

Use of Genomics in Toxicology and Epidemiology: Findings and Recommendations of a Workshop

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The sequencing of the human genome has revolutionized biology and led to an astounding variety of technologies and bioinformatics tools, enabling researchers to study expression of genes, the function of proteins, metabolism, and genetic differences within populations and between individuals. These scientific advances are making an impact in the medical research community and hold great promise for prevention, diagnosis, and treatment of diseases. This developing field also holds great promise for improving the scientific basis for understanding the potential impacts of chemicals on health and the environment. A workshop sponsored by the International Council of Chemical Associations was held to review the state of the science in the application of genomics technologies in toxicology and epidemiology. Further, consideration was given to the ethical, legal, and regulatory issues and their influence on the direction and application of genomics technologies to environmental health research. Four overarching themes emerged from the workshop: Genomics technologies should be used within a framework of toxicology and epidemiology principles and applied in a context that can be used in risk assessment; effective application of these technologies to epidemiology will require suitable biologic samples from large and diverse population groups at the relevant period of exposure; ethical, legal, and social perspectives require involvement of all stakeholder communities; and a unified research agenda for genomics technologies as applied to toxicology, epidemiology, and risk assessment is urgently needed for the regulatory and scientific communities to realize the potential power and benefits of these new technologies. *Key words:* chemical industry, epidemiology, ethics, gene expression, genomics, hazard, proteomics, research needs, risk assessment, toxicogenomics. *Environ Health Perspect* 110:1047–1050 (2002). [Online 5 September 2002]

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A workshop was held on 7–8 March 2001 in Orlando, Florida, to review the state-of-the-science in the application of genomic technologies in toxicology, ecotoxicology, and molecular epidemiology and the importance of these new developments in understanding the potential impacts of chemicals on humans and the environment. Ethical, legal, and regulatory issues and their influence on the direction and application of genomic research were also discussed. The workshop was sponsored by the International Council of Chemical Associations, which is a council of leading trade associations representing chemical manufacturers worldwide. The workshop was attended by more than 80 representatives from industry, academia, and various government agencies from the United States, Canada, Europe, and Japan.

This report highlights the issues and recommendations discussed in each of the three areas: toxicology (including ecotoxicology), epidemiology, and ethical, social, and legal issues. Although the workshop presentations described genomics, proteomics, metabonomics, transcriptomics, and associated bioinformatics

technologies (collectively referred to in this report as “omics”) and the applications of the technologies for risk assessment and epidemiology, the reader is referred to Corton et al. (1999), Afshari et al. (1999), European Centre for Ecotoxicology and Toxicology of Chemicals (2001), and the National Institute of Environmental Health Sciences (NIEHS), National Center for Toxicogenomics (2001) for background information.

Four overarching themes emerged from the workshop:

- “Omics” technology should be used within a framework of toxicology and epidemiology principles so that it can be applied in a context that is understood for risk assessment.
- Effective application of “omics” to epidemiology studies will require suitable biologic samples from large and diverse population groups at relevant time periods of exposure.
- Discussion from ethical, social, and legal perspectives highlighted the fact that the use of “omics” technology will require the involvement of all stakeholder communities (i.e., research, academic, regulatory, public, and industry).

- Recommendations for research and future use are broadly applicable across government, industry, and academia. A unified research agenda as applied to toxicology and epidemiology is urgently needed for the regulatory and scientific communities to realize the potential power and benefits of these new technologies.

It was recognized that “omics” have the potential to reduce uncertainties in risk assessment and facilitate rapid assessments of a chemical’s toxic potential. However, there is a critical need to establish relationships between gene expression data and toxicologic changes, enabling an integration of “omics” information with known toxicologic measures and other approaches to a better understanding of mechanism of chemical effects on biologic systems. In the interim, “omics” findings will likely be misinterpreted, because no guidelines currently exist for correlating quantitative or qualitative changes in gene/protein/metabolite expression with the potential for adverse effects. For example, are changes within cells or tissues after chemical exposure part of the changes associated with normal life processes or adverse biologic effects?

“Omics” technologies are evolving rapidly. Application of these technologies will increase as the number of species with genomes that have been sequenced grows and as costs decrease. Given the speed with which the field is evolving, standardization of research platforms or methods does not appear to be appropriate at this time. However, recommendations for best practices may need to be developed on an international basis for research platforms or methods,

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especially for descriptions of experimental conditions and data quality.

Benefits of the Application of “Omics” to Toxicology and Epidemiology

Common benefits of the application of “omics” technologies for toxicology, ecotoxicology, and epidemiology, as well as distinct benefits to these fields, were identified at the workshop. Progress in achieving these benefits of “omics” technologies will be incremental, and large amounts of information will have to be assimilated. Common key benefits are outlined below.

- Improved understanding of the mechanisms of chemical action and improved understanding of uses and limitations of surrogate models: “Omics” has the potential to enhance our ability to pinpoint the molecular target(s) of toxicants, which in turn will improve the way in which we identify potentially hazardous chemicals, define dose–response relationships for the induction of toxicity, and compare responses in test systems to those relevant species of interest (human or wildlife). Such information will contribute to increased understanding of mode of action and the biologic plausibility of exposure–effect relationships. Collectively, this increased understanding could reduce the need to apply safety factors as uncertainties associated with various aspects of the risk assessment process are reduced [e.g., high- to low-dose extrapolation, animal-to-human extrapolation, extrapolation between ecologic receptor populations (e.g., aquatic species), extrapolation from average to susceptible populations]. This understanding may also lead to the development of more predictive models of toxicity.
- Opportunity for predictive toxicology and chemical screening: “Omics” information should eventually help predict, for some end points, the potential hazard of chemicals within compound classes. The information will also be useful for prioritizing chemicals for testing. “Omics” have the potential to contribute to predictive toxicology approaches and, as such, may reduce the time, cost, and use of animals for toxicity evaluations. Other potential areas for improvement are in study specificity, dose–response assessments, demonstration of human variability, and increased sensitivity in detecting risks. Bioinformatic tools will be essential for defining “predictive” gene sets from toxicogenomics studies and will require a large reference data set that can be broadly accessed. It will take some time to build and interpret these data sets.
- Identification and quantification of susceptible populations: Human health risk assessments require evaluation of susceptible

populations. For example, assessors must address differences in the way individuals metabolize a substance, both in the context of the normal distribution and on the basis of genetic polymorphisms. In the face of uncertainties about the susceptibility of certain individuals to the toxicant, risk assessors apply a safety factor to ensure that susceptible populations are protected. With “omics,” we may be able to better understand the identity, distribution, and size of the susceptible population and to better characterize the gene–environment interactions, which will improve human health risk assessment and improve risk management decisions. For ecologic risk assessment, “omics” has the potential to improve our understanding of population susceptibility. For example, the technology may be useful for developing population-level (e.g., fish, invertebrates) or community-level (e.g., microbes) metrics of genetic susceptibility. “Omics” will also help to identify differences in the way individuals respond to toxicant exposures. Knowledge of the functional impact of genetic differences on a toxicologic response will be required, however, before these data can be used in the context of risk assessment. The implications for risk assessment and protection of susceptible populations are potentially significant.

- Identification of biomarkers of chemical exposure and effects: An important challenge in toxicology and epidemiology is resolving the relationship between effect and exposure. “Omics” tools should inform the search for useful biomarkers of effect and exposure and better characterize the relationships between them, as well as detection of risks from low levels of exposure.

Several additional benefits were identified for toxicology and epidemiology, including generation of hypotheses through cooperative work between epidemiologists and toxicologists, improvement of public health policy making and public understanding of gene–environment interactions, improvement in understanding of attributable risks, development of better attributable risk statements for exposure, and development of better biologic models using gene expression patterns.

Molecular Genetics in Epidemiology

Rapid advances in molecular biology and technologies for measuring and processing data at the molecular level will likely affect the use of biomarkers in population-based epidemiologic studies. Molecular epidemiology studies are proliferating in the scientific literature, exploring markers of genetic damage, genetic biomarkers of exposure, and possible effects of gene–environment interactions.

Existing sources of human biomarker data are being reviewed, and plans are underway

to initiate large-scale human studies to include the collection of potential genetic biomarkers of exposure, effect, and susceptibility. The methodologic challenges underlying epidemiologic studies involving human genetic biomarkers will require careful attention and innovative statistical approaches if the data are to be fully interpreted within the strengths and limitations of each study. Of particular concern are sample size (particularly for testing gene–environment interactions), multiple comparisons, appropriate choice of controls, and interlaboratory variability. Although these are not new methodologic issues, they are particularly applicable to these technologies and present challenges to the validity of studies that incorporate genetic biomarkers.

Multidisciplinary research teams will be essential to conduct molecular epidemiology studies that employ the new genomic technologies. There will be a greater need than ever to evaluate the consistency between epidemiologic and laboratory studies. The multitude of sources of inconsistency in epidemiologic studies implies that replication of studies will be important for inferring causality when employing data generated using “omics.”

Ethical, Legal, and Regulatory Challenges

Ethical, legal, and regulatory implications surrounding the application of genetics and “omics” to environmental health research and risk assessment were identified during the workshop. The collection of genetic information and the individualization of risk assessment data will require heightened social responsibilities on the part of organizations and stakeholders involved in environmental protection and risk management. Topics addressed include the privacy of genetic information, protection of patient confidentiality, implications for regulatory agencies, applications in tort litigation, and potential for discriminatory uses of genetic information by employers and insurers.

Technical Issues to Be Resolved for “Omics” to Be Used

Several technical issues relating to the application of “omics” to toxicology and epidemiology that need to be resolved were identified:

- Technical understanding and shared learning in the public domain: Examples of successful application of “omics” in the public domain are needed in order to gain knowledge of the utility, appropriate applications, and methods for data analysis. It will be important to link “omics” data to toxicologic and human health outcomes, distinguish between changes that are adaptive responses and those that lead to adverse

effects, and establish experimental and data analysis methods to allow for the broad evaluation of the data sets produced from these studies.

- Development and availability of publicly accessible gene expression databases: Efforts to develop publicly accessible databases of gene expression data are underway and need to be continued and expanded. Two organizations currently involved in developing publicly accessible databases are the NIEHS and the International Life Sciences Institute (ILSI 2001). For the databases to be useful, data quality must be assured.
- Establishment of the predictive nature of the assays before widespread use in risk assessment: “Omics” approaches will need to be evaluated to estimate whether these methods are actually predictive of toxicity. It has not been determined what level of change in gene/protein/metabolite expression will alter phenotype (i.e., cause a toxicologic response) and whether observed changes in gene/protein expression are causative, coincidental, or adaptive responses to a chemical. There is a need for proof-of-principle experiments that will distinguish between normal physiologic effects and toxicologic effects of a substance, and they must be clearly anchored in conventional parameters of toxicology (e.g., histopathology, serum enzymes). Furthermore, whether patterns of chemically induced changes in gene expression (i.e., “fingerprints”) are predictive of a toxicologic response needs to be established. Generation of “reference databases” of gene expression changes associated with chemicals that have well-characterized toxicologic effects, supplemented where possible with confirmation in molecular epidemiology studies, will be required to establish the predictive value of gene expression fingerprints.
- Difficulty of obtaining relevant markers of gene expression in humans: Current molecular epidemiology studies using genetic biomarkers are limited to easily obtainable DNA markers of potential susceptibility (genetic polymorphisms). Methods to examine gene expression products in large human populations are also needed, but obtaining large samples of human tissues will be problematic. An additional challenge is to examine gene expression at the time period that is relevant to the health outcome of interest. Recently examined gene expression products may not be relevant to diseases that have long latency periods.
- Absence of background prevalence data in humans: Little information is available on the prevalence of mutations and gene expression patterns across various population groups, lifestyles, and health conditions. This information is needed for proper interpretation of comparisons of gene expression products in differently exposed populations.

Policy Issues to Be Resolved for “Omics” to Be Used

- Privacy/confidentiality/security/discrimination: There is a fear that individuals’ private information derived through the use of “omics” technologies will be revealed to people or entities against the wishes of the individuals from whom data were collected. Furthermore, “omics” data interpretation and disclosure may lead to discriminatory practices. Support should be provided for confidentiality, privacy, and security of genetic information, as well as nondiscriminatory principles and privacy issues that ensure confidentiality and discrimination protection.
- Lack of established principles/guidelines for worker testing: There has been much Congressional, media, and academic criticism of genetic testing in an occupational context. Although some private industries have been sued for inappropriate genetic testing of their employees, others have been sued for not performing or recommending genetic testing of their workers or product users. Therefore, a set of clear principles and professional guidelines should be developed with respect to genetic testing of workers and should include educational outreach within industry sectors.
- Lack of counseling for coping with genetic information: Many people may not want to know their own genetic information, and those who do learn about it may need counseling to understand the implications. There may be a need for increased emphasis on counseling and the availability of trained professionals to assist people in understanding and coping with their genetic information.
- Advice needed for social and ethical issues: Social and ethical issues need to be explicitly addressed at the forefront of the development and use of these technologies. The common rule for human research (Health Research Extension Act of 1985) and subsequent regulation (DHHS 1991), which impose certain requirements for federally funded research, including requirements for informed consent and review of research proposals by institutional review boards, should be widely adopted.
- Premature use of “omics” data: Because of the excitement surrounding the discovery of a new technology, some people may use information based on “omics” data (e.g., in hazard assessment) before its effectiveness is proven. A certain amount of guidance for tests and results is needed to ensure that misrepresentation and misinterpretation of data do not occur. Premature use of genomics data and technology may lead to a false sense of risk and/or security.

- Uncertainty of regulatory positions on genomics data: It is unclear how regulatory agencies will consider and use “omics” information for risk assessment and decision making, given that the predictive nature of the assays has not yet been established. The extent to which “omics” data will be considered or incorporated into safety, hazard, or risk assessments is unknown at this time. There is a concern that there might be premature interpretation on the part of regulators. There should be a concerted effort to aid government agencies in developing approaches and the use of these technologies. The development of multistakeholder guidelines for use of “omics” techniques and data would facilitate good “omics” practices, as would scheduling periodic workshops to provide technical updates, explaining how “omics” information can be used when making regulatory decisions, and supporting scientific and policy resources related to “omics” within federal agencies.
- Other issues: Additional items were identified, including the potential for fraud and misrepresentations, legally mandated disclosures, false positives, proliferation of agency mandates/targets, statutes that do not reflect technologic advances, and inequities as a result of limited access to testing.

Recommendations for Research

Although workshop recommendations were given in the context of the chemical industry, the recommendations for research and future use are broadly applicable across government, industry, and academia and will only be achieved by all stakeholders working together. A unified research agenda as applied to toxicology and epidemiology is urgently needed to realize the potential power and benefits of these new technologies.

Recommendations in the areas of toxicologic research and epidemiologic research were provided as follows:

- Research recommendations for toxicology: Examples/case studies and research projects that evaluate how “omics” can improve risk assessment will be achieved by studying compounds that have well-established toxicologic profiles. Good examples or studies will *a*) demonstrate how “omics” technologies elucidate mechanism of action and dose response (this topic is top priority), *b*) link “omics” information to traditional toxicity tests and end points, *c*) establish the relevance of an “omics” response to phenotype (e.g., distinguish between adaptive and adverse responses), and *d*) demonstrate how “omics” can reduce uncertainties associated with animal-to-human extrapolation.
- Research recommendations for epidemiology: Research should *a*) characterize prevalence

and background frequencies of genetic polymorphisms and their functions, *b*) focus on finding methods to assess gene expression in large numbers of people, *c*) address the statistical and bioinformatics issues, and *d*) pursue a multidisciplinary approach to epidemiology research and development.

Summary

In summary, the workshop discussions recognized the great value and potential that “omics” has for improving toxicology, epidemiology, risk assessment, and the protection of human health and the environment

but cautioned that the technology should be validated and applied according to the principles of toxicology and epidemiology. The applications of “omics” present issues that will require research and collaborative efforts on the part of all stakeholders to resolve.

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