Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment

The new field of toxicogenomics presents a potentially powerful set of tools to better understand health effects from exposures to toxicants in the environment. However, realizing the potential of this nascent field to improve public health decisions will require a concerted effort to generate data, to make use of existing data, and to study data in new ways—an effort requiring funding, interagency coordination, and data management strategies.

The Human Genome Project has been one of the most important biological research projects of all time. The project produced a complete sequence of the chemical makeup of genetic information contained in the DNA in human cells. It also supported the development of many new "genomic technologies," including research tools that allow scientists to look at the complete set of genes in a single experiment (see Box 1). These technologies allow scientists to study, for example, what combinations of genes lead to susceptibility to particular diseases, such as cancer.

Now, scientists are applying genomic technologies to study the potentially adverse effects of pharmaceutical drugs and industrial and environmental chemicals on human health. The new science of *toxicogenomics* provides valuable information on the effects of drugs and chemicals at a molecular level, providing a more complete understanding of their potential toxic effects. Integrating such information into risk assessments could significantly enhance public health and regulatory decisions.

However, leveraging the potential of toxicogenomics will require a coordinated effort to generate more data, make multiple uses of existing data sources, and study data in new ways, perhaps on a scale approaching that of the Human Genome Project. Toxicogenomics also raises some ethical and legal concerns.

This National Research Council report, produced at the request of the National Institute of Environmental Health Sciences

---

Box 1. Genomics refers to an array of methods to study genes and genomes, including:

- **gene sequencing,** which applies various biochemical and bioinformatics tools to study the DNA of organisms.
- **genotype analysis** that looks at genetic variation between individuals and in populations.
- **epigenetics** that studies reversible changes in gene function that can be passed from parent to child.

Transcriptomics (or **gene expression profiling**) is the study of mRNA—the intermediary step between genes and proteins that indicates genes that are active (as opposed to dormant or silent).

Proteomics is the study of proteomes, which are collections of proteins. Proteins carry out the functions encoded by genes.

Metabolomics is the study of the products of biological processes. Such products change in response to such things as nutrition, stress, and disease states.

(NIEHS), provides a broad overview of the benefits of toxicogenomics, the challenges in achieving them, and potential approaches to overcoming the challenges.

Potential to Enhance Toxicology

Genes—sections of a person's DNA in the nucleus of cells that code for cellular functions—are essential to the development of the human body and the maintenance of bodily processes throughout life. Not all genes are "expressed," or actively involved in a cellular function, at all times. Instead, genes may be "turned on" and "turned off" in response to environmental agents or other factors during a person's lifetime. Such changes in gene expression can adversely affect bodily processes and cause illness.

Traditional toxicology typically evaluates responses such as death, disease causation, or microscopic changes in the cells of animals and people. Toxicogenomics produces molecular-level data about genes and how specific toxicants affect gene, protein, and metabolite patterns. Toxicogenomics enables investigators to link toxicant-specific molecular changes with responses in cells, tissues, and organisms.

For example, gene expression profiling shows how exposures to chemicals cause cells in the body to turn on some genes and turn off others, which can change the proteins that are produced by the cell (see figure below for information on genes and proteins). The on-off pattern of the many genes in cells varies for different chemicals, creating a characteristic pattern or "signature"—the genetic calling card of the toxicant. Proteomics and metabolomics allow comparable analysis of protein and metabolite changes.

Potential applications of toxicogenomics include improved methods for screening potential toxicants, monitoring individuals' exposures to specific toxicants, tracking cellular responses to different exposure levels, assessing the mechanisms by which toxicants cause diseases, and predicting variability in individuals' sensitivity to various toxicants.

Use of Toxicogenomics in Risk Assessment

This report recommends that regulatory agencies enhance efforts to incorporate toxicogenomic data into risk assessment. However, these data are not currently ready to replace existing required testing regimens in risk assessment and regulatory toxicology. The report recommends that toxicogenomic technologies be further developed to increase capabilities in the following areas:

Exposure Assessment: Toxicogenomics should be developed further to identify genetic patterns associated with exposure to individual chemicals and, perhaps, to chemical mixtures. Standardized methods for identifying these signatures will be needed.

Hazard Screening: Toxicogenomics should be developed further to enable rapid screening of the potential toxicity of chemicals for drug development purposes and for determining the toxicity of chemicals found in the environment. Upon validation and development of adequate databases, toxicogenomic screening methods should be integrated into relevant chemistry regulatory and safety programs.

Variability in Susceptibility: Susceptibility to toxic effects of chemical
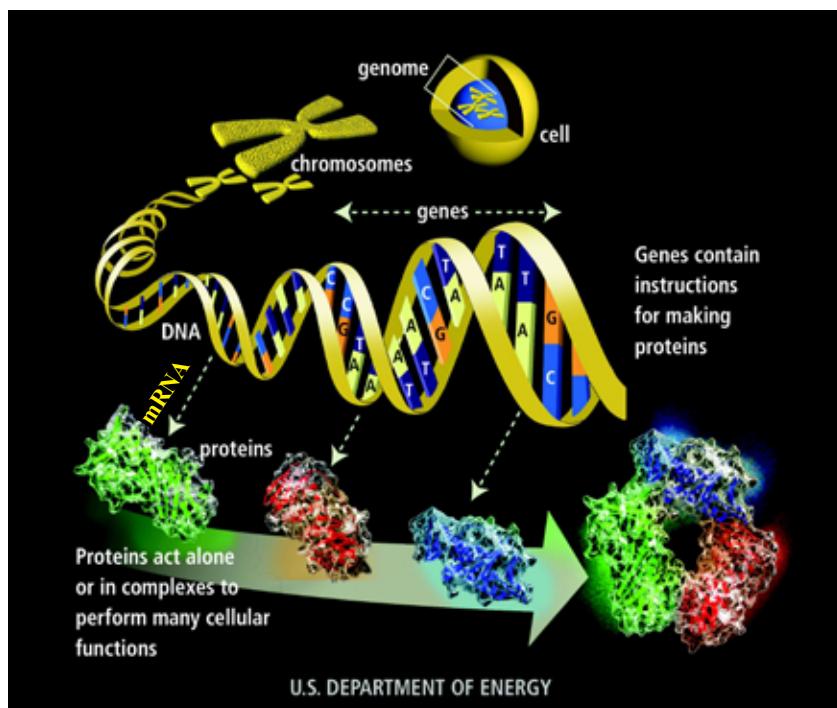
A genome is all of the DNA in an organism. Genes contained within this DNA code for proteins, which perform cellular functions. When a person is exposed to chemicals, cells in the body respond by switching on some genes and switching off others, thus changing the proteins that are produced by the cell.
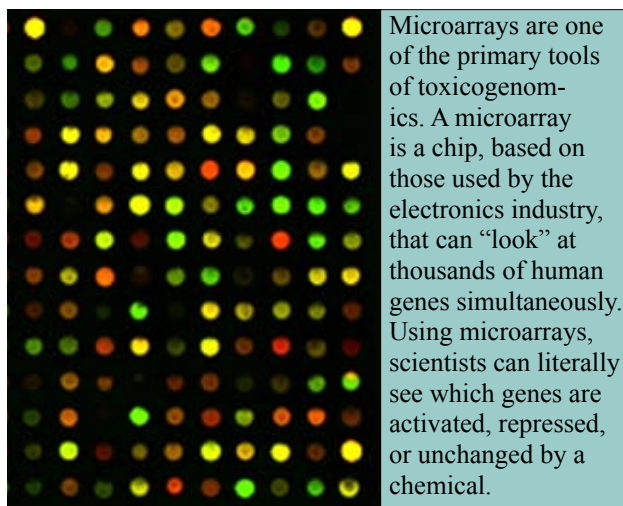
exposures varies from person to person. Toxicogenomic technologies offer the potential to use genetic information to identify susceptible subpopulations and assess differences in susceptibility in larger populations. Toxicogenomics would then be able to inform regulatory processes to susceptibility within a population.

Mechanistic Information: Toxicogenomics can offer insight on the mechanisms by which chemical exposures cause diseases. Tools and approaches for elucidating the mechanisms involved in toxic responses should continue to be developed to enhance risk assessment.

Cross-Species Extrapolation: Traditional toxicology makes use of animal studies, but animal-to-human toxicity extrapolations introduce uncertainty into risk assessment. Toxicogenomics offers the potential to significantly enhance the confidence of such extrapolations by using human cells. Using toxicogenomics to analyze species differences in toxicity will help explain some of the molecular bases for such differences.

Dose-Response Relationships: Toxicogenomics has the potential to improve understanding of dose-response relationships—the understanding of how a given level of exposure to a toxicant affects toxic responses in an individual. This understanding is particularly useful for evaluating the effects of low levels of exposure.

Developmental Exposures: Relatively little is known about the health impacts of fetal and early life exposures to many chemicals in current use. Because of their sensitivity, toxicogenomic technologies are expected to reveal more than has been

Microarrays are one of the primary tools of toxicogenomics. A microarray is a chip, based on those used by the electronics industry, that can "look" at thousands of human genes simultaneously. Using microarrays, scientists can literally see which genes are activated, repressed, or unchanged by a chemical.

possible to date about the potential effects of exposure to toxic substances in early development.

Mixtures: Humans are frequently exposed to multiple chemicals, and it is difficult to determine the effect of each chemical in a mixture. It is unlikely that toxicogenomic signatures will be able to decipher all interactions among complex mixtures, but it should be possible to use mechanism-of-action data to design toxicogenomic experiments to better inform this area of study.

The Need for a "Human Toxicogenomics Initiative"

The report notes that toxicogenomic technologies have matured to the point where they are widely accepted by the scientific community and viewed as producing high-quality data. In order to realize the full potential of toxicogenomic technologies, however, the report recommends that NIEHS and other

Box 2. Human Toxicogenomics Initiative (HTGI)

The report recommends that NIEHS cooperate with other stakeholders in exploring the feasibility and objectives of a "Human Toxicogenomics Initiative" (HTGI). The initiative should include:

1. Creation and management of a large, public database for storing and integrating the results of toxicogenomic analyses with conventional toxicity-testing data.
2. Assembly of toxicogenomic and conventional toxicological data on a large number (hundreds) of compounds into a single database. This includes the generation of new toxicogenomic data from humans and animals for a number of compounds on which other types of data already exist, as well as the consolidation of existing data.
3. Creation of a national biorepository for storing human clinical and epidemiological samples.
4. Further development of bioinformatics tools (e.g., software, analysis, and statistical tools).
5. Consideration of the ethical, legal, and social implications of collecting and using toxicogenomic data and samples.
6. Coordinated subinitiatives to evaluate the application of toxicogenomic technologies to the assessment of risks associated with chemical exposures.

stakeholders explore the feasibility and objectives of a "Human Toxicogenomics Initiative (HTGI)."

The most important focuses of such an initiative would be to collect more data on chemicals using toxicogenomics and to create a public database. This public database would facilitate sharing and use of the volumes of data, which will vastly exceed the data involved in the Human Genome Project. More data on a large number of compounds are needed so that comparisons can be made and data can be mined to identify important relationships.

The Human Toxicogenomics Initiative would support data collection and coordinate the creation and management of a large-scale database that would use systems biology approaches and tools to integrate the results of toxicogenomic analyses with conventional toxicity-testing data. The resulting publicly-accessible HTGI data resource would strengthen the utility of toxicogenomic technologies in toxicity assessment and thus enable better prediction of health risks associated with existing and newly developed compounds (see Box 2).

Ethical, Legal, and Social Issues

The report also addresses the ethical, legal, and social implications of toxicogenomics. When toxicogenomic data are linked to clinical and epidemiological information, it is critical that the privacy, confidentiality, and security of individuals' information be adequately protected. Safeguarding this information will advance important individual and societal interests, and will also prevent indi-

viduals from being dissuaded from participating in research or undergoing the genetic testing that is the first step in individualized risk assessment and risk reduction. The protection of individuals should be considered when developing large-scale biorepositories and databases. Additionally, special efforts should be made to address the impacts of toxicogenomic research and findings on vulnerable populations.

Toxicogenomics is likely to play a role in occupational, environmental, and pharmaceutical regulation and litigation. Regulatory agencies and courts should give appropriate weight to the validation, replication, consistency, sensitivity and specificity of methods when deciding whether to rely on toxicogenomic data.

Education and Training in Toxicogenomics

It is essential that education and training in toxicogenomics become a continuous, ongoing process that reflects the rapid developments in new toxicogenomic technologies. Education and training programs relevant to toxicogenomic applications in predictive toxicology will require cross-discipline collaboration. Information about the scientific and ethical, legal, and social issues toxicogenomics involves should be communicated to the general public, susceptible subgroups, health professionals, government regulators, attorneys and judges, the media, scientists in training, scientists on the periphery of toxicogenomics, and institutions that participate in toxicogenomics research.

Committee on Applications of Toxicogenomic Technologies to Predictive Toxicology: David C. Christiani (*Chair*), Harvard School of Public Health; **Cynthia A. Afshari**, Amgen, Inc.; **John M. Balbus**, Environmental Defense; **James S. Bus**, The Dow Chemical Company; **Bruce F. Demple**, Harvard School of Public Health; **Linda E. Greer**, Natural Resources Defense Council; **Sharon L.R. Kardia**, University of Michigan, Ann Arbor; **George D. Leikauf**, University of Pittsburgh Graduate School of Public Health; **Daniel C. Liebler**, Vanderbilt University School of Medicine; **Gary E. Marchant**, Arizona State University College of Law; **John Quackenbush**, Harvard School of Public Health; **Kenneth S. Ramos**, University of Louisville; **Mark A. Rothstein**, University of Louisville School of Medicine; **Raymond E. Stoll**, Stoll & Associates, LLC; **Roger G. Ulrich**, Calistoga Pharmaceuticals Inc.; **Helmut Zarbl**, University of Medicine and Dentistry of New Jersey; **Marilee Shelton-Davenport** (*Study Director*) and **Karl Gustavson** (*Program Officer*), National Research Council.

Permission granted to reproduce this brief in its entirety with no additions or alterations.