



Applying Toxicogenomics Data in Chemical Regulation

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About the Author

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Executive Summary

Exposure of organisms' cells to environmental toxins may result in changes to normal cell processes and in adverse health effects. Toxicogenomics—the study of “how genomes respond to environmental toxicants”—could offer tremendous opportunities for assessing and preventing adverse human health effects from chemical exposure. This paper provides an overview of the current state of the art of genomic science and technology, and its relevance for risk assessment and chemical regulation, with a focus on the Toxic Substances Control Act (TSCA).

Toxicogenomics data can contribute to the Environmental Protection Agency's (EPA's) chemical review process in several important ways. The applications of toxicogenomics data could play a role in product screening of new chemicals, regulation of listed hazardous chemicals, testing requirements for further generation of risk data, as well as in reporting requirements of “health and safety studies” and known “substantial risks.”

Despite the great potential of these technologies, the paper also discusses the many scientific uncertainties and the consequent regulatory, social, and ethical challenges that still exist. These various uncertainties and challenges are delaying the realization of the potential of toxicogenomics. To help overcome some of the uncertainties and challenges as well as facilitate the use of toxicogenomics data as a tool for chemical toxicity determinations, the paper suggests two key processes that must happen: (1) data must be generated broadly, and (2) data must be validated. Possible mechanisms to meet these goals include the following:

For data generation:

- Amend TSCA to provide EPA with the authority to require companies submitting premanufacture notices (PMNs) under TSCA section 5 to include the results of gene expression assays in their submissions. EPA could incorporate these data into a database of chemical-specific gene expression information. To encourage the development and submission of such data, EPA may provide a “safe harbor” from enforcement and regulation until the methodology has been adequately validated.
- Implement a voluntary program, similar to the voluntary HPV (High Production Volume) Challenge Program, or expand on that program, encouraging companies to conduct genomic testing and to share that data with EPA under a “safe harbor.”

For data validation:

- Develop guidelines for comparison and evaluation of data, including developing Best Management Practices to correlate quantitative or qualitative changes in genes, proteins or metabolic processes with the potential for adverse effects as an interim step. Such efforts have already begun, as in the *Interim Guidance for Microarray-Based Assays: Regulatory and Risk Assessment Applications at EPA*.
- Utilize partial validation to help determine and prioritize where further testing is needed. If unreasonable risk concerns are shown, EPA could shift the burden of proof to manufacturers to carry out further testing without amending TSCA. Under

this approach, EPA would need to develop a scientific-legal doctrine of what toxicogenomics data findings constitute “unreasonable risk,” and to explain how and why the toxicogenomics data are sufficiently reliable to require further testing.

Efforts to generate and collect substantial toxicogenomics data from chemical manufacturers combined with accurate validation and interpretation of this data could greatly enhance the future chemical oversight system.

I. Introduction

Continuous innovations in genomics technologies are revolutionizing our understanding of the biological system, resulting in substantial impacts on the fields of environmental risk science and regulation. Following the decoding of the DNA structure in the 1950s and the more recent sequencing of a draft genome, new opportunities and challenges for the environmental health science community, as well as for government regulators and regulated industry are emerging. Along with scientific advances, new technologies have been developed to enable tracking of the genomics sequences within an organism cell. Such technologies steadily enhance our understanding of the biological system, allowing better examination of environmental disease mechanisms as well as the identification of individual susceptibility to certain toxins.

Still, with supply comes demand, and genomics technologies are now trying to keep pace with the increasing demand for molecular epidemiological and toxicological information. The potential applications of such information are enormous both for risk assessment methods and for regulation; they may significantly impact toxic tort litigation. However, these applications are not without challenges. State-of-the-art genomics science and technology is far from complete, and the uncertainties involved give rise to many scientific, regulatory, social, and ethical challenges.

Because of the broad scope of these issues, this paper focuses only on genomics technologies applicable to toxicological studies, and it attempts to deal only with the applications and implications of such technologies in the context of chemical regulation, particularly under the Toxic Substances Control Act (TSCA). Consequently, this paper omits issues related to genetic susceptibility, and focuses almost exclusively on the role of genomics for understanding and reducing adverse human health effects.

II. Toxicogenomics: Scientific and Technological Background

A. The Current State of Environmental Toxicology

Toxicology, the scientific study of the adverse effects of chemicals on living organisms, is at the interface of chemistry and biology. It is based on three basic scientific propositions: first, all chemical agents are toxic at some dose; second, toxic agents have different effects depending upon their inherent nature and the biological niches in which they interact; and third, data from laboratory animal testing can be extrapolated to human beings. Accordingly, toxicology aims to anticipate dose-response relationships in humans by extrapolating high-dose results of animal testing to estimated human doses.¹

As implied from this methodology, however, uncertainties are inherent in dose-response relationships. Uncertainties may stem from bias in study design and performance (e.g., toxicology studies do not consider socioeconomic status and behavioral factors which may affect individuals' exposures), randomness of sample size, measurement imprecision, variability of exposure conditions (such as natural environment and climate), and individual susceptibility.² While some methods, such as the safety factors approach³ and the linear model,⁴ try to overcome the scientific limitations, some critics believe that these limitations are daunting.⁵

Nevertheless, using molecular biology methods⁶ to evaluate markers of toxic response may offer a more accurate way of assessing human risks. Molecular epidemiology, for example, tests chemical exposure by quantifying the body's chemical burdens or metabolites. It then predicts health effects based on changes in biochemical functions associated with chemical

¹ *Toxicology*, ENCYCLOPEDIA OF PUBLIC HEALTH (Answers Corporation, 2006), available at: <http://www.answers.com/topic/toxicology>, last visited December 2, 2006.

² The National Academies, *The Board on Environmental Studies and Toxicology, Science and Judgment in Risk Assessment*, 164, 189 (1994).

³ Safety factors are based on no-observed-effect levels (NOEL) in animals, which are then reduced by factors of ten based on the assumption that humans are more sensitive than the animals tested, and that human susceptible groups are more diverse; this results in a hundred-fold safety level. An additional ten-fold measure can be added based upon the toxic endpoint involved, or in order to protect children. See, Jan Ziegler, *Toxicity Tests in Animals: Extrapolating to Human Risks*, 101 ENVIRON HEALTH PERSPECTIVE (October 1993), available at: <http://www.ehponline.org/docs/1993/101-5/focus.html>, last visited December 2, 2006.

⁴ In the linear model, the risk to humans is estimated from the dose-response relationship in animals. *Id.*

⁵ When scientists integrate the available toxicological data to arrive at a consensus opinion, they must consider a variety of qualitative experimental factors and make a judgment regarding the relative weight to be given to different toxicological studies. These judgments are made regardless of quantitative estimates of toxicity, thus allowing uncertainties in toxicological methods to spread through to the final assessment of a chemical's toxicity, risk estimates of harm from specific chemical exposures, and the regulatory standard chosen. See, David E. Adelman, *The False Promise of the Genomics Revolution for Environmental Law*, 29 HARV. ENVTL. L. REV. 117, 123-127 (2005).

⁶ Molecular biology methods have been applied to environmental toxicology since the 1980s, and they focus on identifying novel biological indicators ("biomarkers") that provide very sensitive tests for toxicity exposure and disease onset. *Id.*, at 128-129.

exposure. Finally, these methods may measure individual susceptibility to harm from chemical exposures.⁷ A more detailed discussion of other molecular biological methods follows.

B. Overview of Genomics Science

Before addressing various molecular biology methods and the new “omics”⁸ technologies, it is important to understand the basic biological principles behind these technologies. A simplified way to illustrate the function of an organism would be to focus on the function of one cell. One may imagine an organism cell as a factory, within which there is a headquarters (DNA) located in the nucleus, which keeps all the information (the genes) necessary for the operation of the factory. When the headquarters receive an order to produce a product, it searches for a recipe (the active genes) to make this product. Then, it makes some copies of the recipe (mRNAs) and sends them to the manufacturing area, out of the nucleus into the cytoplasm. The mRNA is actually a “blueprint” for the production of proteins, which can be thought of as the functional entities in the cell (although today it is known that various functions are preformed by entities other than proteins). An example of a function for a protein could be the consumption or production of a metabolite.⁹ Today, each of these stages in the “factory process” represents a whole field of biology studies; and the emergence of technologies that allow biologists to follow all the genes’ responses in the genome¹⁰ give rise to fields of study including genomics, transcriptomics, proteomics, and metabolomics.¹¹

When a cell is exposed to a toxic environmental agent, it may respond by changing its normal processes. This can be reflected as qualitative or quantitative changes in gene expression or in downstream effects.¹² Put simply, a post-exposure sequence supposedly starts with changes in gene expression, followed by downstream changes in the proteins those genes code for, and followed by changes in metabolite profiles related to the changes in proteins.¹³ Traditional toxicology methods would involve looking only at changes in single biochemical pathways or at effects on the organism as a whole; however, the recent technological advances in biological research enable researchers to examine simultaneous changes in thousands of genes, as well as in protein and metabolism profiles.¹⁴ These developments have led to a new

⁷ *Id.*

⁸ *Omics* is a neologism referring to a field of study in biology, ending in the suffix “-omics.” It stems from the Greek word for “all”, “whole” or “complete.” See, Omics.org website at: http://omics.org/index.php/What_is_omics, last visited November 11, 2006.

⁹ For a general discussion see, Bruce Alberts et al., *MOLECULAR BIOLOGY OF THE CELL* § 6 (4th ed. Garland Science, 2002).

¹⁰ Traditionally, biologists have been able to follow the response of only a few genes in each level (e.g., changes in the concentration of one specific type of mRNA molecule or protein).

¹¹ EPA’s Science Policy Council, Potential Implication of Genomics for Regulatory and Risk Assessment Applications at EPA, 5-7, (December 2004), available at: <http://www.epa.gov/osa/pdfs/EPA-Genomics-White-Paper.pdf>, last visited November 11, 2006. (“EPA White Paper on Toxicogenomics”)

¹² Jamie A. Grodsky, Genetics and Environmental law: Redefining Public Health, 3 CAL. L. REV. 171, 192 (2005).

¹³ Environmental Defense, TOXICOGENOMICS: HARNESSING THE POWER OF NEW TECHNOLOGY, 5, (2005), available at: http://www.environmentaldefense.org/documents/4532_ToxicHarnessingPower.pdf, last visited November 11, 2006.

¹⁴ EPA White Paper on Toxicogenomics, *supra* note 11.

toxicological approach, toxicogenomics, which allows identification and characterization of the genomics effects of environmental toxicants through gene and protein expression.¹⁵

Research in molecular biology is mainly focused on genes for which correlation between genetic changes and disease development has been identified. These may include metabolic genes, DNA repair genes, and genes associated with cellular replication.¹⁶

C. Overview of Toxicogenomics Technologies

Toxicogenomics is defined as the study of “how genomes respond to environmental toxicants.”¹⁷ This discipline combines expertise in toxicology, genetics, molecular biology, and environmental health. By using technologies that enable measurement of gene sequence variation, gene transcription,¹⁸ protein expression,¹⁹ and metabolite profiles²⁰ in response to environmental stressors,²¹ toxicogenomics can compare gene expression and protein and

¹⁵ The National Institute of Environmental Health Science (NIEHS), the National Center for Toxicogenomics (NCT), Concept Statement, available at: <http://www.niehs.nih.gov/nct/concept3.htm>, last visited November 11, 2006.

¹⁶ Trinia Simmons and Christopher J. Portier, *Toxicogenomics: The New Frontier in Risk Analysis*, 23 CARCINOGENESIS 903, (2002), available at: <http://carcin.oxfordjournals.org/cgi/reprint/23/6/903>, last visited November 12, 2006.

¹⁷ Gary E. Marchant, FORESIGHT AND GOVERNANCE PROJECT, THE WOODROW WILSON INTERNATIONAL CENTER FOR SCHOLARS, GENOMIC AND THE ENVIRONMENTAL REGULATION: SCENARIOS AND IMPLICATIONS, 4, (January 2002), available at: <http://www.law.asu.edu/files/Programs/Sci-Tech/Commentaries/marchantwhitepaper.pdf>, last visited November 11, 2006.

¹⁸ Transcriptomics data are gathered using the micro-array technology. Using a collection of microscopic DNA spots, micro-arrays allow scientists to determine, in a single experiment, the expression levels of thousands of genes within a cell by measuring the amount of mRNA bound to each site on the array. This should provide the opportunity to search for expression signatures reflecting pathways of toxic injury. See e.g., the National Institute of Health (NIH), The National Human Genome Research Institute (NHGRI), DNA Microarray Fact Sheet, available at: <http://www.genome.gov/10000533>, last visited November 11, 2006.

¹⁹ Proteomics data are gathered using technologies such as gel electrophoresis, mass spectroscopy (MS) and micro-arrays that can identify and measure the amounts of hundreds of proteins within the cell simultaneously. These are used to analyze global alterations of protein expression. See e.g., Raymond W. Tennant, *The National Center for Toxicogenomics: Using New Technologies to Inform Mechanistic Toxicology*, 110 ENVIRONMENTAL HEALTH PERSPECTIVES A8, A9, (January 2002), available at: <http://www.ehponline.org/docs/2002/110-1/EHP110pa8PDF.PDF>, last visited November 12, 2006. Also, Proteomics approaches can be used to study covalent post-translational modifications that are directly or indirectly associated with chemical toxicity. Since chemical toxicity principally targets proteins (and not the DNA), proteomics analysis offers an important improvement in toxicology research. See, Kenneth S. Ramos, *A Vision that Challenges Dogma Gives Rise to a New Era in the Environmental Health Science*, ESSAYS ON THE FUTURE OF ENVIRONMENTAL HEALTH RESEARCH 162, 164 (2005), available at: <http://www.ehponline.org/docs/2005/7930/7930.pdf>, last visited December 3, 2006.

²⁰ Metabolomics data are gathered with high throughput technologies such as nuclear magnetic resonance (NMR) spectroscopy and mass spectroscopy (MS), which can characterize tissue-wide patterns of chemical metabolites. See e.g., Charles W. Schmidt, *Metabolomics: What's Happening Downstream of DNA*, 112 ENVIRONMENTAL HEALTH PERSPECTIVES A410, A412, (May 2004), available at: <http://www.ehponline.org/txg/members/2004/112-7/112N07Focus.pdf>, last visited November 11, 2006. These patterns would allow comprehensive assessment of changes in the cellular microenvironment caused by the presence of toxic chemicals. See, Ramos, *supra* note 19.

²¹ THE NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES, TOXICOGENOMIC TECHNOLOGIES AND RISK ASSESSMENT OF ENVIRONMENTAL CARCINOGENS: A WORKSHOP SUMMARY, 4-5, (2005).

metabolism profiles in normal cells with those of cells stressed by exposure to specific environmental agents.²² Simultaneous observation and analysis of these effects on thousands of genes, proteins and metabolites is made possible by using computational tools developed in the field of “bioinformatics.”²³ By creating these opportunities, toxicogenomics can shed light on the process of how normal cells and tissues become diseased.

An extensive literature describing the promises of toxicogenomics²⁴ emphasizes that these new technologies may usher in a new era of more sensitive and reliable biomarkers of toxic exposure, effect, and susceptibility.²⁵ For those biomarkers that can be “validated,” these data may help establish causal associations in tort litigation²⁶ as well as in regulatory practice. In addition, application of genomics methodologies may help reduce use of animal testing and may improve the evaluation of the cumulative effects of multiple chemicals on individual exposure.²⁷

²² EPA White Paper on Toxicogenomics, *supra* note 11.

²³ This field was developed to manage and store vast and varied datasets, identify patterns in the data, make comparisons, determine statistical significance, and work toward standardization of measurement units. *See*, Environmental Defense, *supra* note 13, at 6. According to Ramos, “bioinformatics remains the most significant challenge to future development and maturation of the field of toxicogenomics.” *Supra* note 19.

²⁴ Together with *toxicogenetics*, a discipline that studies the relationship between innate genetic makeup and susceptibility to the effects of toxic substances. *See* Grodsky, *supra* note 12 at 191.

²⁵ Adelman, *supra* note 5, at 118. For more discussion on toxicogenetics and toxicogenomics promises, *see e.g.*, Gary E. Marchant, *Genomics and Toxic Substances: Part I -- Toxicogenomics*, 33 ELR 10071 (2003); Gary E. Marchant, *Genomics and Toxic Substances: Part II -- Genetic Susceptibility to Environmental Agents*, 33 ELR 10641 (2003); Grodsky, *supra* note 12 at 194-8; and Environmental Defense, *supra* note 13, at 7-9.

²⁶ According to Gary E. Marchant, data on genetic susceptibility of individual plaintiffs, and data on genetic biomarkers of exposure and effect, are likely to have the biggest impact in toxic tort litigation. Gary E. Marchant, *Genetic Data in Toxic Tort Litigation*, 14 J. L. & POL'Y 7, 8 (2006). *See also*, Jon R. Pierce and Terrence Sexton, *Toxicogenomics: Toward the Future of Toxic Tort Causation*, 5 N.C.J.L. & TECH. 33 (2003).

²⁷ EPA, *Interim Policy on Genomics*, 3, (Washington, DC, 2002), available at: <http://www.epa.gov/osa/spc/pdfs/genomics.pdf>, last visited December 4, 2006.

III. Applications of Toxicogenomics Data in Chemical Regulation

Since the 1970s, the U.S. government has used risk assessment methods²⁸ to collect data in order to reduce risks to public health (including risks from environmental exposures). As human data are not frequently available, risk assessment relies substantially on toxicological data. Following the recommendations of the President's Science Advisory Committee's panel on the Handling of Toxicological Information, in 1966, several governmental programs began a systematic collection of toxicology data for regulatory purposes.²⁹ Still, traditional methods are insufficient for gathering information on many disease mechanisms, inadequately sensitive for studying low-dose effects, fraught with uncertainty regarding animal-human extrapolation, time consuming, and costly.³⁰

If toxicogenomics technologies yield what they promise, toxicogenomics data may fill some of these gaps. However, commentators also recognize the many challenges ahead. For example, in the *Interim Policy on Genomics* (2002), the EPA acknowledged that “[w]hile genomics offers the opportunity to understand how an organism responds at the gene expression level to stressors in the environment, understanding such molecular events with respect to adverse ecological and human health outcomes are far from established.”³¹ Thus, the Policy concludes that genomics data alone are insufficient as a basis for decision-making, but may serve as supporting information for various assessment and regulatory purposes, on a case-by-case basis.³²

Following the release of the Interim Policy, the Science Policy Council requested that a Genomics Task Force examine the broader applications of genomics data in EPA programs and

²⁸ NRC defined risk assessment as “the qualitative or quantitative characterization of the potential health effects of particular substances on individuals or populations.” NRC, *RISK ASSESSMENT IN THE FEDERAL GOVERNMENT: MANAGING THE PROCESS*, 38, (National Academies Press, 1983). Risk assessment includes four elements: (1) hazard identification - examines epidemiological, clinical, toxicological, and environmental research to determine whether exposure to an environmental agent causes adverse health effects; (2) dose-response assessment – used when epidemiological and clinical data are not available - extrapolates results of adverse health effects of high dose in animal tests to anticipate similar health effects at low dose in humans; (3) exposure assessment - estimates the number and characteristics of people who will be exposed to a hazard at various intensities and durations; and (4) risk characterization - estimates the existence and magnitude of the public health problem; including uncertainties inherent in the process of inferring risk. *Id.* at 18.

²⁹ For discussion on the various programs, see U.S. National Library of Medicine, *Fact Sheet: Toxicology and Environmental Health Information Program*, available at: <http://www.nlm.nih.gov/pubs/factsheets/tehipfs.html>, last visited December 2, 2006.

³⁰ Marchant, *supra* note 17, at 5. A rodent cancer bioassay, for example, may last four years, expending 1,200 animals and millions of dollars in the process. See, Jennifer F. Medlin, *Timely Toxicology*, 107 ENVIRONMENTAL HEALTH PERSPECTIVE A256 (May 1999), available at: <http://www.ehponline.org/docs/1999/107-5/innovations.html>, last visited March 30, 2007.

³¹ EPA Interim Policy on Genomics, *supra* note 27, at 1.

³² *Id.* at 2. For example, a pesticide registrant has cited several published genomic articles to propose an alternative mode of action that would affect human health assessment as part of their data package submission for product registration to EPA's Office of Pesticide Programs. See, EPA White Paper on Toxicogenomics, *supra* note 11, at p. 4.

policies.³³ In December 2004, the Task Force published its findings in a White Paper entitled *Potential Implications of Genomics for Regulatory and Risk Assessment Applications at EPA*.³⁴ In this document, the EPA identified four areas of practice that are likely to be influenced by the generation of genomics information: risk assessment methods, prioritization of contaminants and contaminated sites, monitoring, and reporting.³⁵ The following is a discussion of implications for some of these elements under the Toxic Substances Control Act (TSCA).³⁶

TSCA requires manufacturers to provide data on the health and environmental effects of chemical substances and mixtures, and requires EPA to regulate chemical substances and mixtures that present an unreasonable risk of injury to health or the environment.³⁷ This “unreasonable risk” determination is based on consideration of the substance’s effects on human health and the environment; the magnitude of the exposure to the substance; the benefits of the substance; the availability of substitutes; and the economic consequences of the rule.³⁸ TSCA authorizes EPA, *inter alia*, to require pre-manufacture notification of new chemicals, to promulgate chemical test rules, to regulate or ban chemical substances, and require reporting of health and safety studies or health impacts where a substance presents a substantial risk of injury to health or the environment.³⁹ When performing its responsibilities, EPA is required to consider the cost of the regulation so as “not to impede unduly or create unnecessary economic barriers to technological innovation”⁴⁰

A. Product Screening of New Chemicals (Prioritization of Contaminants)

Under TSCA section 5, any company intending to manufacture or import a new chemical substance or an existing chemical substance with significant new use must give EPA pre-manufacture notification (PMN) of 90 days to enable it to screen the product before its commercialization.⁴¹ The PMN is accompanied by available risk assessment data.⁴² If the new chemical or the new use presents or will present an unreasonable risk of injury to health or the environment, or if the data are insufficient to allow a sound evaluation of the health and the environmental effects, EPA can prohibit or limit its commercialization.⁴³

³³ *Id.*

³⁴ EPA White Paper on Toxicogenomics, *supra* note 11.

³⁵ *Id.* at 10-29.

³⁶ Pub L. 94-469 (1976); 15 U.S.C.A. §§ 2601-2629 (2006).

³⁷ TSCA, § 2(b)(1) and (2); 15 U.S.C.A. § 2601(b)(1) and (2) (2006).

³⁸ 15 U.S.C.A. § 2605(c) (2006).

³⁹ TSCA, §§ 4-6, 8; 15 U.S.C.A. §§ 2603-5, 2607 (2006).

⁴⁰ TSCA, § 2(b)(3); 15 U.S.C.A. § 2601(b)(3) (2006).

⁴¹ 15 U.S.C.A. § 2604(a) (2006).

⁴² 15 U.S.C.A. § 2604(b) (2006).

⁴³ 15 U.S.C.A. § 2604(e) and (f) (2006).

As of 2007, there were about 83,000 chemicals listed in the TSCA inventory, 62,000 of which were already in commerce when EPA began reviewing chemicals in 1979.⁴⁴ EPA has sufficient data on only a portion of these chemicals that would allow a thorough evaluation of the risks they pose for human health and the environment.⁴⁵ EPA reviews approximately 1,500 PMNs for new chemicals or new uses annually.⁴⁶ Traditional toxicological testing for all chemicals in commerce is very costly (\$1-5 million per chemical), time consuming (2-4 years per chemical), and requires significant laboratory capacity.⁴⁷ Lack of money, time and human resources restricts such tests to only a small percentage of the chemicals in commerce.⁴⁸

Because of these constraints, EPA has developed methods to predict chemicals' potential exposure and toxicity levels by comparing the new chemicals with chemicals that have similar molecular structures and for which toxicity information is available,⁴⁹ and has prioritized other chemicals for further evaluation. Typically, chemical prioritization is determined based on production volume, exposure information, persistence, chemical class, analysis of structural analogies, and consideration of more formal structure-activity relationships (SARs); however, data gaps occur at various stages.⁵⁰

Genomics data may be useful for prioritizing PMNs. While traditional testing requires separate tests to evaluate each endpoint, genomics technologies, such as microarrays, can simultaneously monitor all gene expression changes within a cell, thus potentially allowing the evaluation of many toxicological responses in a single assay.⁵¹ Genomics technologies may also allow the development of gene expression and protein and metabolic profile fingerprints that can characterize inexpensively and effectively chemicals with unknown mode of actions (MOAs)⁵² based on their endpoint effect.

Such comprehensive assays along with the characterization of the endpoints may provide high-throughput screening of chemicals and a more efficient approach to risk-based

⁴⁴ Telephone Interview with an official at the Industrial Chemistry Branch, Economic, Exposure and Technology Division (EETD), the Office of Pollution Prevention and Toxics (OPPT), EPA (May 21, 2007); and *Actions Are Needed to Improve the Effectiveness of EPA's Chemical Review Program*: hearing before the Senate Comm. on Environment and Public Works, 109th Cong. (2006) (statement of John B. Stephenson, Director, Nature Recourses and Environment, U.S. Government Accountability Office), available at: http://www.epw.senate.gov/109th/Stephenson_Testimony.pdf, last visited December 23, 2006. ("GAO statement")

⁴⁵ EPA White Paper on Toxicogenomics, *supra* note 11, at 10.

⁴⁶ Linda-Jo Schierow, *The Toxic Substances Control Act: A summary of the Act and Its Major Requirements* 4 CRS REPORT FOR CONGRESS RL31905 (December 1, 2004).

⁴⁷ Marchant, *supra* note 17, at 9-10.

⁴⁸ *Id.*

⁴⁹ GAO statement, *supra* note 44 at 3.

⁵⁰ EPA White Paper on Toxicogenomics, *supra* note 11, at 10.

⁵¹ Marchant, *Toxicogenomics Part I*, *supra* note, 25, (text adjoining footnote 141)

⁵² The term "mode of action" is defined as "a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation." EPA, *Guidelines for Carcinogens Risk Assessment* 1-10 (March 2005), available at: <http://www.epa.gov/IRIS/cancer032505.pdf>, last visited December 16, 2006.

prioritization. Still, it is important to first determine which model to employ for the screening and which endpoints to look for.⁵³ The same approach can also be applied to the voluntary high production volume (HPV) screening processes.⁵⁴ In the near future, these methods may also be used to validate category groupings in HPV screening. In the longer term, these techniques may be used to help correlate an endpoint observed in animal testing with an adverse health effect in humans, supplementing or supplanting animal testing needed to complete the Screening Information Data Set (SIDS).⁵⁵

B. Regulation of Listed Hazardous Chemicals

Under TSCA section 6, EPA is authorized to determine whether to allow and condition the distribution of a certain product in commerce. EPA may promulgate a rule to restrict or ban commercialization or require the labeling of chemicals that present an “unreasonable risk of injury to health or the environment.”⁵⁶

Genomics technologies, as previously mentioned, may enhance the understanding of dose-response mechanisms at the molecular level. Such understanding may result in more sensitive and relevant biomarkers of effect and may help identify low-dose effects characteristic of human exposure.⁵⁷ Biomarkers of effect may apply in “points of departure” (PODs)⁵⁸ determinations when establishing doses at which no adverse effects are seen (NOAEL), and the lowest doses at which an adverse effect is seen (LOAEL).⁵⁹ Limits on doses, established based on changes in gene expression, may result in higher or lower PODs than those established based on frank toxicity methods.⁶⁰ Also, as genomics data may reflect individualized susceptibility to certain toxins, this determination may shift the focus of a NOAEL or LOAEL from entire

⁵³ Marchant, Toxicogenomics Part I, *supra* note, 25, (text adjoining footnote 141).

⁵⁴ The High Production Volume Challenge Program covers chemicals, which are manufactured in or imported into the U.S. in amounts equal to or greater than one million pounds per year. Under this voluntary program, industry chemical manufacturers and importers are committed to develop data summaries of existing hazard data and to conduct testing to fill any data gaps to provide the public with basic information about the chemicals produced in the largest quantities. *See*, EPA, *HPV Challenge Program*, available at: <http://www.epa.gov/chemrtk/>, last visited December 17, 2006.

⁵⁵ EPA White Paper on Toxicogenomics, *supra* note 11, at 11.

⁵⁶ TSCA § 6, 15 U.S.C.A. § 2605 (2006).

⁵⁷ EPA White Paper on Toxicogenomics, *supra* note 11, at 20.

⁵⁸ *Id.*, at 19.

⁵⁹ The specific NOAEL and LOAEL of each chemical are used to determine the level of regulation that would apply to that chemical.

⁶⁰ Currently, organophosphate pesticides are regulated at NOAELs, which are generally much lower than many other chemical classes because the endpoint, cholinesterase inhibition, is determined biochemically, and inhibition can be detected well below levels showing overt toxicity. In contrast, many fungicides or herbicides have relatively high NOAELs because clear pathological alterations only occur in animals at high doses. *See*, EPA White Paper on Toxicogenomics, *supra* note 11, at 20.

population effects towards individualized effects.⁶¹ In this manner, biomarkers of effects may identify populations susceptible to specific industrial chemicals.⁶² Based on such identification, EPA may require warning labels on chemical products, or other regulatory measures.⁶³ In sum, genomics data may significantly impact the way specific chemicals are regulated.

C. Testing Requirement (Risk Assessment)

In order to fill data gaps necessary for decision-making, EPA, under TSCA section 4, may require additional testing of chemicals that may present unreasonable risk or that are produced in substantial quantities and result in substantial human or environment exposure.⁶⁴ Unlike the FIFRA regulatory system, which requires pesticide applicants to prove the safety of their products before registration, under TSCA, EPA carries the burden of proving the need for testing (i.e., significant risk or substantial exposure, insufficiency of existing data, and the necessity of testing to develop the data). EPA must promulgate a testing rule setting forth the standards for the testing based on these triggers.⁶⁵ These tests should identify the hazard, assess the dose-response, assess exposure (i.e., acute, subacute, subchronic, and chronic), and characterize the risks associated with the chemical substance or mixture in question; they may include epidemiologic studies, in vitro tests, or animal tests, among others.⁶⁶

Genomics technologies may have several implications for the TSCA risk assessment process. First, genomics technologies may allow the development of gene, protein or metabolite profile “fingerprints” for the specific known MOA of a chemical agent. These “fingerprints” may also develop new and more cost-effective methods for predicting unknown MOAs for both health and ecological assessments, thus enhancing the ability to identify the hazard posed by a chemical substance or a mixture.⁶⁷ This hazard identification may also assist EPA in establishing the threshold testing standard of “unreasonable risk”—showing that genomics sequences indicate “existing possibility of harm [which] raises reasonable and legitimate cause for concern[.]”⁶⁸ and not just theoretical concern.

⁶¹ While other acts require EPA to set the tolerance standards based on susceptible groups within the population (e.g., FQPA focuses on the special susceptibilities of infants and children. *See*, 21 U.S.C.A. § 346a(b)(2)(C)), the TSCA directs EPA to prevent unreasonable risk based on the entire population sensitivity.

⁶² For example, different human age groups may express varying levels of some metabolic enzymes. Enzyme over- or under-expression could play a part in determining the severity of a toxic exposure. *See*, EPA White Paper on Toxicogenomics, *supra* note 11, at 25.

⁶³ Marchant, *supra* note 17, at 21-2. Labels might include warning for particular populations known to exhibit higher frequencies of an at risk-genetic polymorphism. In the U.S., drug labels already include such warnings. *See* EPA White Paper on Toxicogenomics, *supra* note 11, at 25.

⁶⁴ 15 U.S.C.A. § 2603(a) (2006).

⁶⁵ McKenna Long & Aldridge LLP., TSCA HANDBOOK, 181, (4th ed., Government Institute, 2005).

⁶⁶ 15 U.S.C.A. § 2603(b)(2) (2006).

⁶⁷ EPA White Paper on Toxicogenomics, *supra* note 11, at 18. According to the EPA, pesticide registrants have already cited several published genomics articles as part of the mode-of-action data package submitted for a product registration under FIFRA to propose an alternative MOA that would affect the conclusion of human health assessment. *Id.* at 4.

⁶⁸ *See*, *Ausimont U.S.A. Inc. v. EPA*, 838 F.2d 93, 97 (3d Cir. 1998).

Second, genomics technologies may allow the detection of gene expression patterns that compare histological changes in tissues and the eventual progress of a tumor. This may allow the development of biomarkers of response to predict the outcomes of nongenotoxic chemicals, thus enabling the development of more appropriate methods for dose-response assessments.⁶⁹ EPA believes that the same MOA approach can also enhance identification of dose-response relationships for chemicals that affect other health endpoints (i.e., non-carcinogens).⁷⁰ This will allow for better assessment of the significance of the risk. Furthermore, genomics data that support or reject similarity in chemical agents' MOA in animals and humans may reduce uncertainties in interspecies dose-response extrapolations.⁷¹

Third, EPA anticipates that genomics technologies, such as microarrays, are also likely to lead to the development of simple, sensitive, and informative biomarkers of actual exposure that can be used in humans and ecological species exposure assessments.⁷² In addition, genomics data may improve the ability to assess the cumulative risk resulting from exposure to chemical mixtures (i.e., additive risk, greater than additive, or less than additive).⁷³ When MOA studies become sufficiently reliable to relate exposure to whole-organism adverse effects, risk characterization will become significantly more accurate.⁷⁴

D. “Health and Safety Study” and “Substantial Risk” Reporting

Once the product is on the market, TSCA section 8 authorizes EPA to collect a variety of information from industry to allow appropriate regulation. For example, under section 8(d), EPA can promulgate a rule requiring reporting of any “health and safety study,” including genomics-based epidemiological and toxicological studies.⁷⁵ Based on such information, EPA can determine regulatory actions under section 6 or require additional testing under section 4.

Furthermore, section 8(e) establishes an early-warning system to identify harmful effects in their early stages before clinical disease is manifested, and to help minimize future exposure of affected persons.⁷⁶ Under this section, companies are required to inform EPA immediately

⁶⁹ Currently, EPA uses the linear method for dose-response assessment of genotoxic carcinogens also for nongenotoxic chemicals without plausible MOA. EPA White Paper on Toxicogenomics, *supra* note 11, at 19.

⁷⁰ *Id.*

⁷¹ *Id.*

⁷² *Id.* at 21-2.

⁷³ *Id.* at 28.

⁷⁴ *Id.* at 21-2. Under the Food Quality Protection Act of 1996 (FQPA), EPA is required to assess safety in terms of total exposure to the pesticide as well as to other pesticides; specifically, EPA is required to take into consideration dietary exposure to pesticides among infants and children. 21 U.S.C.A. § 346a(b)(2) (2006).

⁷⁵ 15 U.S.C.A. § 2607(d) (2006). Section 3(6) defines *Health and Safety Study* as “any study of any effect of a chemical substance or mixture on health or the environment or on both, including underlying data and epidemiological studies, studies of occupational exposure to a chemical substance or mixture, toxicological, clinical, and ecological studies of a chemical substance or mixture, and any test performed pursuant to [TSCA].” 15 U.S.C.A. § 2602(6) (2006).

⁷⁶ EPA White Paper on Toxicogenomics, *supra* note 11, at 14-5.

(no need for rulemaking) of any obtained information that reasonably supports the conclusion that a chemical substance or mixture that they manufacture, process, or distribute in commerce presents a substantial risk of injury to health or the environment.⁷⁷ EPA determines “substantial risk” based on the seriousness of the effect or the extent of the exposure; still, both hazard and exposure must occur to establish the risk.⁷⁸

There are three broad categories of effects that are potentially serious enough to trigger reporting obligations: first, human health effects (such as cancer, birth defects, mutagenicity, death, or incapacitation), including evidence of effects which may be derived from designed controlled studies of routine acute toxicity, subchronic toxicity, neurotoxic effects, and eye and skin irritation and sensitization.⁷⁹ A second category is environmental effects (i.e., widespread and previously unsuspected distribution in environmental media) that signify exposure to humans or other organisms has occurred or is likely to occur. Still, contamination has to exceed the benchmarks of the regulatory standard for the specific chemical to be reportable.⁸⁰ The third category relates to emergency incidents of environmental contamination (i.e., a serious threat for humans or other organisms).⁸¹

Genomics technologies can affect reporting requirements under TSCA section 8(e) if changes in gene expression or the protein and metabolic profile can be linked with substantial risk. For example, genomics data showing lower PODs for NOAELs or LOAELs than those currently existing in the regulatory standards for specific chemicals may constitute reportable substantial risk under this section. Another example is genomics data showing bioaccumulated toxicity in the second generation of exposed organisms, which may hint at substantial exposure. EPA has acknowledged that further interpretation of what constitutes significant risk with regard to detected genomics changes is needed before requiring the reporting of genomics response.⁸² Still, since only “obtained information” triggers reporting under TSCA, companies are not required to perform such genomics tests.⁸³

⁷⁷ 15 U.S.C.A. § 2607(e) (2006). A similar provision in FIFRA requires companies to report adverse effects associated with pesticides they commercialize. 7 U.S.C.A. § 136d(a)(2) (2006).

⁷⁸ EPA, TSCA Section 8(e) Reporting Guide June 1991, available at: <http://www.epa.gov/oppt/tsca8e/pubs/rguide.htm#whatissubstantialriskinformation>, last visited December 18, 2006. (“1991 Reporting Guide”)

⁷⁹ For additional discussion of the reportable health effects, *see*, McKenna Long & Aldridge LLP., *supra* note 65 at 233-8.

⁸⁰ *See*, EPA, TSCA Section 8(e); Notification of Substantial Risk; Policy Clarification and Reporting Guidance, 68 FR 33129, 33138 (June 3, 2003), available at: <http://www.epa.gov/EPA-TOX/2003/June/Day-03/t13888.htm>, last visited December 18, 2006. (“2003 Reporting Policy”)

⁸¹ Emergency incidents of environmental contamination are defined as any environmental contamination by a chemical substance or mixture, which (1) seriously threatens humans with adverse health effects, or (2) seriously threatens non-human organisms with population destruction. *See id.*

⁸² EPA White Paper on Toxicogenomics, *supra* note 11, at 15.

⁸³ *Obtained Information* means “Known” information, including that information which a prudent person of similar training, job function, etc., could be reasonably expected to possess. *See*, EPA, 1991 Reporting Guide, *supra* note, 78. It is worth noting that under FIFRA companies may be required to obtain genomic data to prove that the pesticide is safe, for re-registration proposes.

IV. Challenges in Applying Toxicogenomics Data in Chemical Regulation

A. Uncertainties and their Implications for TSCA Provisions

The Achilles heel of the “omics” methods is their validation. As previously mentioned, “omics” methods rely on the premise that sequences in gene expression or protein and metabolic profiles meaningfully indicate exposure to environmental toxins or harmful effects. As discussed below, this premise suffers from inherent technological and scientific limitations. While some of the current obstacles to validate “omics” methods may be minimized as technologies are improved in the future, others may not be overcome as they reflect complications within biological systems themselves. The validation of toxicogenomics technologies was discussed in greater detail in a workshop held at the Committee on Emerging Issues and Data on Environmental Contaminants of the National Academies on July 7, 2005.⁸⁴

1. Technological Uncertainties

The “omics” technologies are in their infancies. While recent advances in microarray technologies to identify gene expression have greatly developed the field of transcriptomics, other technologies to track downstream effects still lag behind, leaving many uncertainties in the fields of proteomics and metabolomics yet to be solved.⁸⁵ Since gene expression is only one aspect of the changes resulting from toxic exposure, the extent to which gene expression can be useful for determining toxicological endpoints as well as mechanisms is limited.⁸⁶

Furthermore, as with any other scientific experiments, the results of toxicogenomics studies (e.g., gene expression) are relative to the specific conditions and time at which these experiments take place, since expression is a dynamic process. “Background noises” can lead to different results from the “same” experiment, undertaken on different occasions. Such dynamism makes it difficult to identify reliable “fingerprints.” One of the challenges in genomics data interpretation is to distinguish background noise from pure biological cellular responses.⁸⁷

In addition, it is well recognized that some of the biological alterations in gene expression may only reflect adaptations to the external agent rather than being indicators of toxicological outcomes. Thus, another challenge in genomics data interpretation is distinguishing the benign or adaptive changes from those representing substantial risk, or in

⁸⁴ NRC, THE COMMITTEE ON EMERGING ISSUES AND DATA ON ENVIRONMENTAL CONTAMINANTS, COMMITTEE ON VALIDATION OF TOXICOGENOMIC TECHNOLOGIES: A FOCUS ON CHEMICAL CLASSIFICATION STRATEGIES, VALIDATION OF TOXICOGENOMIC TECHNOLOGIES: A WORKSHOP SUMMARY, (The National Academies Press, 2007), available at: http://books.nap.edu/catalog.php?record_id=11804, last visited March 31, 2007. (“NRC Validation of Toxicogenomic Technologies Workshop”)

⁸⁵ Schmidt, *supra* note 20, at A415.

⁸⁶ Marchant, Toxicogenomic Part I, *supra* note 25. (Text adjoined footnotes 238).

⁸⁷ *Id.* (Text adjoined footnotes 225-8).

other words, “to establish [a] relationship between gene expression data and toxicological changes.”⁸⁸

In sum, validation is essential on several levels: first, to assure that the particular technology used produces reproducible and reliable results that reflect the state of the biological system being measured; second, that the data analysis approaches are appropriate for the particular question being addressed; and third, that the results of a single test of a group of samples can be generalized to a broader segment of the population, and thus be used in the regulatory context.⁸⁹

2. Scientific Uncertainties

Toxicogenomics testing relies on genetic markers in the form of gene expression. However, genes are not necessarily the only objects that define the entire system; even if it were possible to exactly measure the state of each of the known system elements (i.e., mRNA level, protein level and metabolite level), uncertainties would remain regarding the state of the system as a whole. First, all the elements of the system have not yet been identified; and second, the nature of the relationship between those elements and their effects on the system has not yet been understood.⁹⁰ Also, chemical toxins do not necessarily affect gene expression directly; rather, they may, if at all, cause gene mutations that affect protein function without changing gene expression.⁹¹ Thus, genomics data may not be sufficient to identify the potential risk when no gene expression is shown. Likewise, unless changes in gene expression result from mutation, genomics technologies generally identify short-term changes in genes, proteins, and metabolites; they may not be relevant to diseases that have long latency periods (e.g., asbestos-related diseases).⁹²

⁸⁸ Carol J. Henry et al., *Use of Genomics in Toxicology and Epidemiology: Findings and Recommendations of a Workshop*, 110 ENVIRONMENTAL HEALTH PERSPECTIVE 1047, 1049 (2002), available at: <http://www.ehponline.org/members/2002/110p1047-1050henry/EHP110p1047PDF.PDF>, last visited December 19, 2006.

⁸⁹ NRC Validation of Toxicogenomic Technologies Workshop *supra* note 84, at 5, 31-3.

⁹⁰ Adelman summarizes some of the complexities:

“First, ‘less than two percent of the human genome codes for proteins, while more than fifty percent [consists of] repeat sequences of several types’ that have a currently undefined function. Second, genes themselves are oddly constructed--most are not unbroken segments of DNA code, but instead are interspersed with long segments of non-coding DNA. Third, there are critical processes that are not genetically controlled, yet alter the activity of a gene or its protein product.” (Citation omitted)

Supra note 5, at 154.

⁹¹ *Id.* at 133-4 and supplemented text in footnote 100. Still, other technologies, such as the DNA diagnostic, may identify gene mutation caused by toxic exposure by directly detecting the base of the sequence changes, and by looking for specific patterns of mutational changes induced by specific chemical or physical agents. See Mark S. Ellinger, *DNA Diagnostic Technology: Probing the Problem of Causation in Toxic Torts*, 3 HARV. J. LAW & TEC 31, 42-5 (1990).

⁹² Henry et al., *supra* note 88.

Even if genes were identified and expression did appear, intercellular biology processes such as deactivated enzymes (e.g., NQO1 in benzene metabolism)⁹³ and their associated genes may mitigate the toxicological outcome without leaving a “fingerprint.”⁹⁴ In these cases, gene expressions may be over-interpreted in anticipating the risk.

To add more dimensions to this already complicated issue, it is now scientifically known that the effects of toxic exposures vary greatly across the population (as much as 85- to 500-fold across the U.S. population). Thus, a genetic study may be useful for certain genetic backgrounds and not for others.⁹⁵ This variability may make it difficult to define effective biomarkers for complex genetic susceptibilities because the variation in susceptibility may be difficult to predict.⁹⁶

3. Implications of the Uncertainties to TSCA's Risk Assessments

Lack of thoroughly validated experimental methods and modes of data analysis raises the problematic issue of peer review under the Information Quality Act (IQA) of 2001.⁹⁷ Under this Act, the Office of Management and Budget (OMB) is required to issue guidance to federal agencies designed to ensure the “quality, objectivity, utility, and integrity” of information disseminated to the public.⁹⁸ The act also requires agencies to issue their own information quality guidelines and to establish a petition process that allows affected persons to seek correction of information that does not comply with the OMB guidance.⁹⁹

In 2002, the OMB issued government-wide IQA guidelines to implement the Act.¹⁰⁰ These guidelines require agencies to use “the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices” and to

⁹³ Tracey J. Woodruff, *Overview of US EPA's Benzene Noncancer Risks Assessment and Salient Issue* (Presentation in NRC's Workshop on Use of Toxicogenomics to Understand Toxic Effects and Improve Risk Assessment, November 13, 2006), available at: http://dels.nas.edu/emergingissues/toxicogenomics_meet14.shtml, last visited December 3, 2006.

⁹⁴ Adelman, *supra* note 5, at 138.

⁹⁵ For example, even when chemicals are known to directly cause genetic damage, molecular buffering mechanisms can compensate for mutations that would otherwise adversely affect human health. The effectiveness of such buffering mechanisms is varied among individuals and thus the toxicological response thereto.

⁹⁶ *Id.* at 137-141. Adelman suggests that the most viable approach to incorporate the variability in susceptibility into legal rules is by adding another safety factor into estimates of chemical toxicity, based on the variability in individual toxic susceptibility across the entire U.S. population.

⁹⁷ Pub. L. 106-554 (2001); Section 515 of the Treasury and General Government Appropriations Act for Fiscal Year 2001.

⁹⁸ OMB guidance defines *information* as “any communication or representation of knowledge such as facts or data, in any medium or form;” and indicates that *quality* encompasses elements of utility, objectivity (having been subject to an independent peer review process), and integrity. *See*, Curtis W. Copeland and Michael Simpson, *The Information Quality Act: OMB's Guidance and Initial Implementation*, CRS REPORT FOR CONGRESS RL32532, 5-6, (September 17, 2004).

⁹⁹ *Id.* at 7-8.

¹⁰⁰ Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies; Republication, 67 Fed. Reg. 8452 (February 22, 2002).

use “data collected by accepted methods or best available methods” when disseminating information related to the analysis of risks to human health, safety, and the environment.¹⁰¹ The guidelines furthermore noted that although agencies are encouraging the use of peer reviews in their information development, journal peer reviews may not be sufficient for “influential scientific information” (i.e., information likely to have an important public policy or private sector impact).¹⁰²

In elaborating this approach, the OMB issued its Final Information Quality Bulletin for Peer Review in 2004. This bulletin set forth the minimum requirements for peer reviews of scientific information¹⁰³ that federal agencies rely upon for decision-making.¹⁰⁴ The bulletin first made it obligatory to peer-review influential scientific information. It then went on to direct agencies’ assessment of the adequacy of a peer review. Agencies must consider: (1) the novelty and complexity of the reviewed science; (2) its essentiality to decision-making; (3) other prior peer reviews; and (4) the expected costs and benefits of conducting additional reviews.¹⁰⁵ Finally, the bulletin addressed the peer review of “highly influential scientific assessment,”¹⁰⁶ which requires the agencies to follow a strict scrutiny process as specified in the bulletin.¹⁰⁷

EPA’s initiatives to incorporate genomics data in its various regulatory activities, including in the TSCA process, are likely to trigger the most stringent level of peer review.¹⁰⁸ In such cases, a mere publication in a scientific journal identifying potential risk from a chemical substance or mixture may not be sufficient to validate the data as “quality” data under the OMB’s guidelines and bulletin. In addition, the aforementioned uncertainties in genomics technologies and science will impose even greater burdens on these peer reviews, subjecting EPA’s decisions to petitions for information correction.¹⁰⁹ These two factors may have a great impact on the need for additional testing before EPA can take action under TSCA sections 5 and

¹⁰¹ Copeland and Simpson, *supra* note 98, at 6.

¹⁰² *Id.* at 18.

¹⁰³ *Scientific information* is defined to include “factual inputs, data, models, analyses, technical information, or scientific assessments related to such disciplines as the behavioral and social sciences, public health and medical sciences, life and earth sciences, engineering, or physical sciences.” Final Information Quality Bulletin for Peer Review, 70 Fed. Reg. 2664, 2667 (January 14, 2005). (“IQB”)

¹⁰⁴ Lynn L. Bergeson, *Selected Challenges in Applying Toxicogenomic Data in Federal Regulatory Settings*, GENETICS AND ENVIRONMENTAL POLICY: ETHICAL, LEGAL AND REGULATORY PERSPECTIVE (Richard R. Sharp et al. eds., Johns Hopkins University Press, Baltimore, 2007), in press.

¹⁰⁵ *Id.*

¹⁰⁶ *Highly influential scientific assessments* are a subcategory of influential scientific information and are defined as a scientific assessment that (i) has a potential impact of more than \$500 million in any year, or (ii) is novel, controversial, or precedent-setting or has significant interagency interest. OMB, IQB, *supra* note 103, at 2675.

¹⁰⁷ Bergeson, *Supra* note 104. An agency conducting a peer review of a highly influential scientific assessment is directed more rigorously and has less discretion in planning the peer review agenda for issues such as: individual versus panel review; timing; scope of the review; selection of reviewers; disclosure and attribution; public participation; and disposition of reviewer comments. *See*, Section III of the Final IQB, *supra* note 103, at 2671-2.

¹⁰⁸ *Id.*

¹⁰⁹ According to OMB Watch, in the first year of the implementation of the act nearly three-quarters of the IQA challenges were from industry. *See* Copeland and Simpson, *supra* note 98, at 14. This trend may increase if EPA makes its risk assessment decisions based on innovative and uncertain scientific data, such as genomic information.

6, on the one hand, and on EPA's ability to establish the definition of "may present unreasonable risk" to trigger rulemaking for test requirements under TSCA section 4.

From the industry perspective, the OMB peer review policy may create some obstacles if the safety data submitted by businesses with their PMNs to EPA are also subject to peer review. It is uncertain whether the policy applies to the underlying information or just to the agency assessment of that data.¹¹⁰ In any event, these strict peer review requirements may result in the reluctance of either industry to submit genomics information (and in turn to conduct genomics research at all), or the agency to accept it.

As a first step toward overcoming these challenges, EPA formed the Genomic Technical Framework and Training Workgroup to develop an *Interim Guidance for Microarray-Based Assays: Regulatory and Risk Assessment Applications at EPA*. This guidance will address genomics data submission, quality assurance assessment, analysis approaches, and data management by EPA, academia, and industry.¹¹¹

4. Implications of the Uncertainties to TSCA's Regulatory Provisions

As discussed above, the aim of TSCA is to prevent human and environmental exposure to unreasonable risk, and to ensure that EPA is aware of any potential for substantial risk. Thus, chemical regulation and the authority to request additional information to make a regulatory decision are triggered only upon determination that the chemical substance or mixture in question poses "unreasonable risk of injury to health or the environment."¹¹² Likewise, the duty to report data indicating harmful outcomes is triggered only upon determination that such a chemical may pose substantial risk of injury to health or the environment.

Because unreasonable risk determinations include cost-benefit analyses,¹¹³ uncertainties in genomics science and technology may make it difficult to show that the benefits outweigh the costs. Even where the science is well established, as in the case of asbestos, EPA is generally prohibited by politics to ban the chemical's use, especially when a new chemical, for which there is very little information about actual risk posed, is at stake. Therefore, validation of genomics data is crucial for any meaningful regulatory action under TSCA sections 5 and 6.

Reportable substantial risk, on the other hand, is determined based on the seriousness of the outcome or the extent of the exposure. Although genomics data are expected to reveal new relationships of exposure-effects, it is still premature to determine such relationships based merely on genomics experiments. At this point, genomics data can only raise the suspicion that

¹¹⁰ Lynn L. Bergeson, *Toxicogenomic Data and Federal Regulatory Settings: Managing the Avalanche of Data*, ENVIRONMENTAL QUALITY MANAGEMENT, 4, (Wiley Periodicals, Inc., summer 2005), available at: http://www.actagroup.com/other_pdfs/EQM%20Summer%202005.pdf, last visited November 12, 2006.

¹¹¹ Kathryn Gallagher et al., *Activities to Develop an Interim Guidance for Microarray-Based Assays for Regulatory and Risk Assessment Applications at EPA*, available at: http://www.epa.gov/sciforum/2006/poster_abstracts/disease_susceptibility/DS_Gallagher.pdf, last visited December 20, 2006.

¹¹² TSCA § 6, 15 U.S.C.A. § 2605 (2006).

¹¹³ TSCA § 6(c)(1)(D), 15 U.S.C.A. § 2605(c)(1)(D) (2006); *see also* Corrosion Proof Fittings v. E.P.A. 947 F.2d 1201, 1223 (5th Cir. 1991).

harmful outcomes may be imminent,¹¹⁴ and there is a risk of misinterpretation or over-interpretation of these alterations in the contexts of product safety determination.¹¹⁵ As EPA's Interim Policy on Genomics provides no guidance as to the circumstances under which genomics data are reportable, the regulated community and their advocates are concerned whether such preliminary suspicion constitutes reportable "substantial risk" under TSCA section 8(e).¹¹⁶ Consequently, some argue that under the concept of "fair notice," EPA is required to give advanced notification if it intends to use genomics data in an enforcement action against chemical companies for their failure to report "substantial risk" information.¹¹⁷

B. Collecting and Sharing Data

One of the key elements in advancing prompt validation of toxicogenomics data is creating publicly available databases that can be electronically compared and evaluated.¹¹⁸ Only massive databases of high-quality genomics results, which are compiled in a consistent and well-defined manner, may allow for rigorous conclusions about test results, thus providing a meaningful tool for product screening.¹¹⁹ Such databases may also eliminate the need for peer review of well-established information and may assist EPA in determining the appropriate level of regulation for each chemical.

As discussed above, TSCA theoretically provides EPA with various authorities to collect experimental and clinical data; this could extend publicly-available genomics databases if used effectively. First, under section 5, before introducing new chemicals or using them in the market, chemical manufacturers must submit to EPA in their PMNs any information or test data that might be useful to the Agency in evaluating a chemical's potential to pose unreasonable risk to health or the environment. Second, under section 4, EPA may require the development of additional test data if the existing data are insufficient. Third, under section 8 (d) and (e), manufacturers must submit to the EPA copies of all health and safety studies as well as data showing substantial risk. Additionally, voluntary programs such as the HPV,¹²⁰ the Voluntary

¹¹⁴ Other technologies, such as the DNA diagnostic, can also detect specific patterns of mutational changes induced by specific chemical or physical agents. See Ellinger, *supra* note 91. Such mutational changes are more predictive and can support the preliminary suspicion for risk raised by the genomic data.

¹¹⁵ William D. Pennie et. al., *The Principles and Practice of Toxicogenomics: Applications and Opportunities*, 54 TOXICOLOGICAL SCI. 277, 282 (2000), available at: <http://toxsci.oxfordjournals.org/cgi/reprint/54/2/277>, last visited December 3, 2006.

¹¹⁶ Bergeson, *supra* note 104.

¹¹⁷ Marchant, Toxicogenomic Part I, *supra* note 25. (Text adjoined footnotes 253-4).

¹¹⁸ The National Academies, The committee on Emerging Issues and Data on Environmental Contaminants, *Public Databases: Sharing of Toxicogenomic Data*, 8 EMERGING ISSUES IN ENVIRONMENTAL HEALTH SCIENCES NEWSLETTER, 4, (June 2005), available at: http://dels.nas.edu/emergingissues/docs/EI_issue8.pdf, last visited December 21, 2006. ("The National Academies Issue 8")

¹¹⁹ John M. Balbus, *Ushering in the New Toxicology: Toxicogenomics and the Public Interest*, 113 ENVIRON HEALTH PERSPECTIVE 818 (July, 2005), available at: <http://www.ehponline.org/members/2005/7732/7732.pdf>, last visited December 21, 2006.

¹²⁰ See, The High Production Volume Challenge Program, *supra* note 54.

Information Submission Innovative Online Network (VISION),¹²¹ and the Voluntary Children's Chemical Evaluation Program (VCCEP)¹²² were initiated to further extend EPA's data collection.

Nevertheless, several challenges preclude creating such databases effectively. First, according to the 2005 U.S. Government Accountability Office's (GAO) report, *Chemical Regulation: Options Exist to Improve EPA's Ability to Assess Health Risk and Manage Its Chemical Review Program*, although the TSCA provides EPA with several authorities to collect risk data tests, these authorities have hardly been used because they "place the costly and time-consuming¹²³ burden of obtaining data on EPA, rather than requiring chemical companies to develop and submit data to EPA[,]"¹²⁴ as is the case under FIFRA. As a result, EPA had used its authority to require testing for fewer than 200 of the 62,000 chemicals in commerce when the TSCA was enacted.¹²⁵ Furthermore, there are over 200 HPV chemicals for which chemical companies have refused to provide the minimal test data under the voluntary program.¹²⁶

Second, as with any scientific data, genomics data also may be perceived as the developer's intellectual property. Thus, particularly in competitive private industries, but also in academic laboratories, there is reluctance to share information that can reveal trade secrets, impede competitive advantage, or lead to legal liability in toxic tort litigation.¹²⁷ Although TSCA section 14 forbids the disclosure of confidential business information (CBI), subsection (b) specifically authorizes disclosure of health and safety studies or data obtained from such studies on chemical substances currently in commercial distribution or subject to the PMN or testing requirements.¹²⁸ However, applying this exception requires time and resources to challenge the CBI claims, and in fact, EPA does not challenge many of them.¹²⁹ Also, this exception applies only to data required to be submitted under TSCA, and not to data voluntarily submitted.

The third challenge is to make the data generated by gene and protein expression studies accessible and useful to users. To make use of the vast quantity and variety of the data requires a database designed for computational investigations or data mining.¹³⁰ Rapid technical advances make it all the more difficult to design standard methods for evaluating a variety of

¹²¹ The VISION is an initiative designed, inter alia, to encourage more voluntary reporting and testing; to facilitate retrieval of information to meet U.S. government data needs; and to promote more efficient use of TSCA sections 4 and 8. See MCKENNA LONG & ALDRIDGE LLP., *supra* note 65, at 207-8.

¹²² The VCCEP is designed to develop data on potential health risks to children. Companies participating in the program sponsor the evaluation of 23 chemicals found in human tissues and the environment. *Id.* at 209.

¹²³ Each rulemaking can take from 2-10 years. *Id.* at 6.

¹²⁴ GAO statement, *supra* note 44 at 2.

¹²⁵ *Id.* at 4.

¹²⁶ *Id.* at 5.

¹²⁷ Environmental Defense, *supra* note 13, at 11-2.

¹²⁸ 15 U.S.C.A. § 2613 (2006).

¹²⁹ GAO statement, *supra* note 44 at 3.

¹³⁰ The National Academies Issue 8, *supra* note 118, at 4.

data and comparing inter-laboratory results.¹³¹ One effort to standardize collected and stored microarray data are the Minimum Information About a Microarray Experiment (MIAME) project,¹³² which establishes both the standards for the database and pilot software to demonstrate it. In addition, the MIAME model database is designed to facilitate rapid screening and data mining.¹³³ Another effort is the Chemical Effect in Biological Systems (CEBS) project,¹³⁴ sponsored by the NIEHS National Center for Toxicogenomics (NCT). CEBS will provide a public resource of collected data sets in all “omics” fields (i.e., transcriptomics, proteomics, and metabonomics). This database will integrate and display data in the context of the toxicological endpoint and study design, and will provide quality measures to assess the technical validity of the data and methods to assess and normalize data sets.¹³⁵

C. Ethical and Social Issues

As discussed above, genomics technologies may allow the identification of populations susceptible to specific industrial chemicals, thus potentially allowing tailoring chemical regulations and/or warning labels to specific susceptible groups in the population.¹³⁶ Such labeling might allow exposed or particularly susceptible groups to take preventive measures where possible.¹³⁷ While warning labeling may be a low-cost alternative to regulatory protection in some cases, it may also give rise to ethical and social issues as it shifts the burden of protection from risk-creators and government regulators to individuals.¹³⁸

First, such warning strategies rely on the premise that people know their genotype for the relevant genes and can therefore avoid using the specific chemical product (pesticide or drug) to which they are genetically susceptible.¹³⁹ In fact, even when technology will be relatively cheap and available, it would be unreasonable to believe that all people will examine the genotypes for all of their genes.¹⁴⁰ Further, for various reasons of privacy and personal

¹³¹ Marchant, Toxicogenomic Part I, *supra* note 25. (Text adjoined footnotes 240-1); *see also*, Bergeson, *supra* note 106.

¹³² *See* MIAME website at: <http://www.mged.org/Workgroups/MIAME/miame.html>, last visited December 21, 2006.

¹³³ Environmental Defense, *supra* note 13, at 33. MIAME attempts to identify the essential information for recreating or interpreting of microarray gene expression assay, including details of laboratory techniques, species of animals used, testing conditions, and some measure of quantification and reliability of the results.

¹³⁴ *See* CEBS website at: <http://cebs.niehs.nih.gov/cebs-browser/cebsHome.do;jsessionid=F426E841F064DAB539E4E6BB3E3DB676>, last visited December 21, 2006.

¹³⁵ The National Academies Issue 8, *supra* note 118, at 5.

¹³⁶ TSCA section 6 (as well as FIFRA section 3) provides EPA with the authority to regulate warning labels for chemicals (or pesticides).

¹³⁷ Grodsky, *supra* note 12 at 264.

¹³⁸ *Id.*; *see also*, Marchant, *supra* note 17, at 21-2

¹³⁹ *Id.*

¹⁴⁰ *Id.* Accessibility to genetic susceptibility examinations may also raise complicated issues related to environmental justice, which this paper is not aimed to deal with. The government would have to work out ways for free and widely available access to such examinations, as well as educational means to assure that all levels of people from any background would understand how to access these examinations and how they should use their genotypes information.

autonomy, it is also improper to expect people to do so. Also, as a policy matter, since screening the entire population will require substantial monetary and human resources, these resources might be better spent on efforts to prevent or reduce the exposure of the population as a whole to toxic chemical products.¹⁴¹

Second, this approach assumes that the exposure is a matter of individual choice, which may be the case for some products but not for all.¹⁴² A good example would be chemical products that people are exposed to at their workplace. Once an employer knows that a worker is particularly susceptible to a certain product commonly used at the workplace, it is possible that the employer would avoid employing such a person, rather than try to find an alternative product. This gives rise to complicated issues of discrimination at the workplace based on genetic susceptibility, which this paper does not address.

Third, imposing the duty on manufacturers to warn susceptible individuals of their potential risk from specific chemical products may result in a negative health effect if such a warning allows manufacturers to avoid liability for any resultant damages. Assuming strict product liability does not apply because genetic susceptibility to a product does not mean the product is defective. Would avoiding genotype testing and consuming a product constitute a contributory negligence, for which the injured individual is not eligible for full, if any, compensation? Some lessons can be learned from court decisions on warning labeling on other risky products, such as cigarettes and asbestos, specifically when dealing with the more-than-additive adverse effects of accumulative exposure to both products. Therefore, it would be wise at present to require labeling only if it is possible to ensure that such warning cannot be used against a plaintiff in court, namely that such a warning will not shift the responsibility of harm prevention to the consumer.

¹⁴¹ Grodsky, *supra* note 12 at 265.

¹⁴² *Id.* at 22.

V. Conclusion and Recommendations

In their final remarks in the book *Environmentalism & the Technologies of Tomorrow: Shaping the Next Industrial Revolution*, Robert Olson and David Rejeski write that “[t]he pervasiveness, speed, and complexity of emerging science and associated technologies are exceeding the capacity of the environmental community to respond.”¹⁴³ While this may be true, when trying to keep pace with this never-ending race to develop of new technologies, such as toxicogenomics, government regulators and practitioners should be cautious not to put the cart before the horse – implementation of still unvalidated technologies into the regulatory process may result in undesirable outcomes due to under or overestimation of potential risks.

Toxicogenomics hold in store many promises in the area of environmental risk management. Still, inherent uncertainties both in the science and the relevant technologies require better understanding of the limitations of toxicogenomics. Taking into consideration the aforementioned legal, practical and ethical challenges, the following are suggestions for viable next-step applications under TSCA regulation.

For toxicogenomics data to keep the promise of generating reliable and accurate chemical toxicity determinations, they first have to be generated on a massive scale and then validated. As environmental law scholars have noted, the law can play a significant role in inducing data generation and distribution.¹⁴⁴ As discussed above, TSCA provides EPA with very limited and burdensome authority to require generation of new chemical toxicity testing under section 4. To overcome the obstacle of obtaining data, Dr. Gary E. Marchant suggests requiring companies submitting PMNs under TSCA section 5 to include the result of gene expression assays in their submissions.¹⁴⁵ He suggests that although companies are currently not required to generate any new data to support PMNs, such a requirement would not be “unduly burdensome,” and it would assist in building “an experimental database of chemical-specific gene expression data that would then be available to EPA.”¹⁴⁶ Yet, this requires amending TSCA to provide EPA with the appropriate authority. To encourage the development and submission of such data, EPA may provide a “safe harbor” from enforcement and regulation until the methodology has been adequately validated.¹⁴⁷

Similarly, Dr. David E. Adelman suggests that EPA adopts the approach taken by the voluntary HPV Challenge Program, under which chemical companies have agreed to conduct basic toxicity testing for more than 2,000 HPV chemicals, and apply it to genomics data testing.

¹⁴³ *Environmentalism & the Technologies of Tomorrow: Shaping the Next Industrial Revolution*, 171, (Robert Olson & David Rejeski eds., Island Press, 2004).

¹⁴⁴ See Grodsky, *supra* note 12, at 251-2. (Citing also, John S. Applegate, *The Perils of Unreasonable Risk: Information, Regulatory Policy, and Toxic Substances Control*, 91 COLUM. L. REV. 261 (1991); and Mary L. Lyndon, *Information Economics and Chemical Toxicity: Designing Laws to Produce and Use Data*, 87 MICH. L. REV. 1795 (1989)).

¹⁴⁵ Marchant, *Toxicogenomics Part I*, *supra* note 25. (Text adjoined footnotes 145-6)

¹⁴⁶ *Id.*

¹⁴⁷ *Id.* (Text adjoined footnotes 255).

This would also provide some sort of a “safe harbor” (i.e., low threshold standards that trigger limited regulatory requirements).¹⁴⁸

Of course, once substantial data are collected, these data need to be validated. An essential element of validation is the development of meaningful tools for comparison and evaluation of data. To avoid misinterpretation or overinterpretation of genomics data, regulators must recognize that “toxicogenomics is a tool that provides data that require interpretation—not an end in itself.”¹⁴⁹ Interpretation will be more precise if toxicogenomics data are received under “consistently and appropriately defined methods” and are replicated in repeated studies.¹⁵⁰ Still, such interpretation is not always pure science and it encompasses elements of policy as well.¹⁵¹ Nevertheless, this does not preclude relying on such interpretations when taking precautionary steps to prevent potential harmful exposure to toxins; this just means that the policy element of the decision should be acknowledged and well presented.

Recent legislation has established the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)¹⁵² to formalize validation requirements for test methods used for regulatory purposes. The ICCVAM process is designed “to examine the efficacy of new methods for toxicologic screening relative to existing methods.”¹⁵³ This process can be adapted to toxicogenomics applications as well.¹⁵⁴ Yet, as some scholars have acknowledged, “given the speed with which the field is evolving, standardization of research platforms or methods does not appear to be appropriate at this time.”¹⁵⁵ As an interim step towards standardization, guidelines for Best Management Practices can be developed to correlate quantitative or qualitative changes in genes, proteins or metabolic processes with the potential for adverse effects. Such efforts have already begun in the aforementioned *Interim Guidance for Microarray-Based Assays: Regulatory and Risk Assessment Applications at EPA*.

Well-established validation of toxicogenomics data is a long-term process. Using toxicogenomics data in regulatory applications such as environmental standards or threshold reportable requirements is not viable in the near future. Still, in other applications such as

¹⁴⁸ Adelman, *supra* note 5, at 173-4.

¹⁴⁹ Pennie et al., *supra* note 115, at 281.

¹⁵⁰ “The methods . . . used to determine the expression level of each gene affect the quality and reproducibility of the results derived from any experiment.” See, The National Academies, The Committee on Emerging Issues and Data on Environmental Contaminants, *Workshop on the Validation of Toxicogenomic Technologies*, 9 EMERGING ISSUES IN ENVIRONMENTAL HEALTH SCIENCES NEWSLETTER 4 (October 2005), available at: http://dels.nas.edu/emergingissues/docs/EI_issue9.pdf, last visited December 20, 2006 (“The National Academies Issue 9”)

¹⁵¹ Even choosing between two experimental methods, neither of which is fully precise, is a matter of policy. See, Adelman, *supra* note 5 at 171.

¹⁵² The ICCVAM Authorization Act of 2000, Pub. L. 106-545 (2000). See, ICCVAM Website: <http://iccvam.niehs.nih.gov>.

¹⁵³ The National Academies Issue 9, *supra* note 151, at 5; see also, NRC Validation of Toxicogenomic Technologies Workshop *supra* note 84, at 14-6.

¹⁵⁴ *Id.*

¹⁵⁵ Henry et al., *supra* note 88 at 1047.

chemical prioritization or for the purpose of shifting the burden of proving a product's safety, partial validation may be sufficient to trigger further testing and study. Such an approach may minimize the gap between EPA's authority to regulate pesticides under FIFRA (which puts the burden of proving a product's safety on manufacturers) and its authority to regulate chemicals under TSCA (which puts the burden of proving unreasonable risk on EPA). As mentioned above, to raise unreasonable risk concerns and shift the burden of proof to manufacturers, courts have required EPA to show "existing possibility of harm [which] raises reasonable and legitimate cause for concern."¹⁵⁶ Gene expression, specifically where correlation between changes in genes and disease development has been identified (e.g., metabolic genes, DNA repair genes, and genes associated with cellular replication), may show that harm is not wholly theoretical, even if toxicity determination is not conclusive. Under this approach, EPA should develop a scientific-legal doctrine of what toxicogenomics data constitute "unreasonable risk." It is the role of EPA to explain how and why, even under current uncertainties, toxicogenomics data are nevertheless sufficiently reliable to raise the threshold to require further testing. Such application of toxicogenomics data may enhance genomics data generation and collection and the validation process without amending TSCA.

¹⁵⁶ See, *Ausimont v. EPA*, *supra* note 68.