplete information on the speciation, bioavailability and interaction of contaminants, and the limited ability to test the contaminants in the most sensitive species that may be affected by such contamination. High throughput, automated DNA hybridization array systems are being developed for the direct, rapid and affordable assessments of soil and sediment toxicity at the gene expression level.[10] These assays could use DNA microarrays containing the genes of standard ecotoxicity test species (e.g., flathead minnow, *Daphnia*, and *Arabadopsis*) to interrogate gene expression changes in organisms of those species exposed to the contaminated soil or sediment. Differential expression of stress- response and other genes known to be involved in toxicity response can thus be evaluated.

Scenario 6: Hazardous Waste Site Risk Assessment

EPA is considering bioremediation to complete the clean-up at an abandoned hazardous waste disposal site bordering an ecologically important wetland. Local environmental groups are concerned that the large quantity of soil with low-level contamination at the site presents an ongoing risk to local wildlife species, and are pressuring EPA to require removal of all the contaminated soil, which would be much more expensive than the bioremediation option. A contractor hired by a group of potentially responsible parties conducts a series of studies showing that leachate from the contaminated soil not only fails to cause toxicity in standard ecotoxicity test species, but also induces no change in gene expression in those studies. Do these types of test results provide EPA with adequate assurance to proceed with the less stringent bioremediation option?

In addition to evaluating the sufficiency of the clean-up of hazardous waste sites, gene expression data may be useful for prioritizing contaminated sites. Indeed, in the foreseeable future EPA might want to consider adding gene expression assays to its hazard ranking scheme for establishing the National Priorities List ("NPL") under Superfund.

5. Surveillance and Early Warning

In many cases, environmental risks are not discovered until they are manifested in human disease or death. An early-warning system capable of identifying toxic responses in their early stages, before clinical disease manifests itself, would permit early intervention to monitor and treat affected persons in a more timely and effective manner. Such a detection system would also minimize further exposure to those and other persons. The system could be applied in a number of groups ranging from residents living near a polluting facility or hazardous waste site to a cohort of individuals exposed to a potentially hazardous substance, such as consumers using a particular household product that is suspected of toxicity.

Scenario 7: Surveillance of Pesticide-Exposed Residents

EPA has received anecdotal reports that a commonly used household pesticide has been linked with a variety of health effects including dizziness, headaches, and nausea. Some public health experts have expressed concern about the potential for the pesticide to cause more permanent and serious health effects. A small epidemiology study sponsored by the manufacturer of the pesticide found an increase in cholinesterase inhibition and neurological problems in residents of homes that have used the pesticide, but these increases were not statistically significant. If tests indicated that residents exposed to the pesticide produced a gene expression profile that is characteristic of a known toxicological mechanism, would this result be sufficient to trigger more regulatory attention by EPA? If the tests showed no toxicologically significant changes in gene expression in the exposed residents, would EPA be reassured that the pesticide would not require more extensive study or regulation?

The value of gene expression assays over traditional toxicological endpoints for such surveillance programs for potentially at-risk groups is that they provide a more sensitive and earlier indication of a potential risk. One of the inevitable consequences of using a more sensitive assay is that the results will require careful interpretation and the exercise of judgment by both regulators and companies to avoid false alarms while recognizing truly significant early toxicological responses.

Scenario 8: **TSCA Section 8(e) Reporting**

Section 8(e) of the Toxic Substances Control Act requires the manufacturer of a product to report to EPA information received indicating the potential for a significant risk from its products. If a manufacturer obtains data showing that one of its chemical products induces gene expression changes in animal studies, but there is no other indication of toxicity, is the company required to report that data under section 8(e)? Is the requirement to report stronger if the gene expression changes are characteristic of a known mechanism of toxicity?

II. Susceptibility Genes

A. Scientific Summary

One of the first pay-offs of the Human Genome Project and companion efforts to analyze the human genome is the identification of a growing number of genetic variations that affect

individual susceptibility to xenobiotics.[11] Many of the most frequent genetic polymorphisms that have been identified in the human gene pool appear to affect our individual susceptibility to disease from exposure to toxic substances.[12] For example, about 10 percent of the Caucasian population carries a variant of one cytochrome p450 gene (*CYP1A1*) that increases the rate of metabolism of certain substances and thus the formation of reactive metabolites. This genetic variant has been associated with increased lung cancer risk in smokers in some (but not all) studies.[13] In approximately fifty percent of the Caucasian population, a gene (*GSTM1*) coding for one in another set of metabolic enzymes (the glutathione S-transferases) is completely deleted, which is associated with an increased risk of bladder and lung cancer from exposure to several toxic substances normally detoxified by the *GSTM1* enzyme.[14]

The National Institute of Environmental Health Sciences ("NIEHS") established the Environmental Genome Project in 1997 to identify variations of genes that affect susceptibility to environmental agents.[15] The genes affecting individual susceptibility to environmental agents include those affecting metabolism, DNA repair, cell cycle control, receptors, and immune function.[16] To date, approximately 500 relevant genes have been identified as part of this effort.[17]

Even though tremendous progress has been made in understanding genetic susceptibility over the past few years, attempts to define the genetic susceptibility of an individual are complicated by several factors. To begin with, most of the genes affecting susceptibility are probabilistic rather than deterministic, in that they only increase the risk of disease and are neither necessary nor sufficient to cause disease.[18] The susceptibility genes are generally quite frequent in the population, but the increased (or decreased) risk in any one individual carrier is relatively modest.[19] Moreover, research on genetic susceptibility markers often produces inconsistent results, with some studies finding a significant increased (or decreased) risk of disease from a particular gene-environment interaction, while other studies report no such effect.[20]

Even when a susceptibility genetic marker has been unambiguously identified, its effects

can vary across individuals for a variety of reasons. Some increases in susceptibility are dose-dependent, in that they primarily increase an individual's susceptibility to a toxic agent relative to the general population only at low or high doses. Certain associations appear to be ethnic-dependent, in that the susceptibility associated with a particular gene appears to be limited to particular ethnic groups and is not seen in other groups even when the same gene is present.[21] The distribution of gene frequencies also varies significantly between different ethnic groups.[22] Finally, individual susceptibility to potentially toxic agents is rarely determined by a single genetic locus, but rather is the combined influence of many different genes.[23] Thus, even if testing identifies a specific gene variant with a significant effect on individual susceptibility to a particular agent, the magnitude and nature of the susceptibility conferred by the gene may vary depending on the other gene variants present in a given individual.

Despite these complications, recent findings identifying and characterizing genetic markers of susceptibility demonstrate that there are substantial inter-individual differences in responses to, and risks from, toxic exposures. Perhaps even more important than the knowledge of the existence of frequent genetic heterogeneity within the population is the increasing capability to identify individuals who are more or less susceptible.[24]

B. Potential Regulatory Applications

1. Risk Assessment Practice

EPA currently applies a standard 10-fold uncertainty factor for interindividual variation in susceptibility in calculating a reference dose ("RfD") or reference concentration ("RfC") for non-carcinogens. This default 10-fold uncertainty factor has no specific scientific justification -- it is simply a reasoned policy assumption in the absence of available data. With the identification of genetic polymorphisms affecting susceptibility to environmental agents, it may be possible to replace default assumptions about the differences in susceptibility within the population with science-based data.

Scenario 9: **Data-Based Uncertainty Factors**

Assume that genetic studies indicate two relevant genotypes affecting the metabolism of a particular non-carcinogenic chemical. Assume also that the data indicates that there is a 20-fold difference in susceptibility to that chemical (i.e., individuals with genotype A generally develop a toxic response at a concentration 20-fold lower than individuals with genotype B). How should EPA use this data to calculate RfD or RfC? If EPA decides that the data are robust enough to replace the default uncertainty factor, there are at least two possible perspectives on the new uncertainty factor that should be applied. The first view is that the current default factor is under-protective because it only covers a 10-fold difference in susceptibility, whereas the new data indicates that there is a 20-fold difference within the population. Under this view, a larger uncertainty factor (i.e., 20) is warranted. The alternative view is that the 10-fold uncertainty factor actually covers a 100-fold difference in susceptibility within the human population. If we assume that differences in susceptibility are normally distributed around the "average" person, and that the 10-fold uncertainty factor is applied to the response of that "average" person, then the 10-fold uncertainty factor actually encompasses a 100-fold difference in susceptibility between the most susceptible (i.e, 10x more susceptible than average) and least susceptible (i.e., 10x less than average) individuals in the population. According to this view, the data showing a 20-fold difference between the most and least susceptible groups in the population therefore suggests that the default 10-fold uncertainty factor is over-protective, and that a smaller uncertainty factor (in the range of 5-fold) is justified. Finally, genetic polymorphisms are only one source of variation in human susceptibility. Other factors affecting susceptibility include age, gender, nutritional status, pre-existing health conditions, and past occupational and environmental exposures. How should these susceptibility factors be integrated with genetic susceptibility in evaluating the appropriate uncertainty factor for interindividual variation?

The discovery of widespread genetic variations in susceptibility to toxic substances may undermine one of the assumptions underlying the current approach to risk assessment and regulation of non-carcinogenic compounds. The current approach assumes that there is a threshold level below which no adverse effects occur. While such a threshold may indeed be realistic for any individual, the implication of genetic heterogeneity is that there is no threshold that is applicable to the entire population.[25] In the absence of a scientifically definable threshold for the population, the approach of establishing RfDs and RfCs at levels that will protect the entire population is no longer plausible, to the extent that was the initial objective.[26] With the increased knowledge on the existence and consequences of genetic variations in susceptibility, EPA will thus be faced with making explicit policy and social judgments about what percentage

of the population should be protected.

Unlike the practice for non-carcinogens, EPA does not expressly adjust its risk assessment for carcinogens to account for susceptible sub-populations. The default linear, no-threshold assumption used in carcinogen risk assessment, as well as the practice of basing such risk assessments on the response of the most sensitive species and sex of animals tested, may provide some protection for susceptible groups. The finding of widespread genetic heterogeneity in susceptibility to environmental toxicants may require changes to standard carcinogenic risk assessment practices that generally treat the human population as homogenous. As one commentator argues:

> [R]isk assessments by agencies such as the U.S. Environmental Protection Agency have assumed that the population is biologically homogeneous in response to carcinogens. This default assumption can lead to underestimates of risk to the population and to sensitive subgroups, leading to standards and policies that are not adequately health protective or equitable.[27]

Given the significant differences in susceptibility that may result from critical genetic polymorphisms, it may be appropriate to calculate risks separately for different genotypes. EPA's recently proposed revisions to its carcinogen risk assessment guidelines call for identification of susceptible subgroups and calculation of separate risk estimates for such groups. These revisions, however, provide minimal guidance on how this should be done. Such an undertaking would involve many complexities, as the next scenario demonstrates.

Scenario 10: **Stratified Risk Assessment for Susceptible Subgroups**

Tobacco smoke is one of the carcinogenic agents for which the most evidence exists of significant genetic polymorphisms affecting risk. EPA may therefore find it appropriate to stratify its future risk assessments of environmental tobacco smoke to separate out susceptible subgroups that may be particularly at risk from exposure to second-hand smoke. In conducting separate risk estimates for susceptible subgroups, consider some of the complexities that would face the Agency. Some genetic susceptibilities to environmental tobacco smoke have been observed in some ethnic groups and locations (e.g., China) but not others. In addition, some genetic susceptibilities appear to increase risk relative to the general population only at high exposure levels, whereas others increase risk only at low exposure levels. Finally, there appears to be several different types of genes affecting susceptibility to tobacco smoke, and therefore it may not be feasible to separate different susceptible groups based only on polymorphisms at a single gene locus.

2. Regulations Based on Susceptible Subgroups

The text or legislative history of several federal environmental statutes expressly require EPA to consider susceptible subpopulations. For example, section 108(f)(1)(C) of the Clean Air Act requires the EPA Administrator to provide to federal, state and local regulators information on "measures which may be employed to reduce the impact on public health or protect the health of sensitive or susceptible individuals or groups." Although this particular statutory provision has not had much practical impact, the protection of susceptible subgroups has played a major role in the establishment of national ambient air quality standards under section 109. EPA is required to set NAAQS at a level which are "requisite to protect the public health" with "an adequate margin of safety." Although the statutory language does not refer explicitly to susceptible subgroups, the legislative history of the Act states:

> [T]he Committee emphasizes that included among those persons whose health should be protected by the ambient standard 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 a group.
>
> Ambient air quality is sufficient to protect the 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 or class of such agents (related to a period of time) which will protect the health of any group in 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 a sensitive group that is attributable to the condition of the ambient air.[28]

Consistent with this Congressional directive, EPA has promulgated NAAQS which are intended to protect identifiable susceptible subgroups within the population, such as children with asthma. Not surprisingly, the level of protection needed to protect sensitive subgroups becomes the critical factor in the setting of air standards, to the extent that EPA's risk assessment and regulatory analysis focuses primarily on such susceptible subgroups. As genetic variants are identified that confer susceptibility to toxicants (including air pollutants) are identified, it is likely that in the near future people carrying a particular susceptibility gene may become the sensitive subgroups on which air standards are based. While the legislative history is clear that EPA is required to protect susceptible subgroups and not the most susceptible individuals, EPA likely will face a difficult issue in determining how frequent a genetic polymorphism must be in the population to constitute a susceptible subgroup for purposes of setting air quality standards.

Scenario 11: **NAAQS and Susceptible Populations**

Individuals with a genetic disorder known as alpha-1 antitrypsin deficiency (Alpha-1) have a predisposition to emphysema and other serious lung diseases from exposure to smoke or dust. The Alpha-1 Society, a support group for patients and families with Alpha-1, files a petition with EPA requesting that EPA revise the fine particulate matter NAAQS to provide better protection for people with Alpha-1. The petition is based on studies showing that fine PM at almost any level causes significant lung damage and health effects in people with Alpha-1 disease. How would EPA respond to this petition? If a standard set at zero (or background levels) was the only option that would protect these genetically impaired individuals from lung damage, would EPA set the standard at such level even though it would be infeasible for an industrial society such as the United States to comply with such a standard? An estimated 100,000 Americans are believed to be severely deficient in the alpha-1 antitrypsin protein. If only 1,000 Americans carried a genetic trait requiring a zero-level standard, would EPA set the standard any differently? What if there were only 100 people with the trait? Ten people? To what extent does the susceptible subgroup have to be identifiable? While people with Alpha-1 may be an identifiable group, what about a genetic variant known to be present in the population and to confer susceptibility to an air pollutant, but for which there is presently no commercially test available for identifying individuals carrying that gene variant? Finally, does the air quality standard need to be set at a level which will protect every individual within the susceptible subgroup, or only some subset of that subgroup? If the latter, what degree of protection is required?

The 1996 amendments to the Safe Drinking Water Act (SDWA) require EPA to "conduct a continuing program of studies to identify groups within the general population that may be at greater risk than the general population of adverse health effects from exposure to contaminants in drinking water."[29] The statute expressly limits this undertaking to subpopulations that are "identified and characterized."[30] In its first report to Congress on susceptible subpopulations under the SDWA in December 2000, EPA concluded that because "genetic influences are complex and still poorly understood," it "is unclear to what extent individuals with heightened sensitivities due to genetic factors meet the statutory criterion of 'subpopulations that can be identified and characterized.'"[31] While directing EPA to study and report to Congress its findings on susceptible subpopulations, the SDWA is silent on whether and how EPA should apply these data on susceptible subpopulations in regulatory decisions for drinking water contaminants.

Scenario 12: **Drinking Water Standards for Susceptible Populations**

Glutathione-S-tranferases (GSTs) are an important set of metabolic enzymes that play a critical role in the detoxification of many organic chemicals. The genes coding for these enzymes are highly polymorphic, in that several different variants of the genes for key enzymes in this family exist at significant frequencies in the human population. EPA is proposing to set drinking water standards for the first time for a chemical contaminant on its SDWA Contaminant Candidate List. The chemical appears to be a non-genotoxic carcinogen that may exhibit a threshold. EPA has data showing significantly different cancer potency values and threshold levels for the chemical in ten different GST genotypes prevalent in the U.S. population. How should EPA use this information in setting a Maximum Contaminant Level Goal (MCLG) and Maximum Contaminant Level (MCL) for the chemical in question? Should EPA base the MCLG solely on the most susceptible GST genotype? Does it matter how frequent this GST genotype is in the general population? In conducting a cost-benefit analysis for the MCL, should EPA conduct a tiered analysis for each genotype, calculating the costs and benefits of each alternative standard separately for each genotype, which are then aggregated to produce an overall cost-benefit comparison?

4. *Product Labeling and Self-Help*

The possibility that individuals who are genetically susceptible to a particular product or chemical could be identified creates the potential for a paradigmatic shift in environmental regulation from protecting the entire population with a generic standard towards more individualized interventions that emphasize appropriate warnings and self-help measures. This new approach is most salient for individually administered or used products such as pharmaceuticals. Many pharmaceuticals have had to be removed or kept from the market because of their potentially adverse side-effects in a small percentage of the population.[32] If, as now seems likely, most or all of these adverse effects occur in an identifiable segment of the population that carries a particular genetic polymorphism making that person susceptible to the side-effects, it may be possible to prevent adverse effects without removing the product from the market. If people know their genotype for the relevant gene(s), they could avoid taking drugs to which they are genetically susceptible, assuming that the drugs carried the appropriate genetic warning.

The same approach may apply to some chemical products. If most risks from a particular chemical product can be attributed to genetic susceptibility in some proportion of the public, then

appropriate warnings to, and avoidance behavior by, such persons may be the most effective measure to prevent risks. This approach may also be much less expensive than population-wide protective regulations. Of course, this approach assumes that exposure is a matter of individual choice, which may be the case for some products but not for many ubiquitous pollutants. It also assumes that the non-susceptible general population will be subject to negligible or acceptable risk from uncontrolled exposure to the product. Nevertheless, in certain situations, appropriate warnings to susceptible individuals so that they can take effective precautions to avoid exposure may be the most effective and affordable regulatory approach.

Scenario 13: TCE, *CYP2E1* and Alcohol

Trichloroethylene (TCE) is a widely used industrial solvent. Individuals with a particular variant of one of the cytochrome p450 metabolic enzymes (*CYP2E1)* appear to be more susceptible to cancer from TCE exposure. This risk is exacerbated when the individual also consumes alcohol, which is metabolized using some of the same enzymes as TCE. If the risks from some uses of TCE appeared to involve primarily voluntary use or exposure to the solvent by individuals carrying the *CYP2E1* gene, to what extent should EPA rely on warnings to such individuals to manage those TCE risks? Would EPA warnings against drinking alcohol to people exposed to TCE, either voluntarily or involuntarily, be an effective and acceptable form of environmental protection?

4. Environmental Justice

Genetic susceptibilities to environmental pollutants may also raise environmental justice issues. The traditional environmental justice paradigm has been to safeguard minority or low income populations who have been exposed to disproportionate risks resulting from higher exposures to environmental contaminants. The higher exposure typically occurs to the population of concern clustered in a specific geographical area.

Some commentators have argued that environmental justice principles, and presumably legal protections, should also apply to genetically susceptible subgroups. Such application of environmental justice would be consistent with the ethical principle that individuals should not be exposed to disproportionate environmental risk based on intrinsic factors beyond their control.

Yet, application of environmental justice to genetic susceptibility would involve several shifts from the traditional environmental justice paradigm. First, genetically susceptible individuals are not concentrated geographically into a local community, but rather are likely to be dispersed throughout the general population. This application would not be without precedent. For example, EPA's National Environmental Justice Advisory Committee has recently been evaluating environmental justice issues with regard to fish consumption by subsistence fishermen and Indian tribes, which are not always concentrated in a particular location.

A second issue is whether environmental justice applies to disproportionate risk or disproportionate exposure. As discussed above, the traditional environmental justice paradigm addresses the unfairness of inequitable *exposure* to toxic substances by poor or minority groups due to factors such as their lack of empowerment to resist polluting facilities. Should environmental justice also apply to people who are not exposed to higher levels than the general population, but who are at an elevated risk from that exposure?

Finally, genetic susceptibilities are not always concentrated in specific racial groups or low income populations, although some genetic polymorphisms conferring susceptibility are more concentrated in some racial groups than others.[33] To the extent that environmental justice applies to genetic susceptibility, does it apply only to those genetic susceptibilities that are disproportionately concentrated in particular ethnic groups? Do they have to be disadvantaged ethnic groups? Because race itself has no direct causal role in the higher risks that genetically susceptible groups may face, it makes little policy sense to apply environmental justice to those genetic susceptibilities that are clustered in particular racial groups but not to genetic susceptibilities more evenly spread throughout the population. Yet, both the legal and policy underpinnings of environmental justice policies are based primarily on race.

Scenario 14: **Environmental Justice and Susceptible Subpopulations**

A citizen's group files a petition under EPA's Environmental Justice guidelines claiming that a State's approval of an air pollution permit for a new facility will have a substantial and adverse disparate impact on individuals in the local community carrying a particular genetic polymorphism. This polymorphism makes them particularly sensitive to one of the pollutants emitted by the new facility. There is no evidence that persons with such susceptibility receive higher exposures than any other segment of the population. How would EPA address this complaint? From an environmental justice perspective, is it necessary that the susceptible genetic polymorphism be primarily found in a disadvantaged racial group?

Another example of the potential interaction of genetic susceptibility and environmental justice is raised by the common home gardening pesticide rotenone. Recent studies have suggested that rotenone may cause or contribute to the development of Parkinson's disease in individuals with certain genetic susceptibilities, and this risk factor appears to be higher for Caucasian and Hispanic populations than for African Americans. (*See* Charles W. Schmidt, *Toxic Triggers: Genes , Pesticides, and Parkinson's Disease*, Genome News Network (Mar. 12, 2001) (available at http: gnn.tigr.org/articles/03_01/Toxic_triggers.shtml). How would EPA incorporate environmental justice into its decisionmaking process for this pesticide?

5. Americans with Disability Act

The Americans with Disability Act ("ADA") requires that no person with a disability shall be denied the benefits of the services, programs, or activities of a public entity, or subjected to discrimination by any such entity, because of his or her disability. The ADA defines "discrimination" as a failure 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 such policies, practices, or procedures.

In 1999, an organization called "Save Our Summers" filed the first lawsuit under the ADA claiming that the statute applied to environmental programs. The lawsuit claimed that a permit issued by the Washington Department of Ecology violated the ADA because it authorized burning of wheat stubble which produced smoke that prevented two nearby children, one with asthma and one with cystic fibrosis, from availing themselves of public facilities such as schools, roads, and parks. Washington State defended the case by arguing that the ADA did not apply to activities regulated and permitted under the Clean Air Act. After the U.S. district court denied the plaintiff's motion for a preliminary injunction based on its preliminary conclusion that the

ADA claims were foreclosed by the comprehensive regulatory scheme of the CAA, the U.S. Department of Justice ("DOJ") filed an *amicus curiae* brief arguing that the ADA and CAA could be read harmoniously. According to the DOJ, the ADA could apply to environmental programs and require reasonable accommodations for disabled persons, but could not be used to effect a fundamental modification of an existing statutory scheme. Based in large part on this argument by the federal government, the district court refused to dismiss the case,[34] which then settled prior to trial.

Persons with a known genetic susceptibility to an environmental pollutant may therefore argue that the ADA requires more stringent environmental protection, at least where such added protection would not fundamentally alter the existing statutory scheme. It will be up to regulatory agencies in the first instance, and to the courts ultimately, to determine whether and how the ADA applies to environmental regulation.

Scenario 15: The ADA and Environmental Permits

EPA has permitting authority under the Clean Air Act in Maryland. A permitted facility in that state requests a two-year variance from a certain regulatory requirement based on feasibility. EPA is inclined to grant the request for a variance, but its decision to grant or deny the request is entirely discretionary. A family residing near the facility objects to the proposed variance on the ground that several members of the family carry a genetic susceptibility to pollutants emitted by the facility, and that the variance would result in increased emissions that would unnecessarily limit their activities in violation of the ADA. How should EPA respond to this argument? Would a requirement under the ADA to deny an otherwise discretionary waiver constitute a fundamental alteration of the Clean Air Act?

Conclusion

Toxigenomics and the identification of environmental susceptibility genes are rapidly and fundamentally transforming the practice of toxicology. As stated in one recent review, "[u]nlike other new approaches or methods in toxicology that have been adopted slowly, genomic,

proteomic and metabonomic methods are being evaluated and adopted rapidly by industry, academia and regulatory agencies. There is evidence that the practice of toxicology has begun to change and that change can be expected to occur rapidly."[35]

Just as toxicogenomics is rapidly changing toxicology, it is also likely to fundamentally transform environmental regulation, which often relies on the output of toxicological studies. As this White Paper demonstrates, there are numerous potential applications of toxicogenomics and susceptibility genes for environmental regulation. Many of these potential applications will create difficult policy issues for EPA, such as whether to base environmental standards on the most genetically susceptible subgroups in the population. There will also be many challenges in collecting, interpreting, validating, and applying these data in a reliable manner. While other federal agencies such as the National Institute of Environmental Health Sciences are taking the lead in assembling and standardizing genomic data relevant to environmental exposures, it will be front-line regulatory agencies such as EPA that will ultimately have the challenge and opportunity of applying genomic data to specific environmental risk assessments and regulatory decisions.

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ENDNOTES

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[8]National Institute of Environmental Health Sciences, News Release: National Center for Toxicogenomics to Study Genetic Basis of Disease Caused by Environmental Pollution (Dec. 7, 2000) (http://www.niehs.nih.gov/nct/pr07de00.htm).

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[10]Herbert L. Frederickson et al., *Towards Environmental Toxicogenomics – Development of a Flow-Through, High-Density DNA Hybridization Array and Its Application to Ecotoxicity Assessment*, 274 SCI. TOTAL ENVT. 137 (2001).

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[12]Kenneth Olden & Janet Guthrie, *Genomics: Implications for Toxicology*, 473 MUTAT. RES. 3, 3-4 (2001). Two types of susceptibility genes can be distinguished. *Id.* at 8. One category, which includes genes such as BRCA1 which predispose the carrier to breast cancer, increase the risk of one or more diseases independent of any environmental exposure. The second category of susceptibility genes, which are the primary focus of the present paper, are those that increase the risk of disease from exposure to particular toxic agents. *See also* Neil Caporaso & Alisa Goldstein, *Cancer Genes: Single and Susceptibility: Exposing the Difference*, 5

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[14] *See* Radim J. Sram, *Effect of Glutathione S-transferase M1 Polymorphisms on Biomarkers of Exposure and Effects*, 106 ENVTL. HEALTH PERSP. 231, 231–32 (Supp. 1 1998).

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[16]Rothman et al., *supra* note , at C3.

[17]*See* Susan M. Booker, *Environmental Genome Project: A Positive Sequence of Events*, 109 ENVTL. HEALTH PERSPECT. A22 (2001).

[18]Olden & Guthrie, *supra* note , at 5. The susceptibility genes are therefore different than deterministic disease-causing genes such as those that cause cystic fibrosis, Tay-Sachs disease, or Huntington's Disease.

[19]*See* Caporaso & Goldstein, *supra* note , at 60.

[20]Au, *supra* note , at 215-17.

[21]Au, *supra* note , at 217.

[22]Au, *supra* note , at 217-19.

[23]*See* Weber, *supra* note , at 182; Au, *supra* note , at 217.

[24]*See* Wendell W. Weber, *Effect of Pharmacogenetics on Medicine*, 37 ENVTL. & MOLECULAR MUTAGENESIS 179 (2001).

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[35]Aardema & MacGregor, *supra* note , at 3.