Summary Report

International Council of Chemical Associations (ICCA) Genomics Workshop

March 7 & 8, 2001
Embassy Suites
Orlando, Florida

Prepared for
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Arlington, VA 22209

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CONTENTS

ACKNOWLEDGEMENTS

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INTRODUCTION

A workshop was held on March 7 and 8, 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 effects 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 (ICCA), which is a council of leading trade associations representing chemical manufacturers worldwide. The workshop was attended by over 80 representatives from industry, academia, and various government agencies (see Exhibit 1).

The workshop agenda is provided in Appendix A. In summary, the first day and part of the second day of the workshop were devoted to speaker presentations. The majority of the second day consisted of breakout group discussions, each focusing on one of three topic areas: (1) toxicology, (2) epidemiology, and (3) ethical, legal, and regulatory challenges. The goal of these discussions was to identify options for the global chemical industry to consider as it develops a research strategy that incorporates new genomic technologies. The workshop closed with presentations from the breakout groups to the plenary group.

Exhibit 1
Affiliations of Participants and Observers Who Attended the ICCA Genomics Workshop

American Chemistry Council
Applied Pharmacology & Toxicology, Inc.
Arizona State University
Aventis Crop Science
Bayer AG
The Bureau of National Affairs
Brixham Environmental Laboratory, AstraZeneca
Chemical & Engineering News
Chemical Evaluation and Research Institue
CIIT Centers for Health Research
Columbia University, School of Public Health
Dow Chemical Company
Duane, Morris & Heckscher
DuPont Haskell Laboratory
ECETOC
European Chemical Industry Council (CEFIC)
ExxonMobil Biomedical Sciences
ExxonMobil Corporation
Federal Institute for Consumers Health Protection
Florida International University
Health Canada
Health Effects Institute
ICF Consulting
Institute for Bioethics, Health Policy and Law
International Life Sciences Institute (ILSI)
Japan Chemical Industry Association (JCIA)
Japan External Trade Organization (JETRO)
The Keefer Group
Lovelace Respiratory Research Institute
McArdle Laboratory, University of Wisconsin
Monsanto Company
National Center for Toxicological Research
National Institute of Child Health and Human Development
National Institute of Environmental Health Sciences (NIEHS)
National Institute of Occupational Safety and Health
National Institute of Public Health and Environment
National Research Council
Okayama University
Oregon State University
Procter & Gamble Company
Queen Mary, University of London
Rhodia Inc.
SC Johnson Polymer
Shell International BV
Sunoco, Inc.
Syngenta Crop Protection
Sygenta CTL
Thomas Jefferson University
TNO Nutrition and Food Research
Toyo Kohan Co., Ltd.
Union Carbide Corporation
University of Louisville
University of Maryland
University of North Carolina at Chapel Hill
University of Oklahoma
U.S. Environmental Protection Agency (U.S. EPA)
U.S. Geological Survey
U.S. Occupational Safety and Health Administration

This workshop report presents highlights from the speaker presentations from each of the three sessions and summaries of the breakout groups' conclusions and recommendations. Abstracts of the speakers' presentations are provided in Appendix B.

1. SESSION HIGHLIGHTS

1.1 Session I: Application of "Omics" Technology to Toxicology

The general theme of the speaker presentations in Session I was that genomics, proteomics, metabonomics, transcriptomics (all of which make up "omics" – see Exhibit 2) and associated bioinformatics technologies have the potential to reduce uncertainties in risk assessment and facilitate rapid assessments of a chemical's toxic potential. It was clear during the session that discussion regarding the use of "omics" in risk assessment must involve all sectors (i.e., industry, government, academia).

"Omics" technologies are now available and evolving rapidly. Application of these technologies will increase as the number of "sequenced" species grow and costs decrease. The general agreement within the session was that cross-platform method standardization and/or selection of a single technology platform are not necessary or appropriate at this time as functional genomics approaches are rapidly evolving. Recommendations for "best practices" may however need to be developed for a given platform or method, especially as they relate to annotation of experiment conditions and description of analytical "robustness" to ensure data quality. It was also suggested that discussions on data quality/annotation for toxicogenomics studies occur on an international level.

"Omics" will contribute to our understanding of toxicants' mechanism of action. Research on this topic is already underway. There is a critical need to establish relationships

Exhibit 2
What do we mean by "Omics"?

The term "Omics" is used here to denote the set of developing technologies that enable researchers to study and describe biological events in a comprehensive way at the molecular level. These technologies include:

Genomics – the techniques available to identify the DNA sequence of genetic material (e.g., chromosomes) and expression of genes in response to stressors, such as drugs and toxicants;
Transcriptomics – the techniques available to identify the messenger RNA (mRNA) from actively transcribed genes, also referred to as transcript profiling;
Proteomics – the techniques available to identify proteins made by genes
Metabonomics – the techniques available to identify the presence and concentration of metabolites in a biological sample; and
Toxicogenomics -- the collection, storage, and interpretation of information about genomic activity and proteomics.

Sources: ECETOC White Paper on Genomics, Transcript Profiling, Proteomics, and Metabonomics (March 2001) and NIEHS' National Center for Toxicogenomics Web Page (April 2001).

between gene expression data and toxicological changes enabling an integration of "omics" information with known toxicological measures and other approaches to a better understanding of mechanism of chemical effects on biological systems. There is a real potential that "omics" findings will be misinterpreted as there are no guidelines for interpreting which or how much of a gene/protein/metabolite expression change constitutes an adverse effect. Changes within a cell or tissue in response to environmental stimuli are normal life processes, and it needs to be determined whether observed changes after chemical exposure are associated with adaptive responses or adverse effects.

These technologies have the potential to contribute to predictive toxicology approaches and, as such, may reduce the time, cost, and use of animals for toxicity evaluations. 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.

"Omics" will also help in identifying differences in the way individuals respond to toxicant exposure. The implications for risk assessment and protection of susceptible subpopulations are significant. Knowledge of the functional impact of genetic differences on a toxicological response will, however, be required before these data are used in the context of risk assessment.

In addition, it was clear that a dedicated ecologically-focused workshop is needed to address the wider implications and application of "omics" to ecological risk assessment.

1.2 Session II: Molecular Genetics in Epidemiology

The speaker presentations in Session II focused on how rapid advances in molecular biology and technologies for measuring and processing data at the molecular level will likely impact the use of biomarkers in population-based epidemiological 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 collection of potential genetic biomarkers of exposure, effect, and susceptibility. The methodological challenges underlying epidemiological studies involving human biomarkers will require careful attention and possibly innovative statistical approaches if the data are to be fully interpreted within the strengths and limitations of the study.

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 epidemiological and laboratory studies.

The multitude of sources of inconsistency in epidemiologic studies implies that replication will be even more important for inferring causality than in the past.

1.3 Session III: Ethical, Legal, and Regulatory Challenges in Applying Genomic Technologies to Toxicology and Risk Assessment

The speaker presentations in Session III explored the ethical, legal, and regulatory implications surrounding the application of genomic technologies to environmental health research and risk assessment. The development of gene expression patterns, or "fingerprints," of potential toxicant exposure and the individualization of risk assessment data will require highlighted social responsibilities on the part of stakeholders involved in environmental protection and risk management. The topics addressed by the speakers included 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.

2. BREAKOUT GROUP REPORTS

The objective of the breakout groups was to identify options for the global chemical industry to consider as it develops a research strategy that incorporates new genomic technologies. Benefits, issues, and recommendations identified by the groups are summarized in the sections that follow.

2.1 Breakout Group 1: Toxicology (Mammalian & Environmental)

Breakout Group 1 (Toxicology) discussed the questions presented in Exhibit 3 with a focus on the potential advances that "omics" will bring to toxicology, ecotoxicology, and risk assessment.

Exhibit 3
Breakout Groups 1 (Toxicology) and 2 (Epidemiology) Questions

1. What are the top five likely benefits for the application of these technologies?
2. What are the top five major issues regarding "omics" data interpretation and application to hazard identification and risk assessment?
3. What is the timing for progression/application of the technology to hazard identification/ characterization and risk assessment (i.e., five, ten, fifteen years from now)?
4. What impact can the chemical industry have in incorporating genomic technologies into the risk assessment process?
5. What is the group's recommendation for a strategy for the chemical industry to address these issues?

2.1.1 Benefits of the Application of "Omics" Technologies to Toxicology and Risk Assessment

The Toxicology Breakout Group identified the top five likely benefits of the application of "omics" technologies for toxicology and ecotoxicology, which are presented below. The group recognized that progress in achieving these benefits of "omics" technologies would be

incremental. The science is not likely to advance in great leaps, but rather through smaller achievements as we assimilate and interpret large amounts of information.

Improve understanding of the mechanism of chemical/drug action and improve understanding of uses and limitations of surrogate models. "Omics" will 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 the test systems with those of the species (human or wildlife) we wish to protect. Collectively, this increased understanding could reduce the need to apply safety factors as uncertainties associated with the various aspects of the risk assessment process are reduced (i.e., high-to low dose extrapolation, animal-to-human extrapolation, extrapolation between ecological receptor populations (e.g., aquatic species), susceptible subpopulations). This understanding may also lead to the development of more predictive models of toxicity. The group anticipated that this benefit will become realized more broadly in the coming year and continue incrementally into the future.

Opportunity for predictive toxicology and chemical screening. "Omics" information should eventually help predict the expected hazard of chemicals within compound classes. The information will also be useful for prioritizing chemicals for testing. The group agreed that this benefit is being realized now, to a limited extent, and will expand in the next five to ten years.

Identification and quantification of susceptible subpopulations. Human health risk assessments require discussion of susceptible subpopulations. For example, assessors must address differences in the way individuals metabolize the 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 subpopulations are protected. With "omics," we may be able to better understand the identity, distribution, and size of the susceptible subpopulation, which will improve human health risk assessment by reducing uncertainty and improving risk management decisions. For ecological risk assessment, "omics" will 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. The group was unable to predict the timing of this benefit.

Identification of biomarkers of chemical/drug exposure and effects. An important challenge in toxicology is resolving measures between effect and exposure. Toxicogenomic tools should inform the search for useful biomarkers of effect and exposure and better characterize the transition between them. The group was unable to estimate the timing of the realization of this benefit, due to its dependence on progress in other areas.

The Toxicology Breakout Group members suggested that additional benefits of "omics" technology include assistance in identifying genes involved in disease and improved risk assessment of chemical mixtures.

2.1.2 Issues Regarding Application of "Omics" to Toxicology and Risk Assessment

The Toxicology Breakout Group identified and discussed the issues associated with "omics" data interpretation and application to hazard characterization and risk assessment.

Need for technical understanding, examples, and shared learning in 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. In these studies, it will be important to link "omics" data to toxicological outcome, where possible, distinguish between gene expression changes that are adaptive responses versus those that lead to adverse effects, and establish clearly described experimental and data analysis methods to allow for the broad evaluation of the data sets produced from these studies. Data sets addressing the above mentioned issues should become available within the next two years, given the increased research activity in toxicogenomics by individual laboratories and consortia efforts, such as the ILSI Subcommittee on Genomics and Proteomics and the NIEHS Toxicogenomics Consortium devoted to the application of toxicogenomics to risk assessment.

Development and availability of a publicly accessible gene expression database. The efforts to develop a publicly accessible database of gene expression data are underway as sponsored and encouraged by the NIEHS, NIH, ILSI, and others. It will be important for industry to engage in discussion around database design to ensure that the databases are useful (including data quality considerations) (i.e., relevant for risk assessment) and that functional genomics data are related to classical toxicological responses. The group anticipates that these issues will be addressed within the next five years.

Predictive nature of the assays has not yet been established. "Omics" approaches will need to be validated to confirm 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 toxicological 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 pharmacological effects and toxicological 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 toxicological response needs to be established. As alluded to in the previous paragraph, generation of "reference databases" of gene expression changes associated with chemicals that have characterized toxicological effects will be required to establish the predictive value of gene expression "fingerprints". It was suggested that this issue could be resolved over five years for many endpoints that have not yet been studied. Illustrative examples developed in the near term (i.e., next two years) will help.

Need for "genome closure" and improved annotation. Genomes need to be completely sequenced, and each gene and its associated product and function needs to be identified (i.e., reach genome closure) with consistent nomenclature. This will facilitate the mechanistic interpretation of toxicogenomics data and comparison of data across multiple technology platforms. For ecotoxicology, this includes genome identification for important species and the

use of this information to produce "omics" reagents such as microarrays. This issue is also important for cross-species extrapolation (e.g., animal-to-animal, animal-to-human) in that functional differences can be identified and evaluated for how they might impact mechanism of action and dose-response assessment. This issue will gradually be resolved over the next five years.

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 "potentially referable" findings (i.e., findings that may have a safety or hazard implication) is unknown. There is a concern that there might be premature interpretation on the part of the regulators. The lack of clarity of the regulatory position regarding genomics findings could be an impediment to research. The group suggested that this issue is currently presenting itself and will become critical as the "omics" database develops (within a year of the development of the database).

The group identified several additional issues, including:

- Resolution of laboratory/platform differences;
- Low throughput or processing rate (especially for proteomics and metabonomics);
- Cost of technologies and studies (which may limit comprehensive replication of results and discourage exploratory applications);
- Need for proactive storage of biological material by traditional toxicology disciplines that might be used in "omics" studies later (e.g., high production volume (HPV) chemical testing) and coordinated efforts to save tissue; and
- Need for realistic understanding of the limitations of the technology.

2.1.3 Recommendations for the Chemical Industry

Based on the benefits and issues the group identified earlier in the discussion, the Toxicology Breakout Group generated the following recommendations for the chemical industry.

- Generate examples/case studies and support research projects that evaluate how "omics" can improve risk assessment by studying compounds that have a well established toxicological profile. Good examples or studies will:

  - demonstrate how "omics" technologies elucidate mechanism of action and dose-response (this topic is of top priority);
  - link "omics" information to traditional toxicity tests and endpoints;
  - establish the relevance of an "omics" response to phenotype (e.g., distinguish between adaptive and adverse responses); and
  - demonstrate how "omics" can reduce uncertainties associated with animal-to-human and animal-to-animal extrapolation.

- Track and partner with "omics" risk assessment applications demonstration and validation efforts (e.g., ILSI's pilot study) to learn from them and leverage investments.

- Engage in database discussions to ensure industry needs are met as an international publicly accessible gene expression database is built. It will be important for industry to provide input on data quality and data requirements, promote risk assessment context for the database, and, wherever possible, contribute data for the database.

- Form an international consortium of industry, academic, and government scientists (i.e., a tripartite group) to (1) provide strategic and management guidance to the chemical industry as it conducts research on the applications of "omics" to risk assessment, and (2) address issues associated with informatics, data management, and data quality. Discussions with the regulatory community regarding the use of "omics" data in risk assessment should also be encouraged within this consortium. A workshop could be held to start the discussion and begin addressing the data issues.

- Sponsor a workshop that focuses on the application of "omics" to ecotoxicology and ecological risk assessment considering some of the potentially unique aspects and questions of applying omics to ecotoxicology.

In summary, the chemical industry (and other organizations) cannot mandate or predict scientific progress in "omics" as it relates to toxicology. However, it can assist in the development of the scientific infrastructure and learning which equals progress.

2.2 Breakout Group 2: Epidemiology

Breakout Group 2 (Epidemiology) also discussed the questions in Exhibit 3 with a focus on how "omics" technologies will impact molecular epidemiology research.

2.2.1 Benefits of the Application of "Omics" Technologies to Epidemiology

The Epidemiology Breakout Group suggested that the top five benefits of "omics" to epidemiologic research are:

- Identification of susceptible populations or individuals and characterization of gene-environment interactions;
- Contribution to mode of action and biological plausibility of exposure effect relationships;
- Detection of risk from low level of exposure;
- Improvement of study specificity and sensitivity in detecting risk; and
- Improvement of dose-response assessment and demonstration of human variability in risk assessment.

The Epidemiology Breakout Group identified several additional benefits, including:

- Generation of hypotheses through cooperative work with toxicologists;
- Provision of insights on biological plausibility of associations from other research;
- Development of better diagnostic tests;
- Development of early markers of effect;
- Support for early warning research;
- Improvement of public understanding of gene-environment interactions;
- Improvement of public health policy-making;
- Improvement of extrapolation from animal studies to predict human risk;
- Improvement in understanding of attributable risks;
- Development of better attributable risk statements for exposure; and
- Development of better biological models using gene expression patterns.

2.2.2 Issues Regarding Application of "Omics" to Epidemiology

The Epidemiology Breakout Group also identified several current issues and challenges for the study of epidemiology.

- Difficulty in obtaining markers of gene expression products due to timing, tissue accessibility, etc.;
- Need for determining background prevalence of mutations and gene expression patterns across various population groups with differences in lifestyles, and health conditions;
- Need for understanding of the biological significance of genetic polymorphisms; and
- Statistical challenges posed by handling a large number of parameters, including:

    - multiple comparisons;
    - tests for interaction;
    - sample size; and
    - study design/conduct issues.

2.2.3 Recommendations for the Chemical Industry

Having established principal benefits and challenges, the Epidemiology Breakout Group recommended four distinct areas for the involvement of the chemical industry in the risk assessment process. The group also identified four associated research strategies.

- Help characterize prevalence and background frequencies of genetic polymorphisms and their functions. Research strategies include (1) collaboration with NIEHS and other entities (e.g., universities, CIIT Centers for Health Research) to augment current projects; (2) exploration of similar efforts in other

countries; and (3) involvement in the longitudinal cohort study detailed by Dr. Germaine Buck in her presentation (refer to her abstract in Appendix B).

- Focus a research program on finding methods to assess gene expression in large numbers of people. Research strategies include the pursuit of studies to develop methods to assess gene, protein, or metabolite expression in accessible biological materials.

- Address the statistical and bioinformatics issues identified as challenges. Research strategies include sponsoring studies through competitive Request for Applications (RFAs) that address statistical issues.

- Pursue a multidisciplinary approach to epidemiology research and development. Research strategies include performing case studies that address the whole exposure effects continuum and expanding CIIT Centers for Health Research to include a molecular epidemiology center of excellence.

2.3 Breakout Group 3: Ethical, Legal, and Regulatory Challenges

Breakout Group 3 (Ethical, Legal, and Regulatory Challenges) discussed ethical, legal, and regulatory issues that arise when applying genomic technologies to safety and risk assessment and discussed the questions presented in Exhibit 4.

Exhibit 4
Breakout Group 3 (Ethical, Legal, and Regulatory Challenges) Questions

1. What are the top five likely benefits for the application of "omics" technologies and likely timeframe for incorporation into safety and risk assessment process?
2. What are the top five major ethical, legal, and regulatory issues regarding "omics" data acquisition, interpretation, and application to hazard identification and risk assessment?
3. Based on the answers to questions one and two, what are the most critical areas of focus for the chemical industry and the potential impact?

2.3.1 Benefits of the Application of "Omics" Technologies

The Ethical, Legal, and Regulatory Challenges Breakout Group discussed general benefits of genomic technologies, not just for the chemical industry, but for society as a whole. The group's top five benefits are listed below.

Early disease indicators and intervention. Early signs of disease can be used to inform an individual of a disease early in its on-set and, therefore, enable the use of a more refined treatment approach. By informing individuals early of their disease, individuals can make preparations in their life. Specifically, detection of early biomarkers of the disease process using genomics (1) allows early intervention and precautions in disease; (2) allows for both a better

sense of the quantity of exposure and who is exposed (both an individual and population value); (3) encourages more specific clinical intervention and/or prevention; and (4) enables improved decision-making on prevention and/or intervention.

Scientific advancement. With respect to animal-to-human extrapolations, genomic technologies can provide information that advances toxicology and health research (science), including better understanding of mode of action. Scientific advancements could also possibly lead to reduced reliance on animal studies.

Use of beneficial products with protection of susceptible subgroups. Genomic technologies may help identify susceptible subgroups, therefore allowing certain hazardous substances with known risk to be used and to benefit society by ensuring that risks to susceptible subgroups are avoided. For example, pharmaceuticals that have been taken off the market because they cause adverse side-effects in a small number of people could be "rescued" and returned to the market if susceptible individuals can be identified and mechanisms were put it place to ensure susceptible people are not exposed. Genomic technologies could therefore allow the use of products that are very beneficial to a potentially large part of the population but currently are not viable because susceptible subpopulation cannot be identified.

Augmented individual autonomy. Genomic information may provide individuals with more autonomy in managing their risks (in both the workplace and private life) and inform people of their own potential susceptibility. For example, people commonly overestimate the risk to other people (e.g., over 50 percent risk, when really it may be 20 percent), yet underestimate their own risk (e.g., say 5 percent).

More informed regulations. As stated above, "omics" technology might provide better information on individual susceptibility and, therefore, allow for more informed institutional and regulatory decisions.

Improved therapies. Genomic technologies may lead to better methods to cure people and treatment of disease. In addition to focusing on protection, diagnosis, and intervention, genomic technologies could open the door to understanding the mechanisms, science, and different types of interventions that are possible.

The group identified several additional benefits, including:

- Reduced reliance on animal testing;
- Enhanced confidence in animal tests;
- Information to help identify potential hazards through high throughput screens;
- Reduced reliance on "old" epidemiologic methods;
- Information that will help resolve tort litigation;
- Reduction in the number of ill people in the workplace and community; and
- Improved identification of regulatory priorities.

2.3.2 Issues Regarding "Omics" Data Interpretation and Application

Breakout Group 3 discussed ethical, legal, and regulatory issues associated with "omics" data interpretation and application. The group's top five issues are presented below.

Potential for Discrimination/stigma. Genomic data interpretation and application may lead to the discrimination of a person by others. Genetic information could be used to make decisions regarding a person's life, both in the workplace and private life.

Lack of public understanding of genomics applications. The lack of public education and understanding of genomics and how these technologies relate to risk assessment is an issue. Many in the public, including professionals and physicians, consider "genetics" to be limited to cloning or genetically modified organisms (GMOs).

Privacy/confidentiality/security. There is a fear that private information determined through the use of "omics" technologies will be revealed to people or entities against the wishes of the individual from whom the information was collected. In addition, some individuals may prefer not to know certain information about their own genetic predispositions and susceptibilities, an interest, which could be jeopardized by inappropriate collection, use, and disclosure of genetic information.

Lack of counseling for coping with genetic information. Many people do not want to know their genetic information and those who do learn about it need counseling to understand. There have been cases in which people committed suicide when they learned that they have a genetic predisposition to cancer. The concern is that there is a lack of effective counselors to assist people in understanding and coping with their genetic information.

Premature use of genomics data. Due to the excitement surrounding the discovery of a new technology, some people are using the technology before its effectiveness is proven. A certain amount of institutional guidance for tests and results is needed to ensure that misrepresentation and misinterpretation of data does not occur. Premature use of genomics data and technology may lead to a false sense of risk and/or security.

The Ethical, Legal, and Regulatory Challenges Breakout Group identified several additional issues, which included:

- Potential for fraud and misrepresentations;
- Potential for false sense of safety/risk;
- Legally-mandated disclosure;
- False positives;
- Proliferation of agency mandates/targets;
- Statutes that do not reflect technological advances; and
- Inequality as a result of limited access to testing.

2.3.3 Recommendations for the Chemical Industry

The Ethical, Legal, and Regulatory Challenges Breakout Group identified five important focus areas for the chemical industry. These recommendations are presented below.

Support confidentiality, privacy, and security of genetic information. Support non-discriminatory principles and privacy issues that ensure confidentiality and discrimination protection. For example, the chemical industry should participate in addressing confidentiality, privacy, and security issues by adopting a "bill of rights of examinees." The industry might also consider and support appropriate legislation, such as extending the patient/doctor privilege to the practice of occupational medicine.

Seek input from external advisors (specifically for social, ethical issues). This second recommendation relates to the influence of ethical, legal, and regulatory issues on research direction and outreach education. Chemical companies have established ethics advisory boards and science advisory boards, but no external advisory group to address ethical, legal, and regulatory challenges has been established. The American Chemistry Council and individual companies should seek external advice on social, ethical, and legal aspects of genomic technologies (in addition to other occupational health issues that arise in the workplace with social, ethical, and regulatory implications). The chemical industry should also adopt the common rule for human research, which imposes certain requirements for federally-funded research, including requirements for informed consent and review of research proposals by institutional review boards. The rule can be found in 45 CFR Part 46.

Establish principles/guidelines for worker testing. Some employers are sued for inappropriate genetic testing of their employees, and there has been much Congressional, media, and academic criticism of genetic testing in an occupational context. At the same time, some companies have already been sued for not performing or recommending genetic testing of their workers or product users. Therefore, the chemical industry should develop and set clear principles and professional guidelines with respect to genetic testing of workers and develop education outreach within the industry. These guidelines and educational outreach materials need to be communicated and distributed to all levels within chemical companies (from CEO to factory workers). Industry guidelines on the appropriate use or non-use of genetic testing of workers needs to come from the industry, but outside experts can be used to assist with this task. Internal resources in occupational health and safety will be needed to handle genetic susceptibility issues and ensure guidelines are being followed.

Work to educate the public on genomics. It is a challenge to keep regulators, decision-makers, professional groups, and the general public informed about "omics." Industry can address this challenge by facilitating the development of multi-stakeholder guidelines for use of the technologies and data to ensure good genomic practices; schedule periodic workshops to provide technical updates; explain how "omics" information can be used when making regulatory decisions; and support scientific and policy resources related to genomics and "omics" technologies within the federal agencies.

APPENDIX A: ICCA GENOMICS WORKSHOP FINAL AGENDA

ICCA Genomics Workshop Final Agenda – March 7 & 8, 2001, Orlando, Florida

March 7

7:00 – 8:00 AM	Registration and Continental Breakfast
8:00 – 8:05 AM	Introduction, Welcome, Workshop Objectives Workshop Chair**: Carol Henry** – Vice President, Science and Research, American Chemistry Council
	Session I: Application of "Omics" Technology to Toxicology
8:05 – 8:10 AM	Introductory Comments *Session Chairs:* **Lewis Smith** – Head, Health Assessment & Environmental Safety, Syngenta **Ray Tennant** – Chief, Laboratory of Environmental Carcinogenesis and Mutagenesis, National Institute of Environmental Health Sciences
8:10 – 8:50 AM	Overview of Genomics, Expression Profiling Techniques, Metabonomics and Bioinformatics *Speaker:* **Chris Corton** – Scientist II, CIIT Centers for Health Research
8:50 – 9:50 AM	Application of "Omics" for Gaining Mechanistic Understanding/Mode of Action for Reducing Uncertainty in Risk Assessments ➢ Application of Genomics to the Definition of the Molecular Basis for Toxicity Speaker: **Bill Pennie** – Head of Investigative Toxicology, Sygenta ➢ Classifying and Understanding Chemical Toxicants Using DNA Microarray Technologies *Speaker:* **Chris Bradfield** – Professor of Oncology, University of Wisconsin
9:50 – 10:20 AM	High Throughput Genotyping Using DNA Microarray Technology *Speaker:* **Fred F. Kadlubar** – Director, Division of Molecular Epidemiology, National Center for Toxicological Research
10:20 – 10:45 AM	**Break**
10:45 – 11:30 AM	Application of "Omics" to Predictive Toxicology: Toxicogenomics at NIEHS *Speaker:* **Rick Paules** – Director of Toxicological Gene Expressions Studies, NIEHS Microarray Center
11:30 – 12:00 PM	Ecotoxicogenomics: The Challenge of Integrating Genomics into Future Ecological Risk Assessment of Chemicals *Speaker*: **Jason Snape** – Research Scientist, Brixham Environmental Laboratory, AstraZeneca

March 7 (continued)

12:00 – 12:30 PM Panel Discussion: Potential Implications of "Omics" on Toxicology and Risk Assessment Approaches
Co-Chairs:
Lewis Smith – Syngenta
Ray Tennant – National Institute of Environmental Health Sciences

12:30 – 1:30 PM **Lunch**

Session II: Molecular Genetics in Epidemiology

~~Introductory Comments~~
1:30 – 1:45 PM ~~*Session Chair*: **Dick Albertini** – Research Professor, University of Vermont~~
(Jane Teta, Union Carbide substituted for Dr. Albertini)

1:45 – 2:45 PM Evolution of Epidemiologic Research for Assessment of Gene-Environment Interactions

- Methodologic Issues in the Design and Conduct of Epidemiologic Studies of Gene-Environment Interaction
  Speaker: **Bob Millikan** – Associate Professor, University of North Carolina at Chapel Hill
- Challenges to Interpretation of Gene-Environment Research
  Speaker: **Paul A. Schulte** – Director, Education and Information Division, National Institute for Occupational Safety and Health

2:45 – 3:15 PM Existing and Potential Sources and Uses of Human Genetic Biomarker Data
Speaker: **Germaine M. Buck** – Chief, Epidemiology Branch, National Institute of Child Health and Human Development

3:15 – 3:45 PM **Break**

3:45 – 4:15 PM Panel Discussion regarding Epidemiology Issues and Risk Assessment

4:15 – 4:45 PM Observations on the Sessions and Charges to Breakout Groups
Rappateurs:
Bob LeBoeuf – The Procter & Gamble Company
Jane Teta – Union Carbide Corporation

4:45 – 5:00 PM Closing Remarks and Adjourn
Workshop Chair: **Carol Henry** – American Chemistry Council

6:00 – 7:00 PM **Cocktails and Reception**

7:00 – 9:00 PM **Dinner**
~~Interdisciplinary Collaboration~~
~~*Speaker:* **Dick Albertini** – University of Vermont~~
(Cancelled)

March 8

Session III: Ethical, Legal, and Regulatory Challenges in Applying Genomic Technologies to Toxicology and Risk Assessment

8:00 – 8:10 AM	Introductory Comments *Session Chair*: **Gary Marchant** – Associate Professor, Arizona State University, College of Law
8:10 – 8:40 AM	Ethical and Regulatory Impacts of Toxicogenomic Research Speaker: **Richard R. Sharp** – Biomedical Ethicist, NIEHS
8:40 – 9:10 AM	Genetics, Workplace Medical Examinations, and the Practical Value of Bioethics *Speaker:* **Myron Harrison** – Senior Health Advisor, Department of Safety, Health, and Environment, ExxonMobil
9:10 – 9:40 AM	Ethical, Legal, and Social Issues (ELSI) and the Workplace *Speaker:* **Mark A. Rothstein** – Director, Institute for Bioethics, Health Policy and Law, University of Louisville
9:40 – 10:10 AM	Panel Discussion regarding ELSI and Risk Assessment
10:10 – 10:15 AM	Summary and Charge to Breakout Groups *Workshop Chair:* **Carol Henry** – American Chemistry Council
10:15 – 10:30 AM	**Break**
10:30 – 2:00 PM	**Breakout Group Discussions** ➢ Group 1: Toxicology (Mammalian & Environmental) *Lead:* **Bob LeBoeuf –** The Procter & Gamble Company *Recorder:* **Chris Corton –** CIIT Centers for Health Research ➢ Group 2: Epidemiology *Lead:* **Jane Teta –** Union Carbide Corporation *Recorder:* **Vanessa Vu –** U.S. EPA ➢ Group 3: Ethical, Legal, and Regulatory Challenges *Lead*: **Gary Marchant –** Arizona State University *Recorder:* **Steve Lewis –** ExxonMobil Biomedical Sciences
12:00 – 1:00 PM	**Working Lunch**
1:45 – 2:00 PM	**Break**
2:00 – 2:30 PM	Breakout Group 1 Report and Q & A
2:30 – 3:00 PM	Breakout Group 2 Report and Q & A
3:00 – 3:30 PM	Breakout Group 3 Report and Q & A
3:30 – 3:45 PM	Wrap-up and Next Steps *Workshop Chair:* **Carol Henry** – American Chemistry Council

APPENDIX B: ICCA GENOMICS WORKSHOP SPEAKER ABSTRACTS

Disclaimer: The statements made in the abstracts are solely those of the authors and do not necessarily represent views or conclusions of the American Chemistry Council, CEFIC, or JCIA.

Overview of Genomics, Expression Profiling Techniques, Metabonomics and Bioinformatics

J. Chris Corton, CIIT Centers for Health Research

Recent technological developments in the global analysis of components of biological systems have brought about a revolution in biomedical science in the 21st century. It is now possible to assess the levels of hundreds or thousands of gene transcripts simultaneously after chemical exposure (transcriptomics). Techniques are also being developed or refined that can assess changes in the levels of thousands of proteins (proteomics) or endogenous metabolites (metabonomics). Combined, these technologies will have a significant impact on biological research by elucidating the link between changes in the readout of genetic information with physiological or pathological outcomes, as well as identifying relevant biomarkers of action. This large-scale analysis will allow toxicologists to take a new look at important problems of chemical action that cannot be completely unraveled using nongenomic techniques. A major challenge in using data derived from these techniques is to correctly interpret the functional significance of the changes in relation to the biological system being analyzed. Chemical exposure can alter large batteries of genes and proteins, many of which have nothing to do with toxicity and in fact, may reflect adaptive changes that protect against the stress of the exposure. Definition of relevant dose- and time-response relationships that link genomic changes to biological outcomes will have to made. This presentation will introduce the concept of global analysis of cellular components after chemical exposure. Expression profiling techniques including transcriptomics and proteomics will be reviewed. Promising new techniques that could confirm expression profiling data by measuring global changes in the metabolites regulated by these proteins will also be reviewed. Lastly, the rapidly evolving area of bioinformatics will be discussed giving examples of how the structured data can be useful in interpreting mechanisms of chemical action.

Application of Genomics to the Definition of the Molecular Basis for Toxicity

William D. Pennie, Syngenta Central Toxicology Laboratory

Technologies designed to characterise gene expression on a large scale are now impacting many areas of biology, including toxicology. These approaches, when applied to toxicology, are termed “toxicogenomics” and promise to greatly facilitate mechanism-based research on toxicant action with the longer term possibility of assisting in the identification of potential toxicity issues earlier in the development of new pharmaceutical, agrochemical and chemical products. An example of such a platform developed in our laboratory is ToxBlot II, a custom microarray containing cDNAs representing almost 13,000 human genes chosen on the basis of their potential relevance to a broad range of toxicities. ToxBlot II can assist in characterising many outcomes including processes as diverse as immune system response, receptor biology, signal transduction, protein modification, membrane transport, growth and development, metabolism, oxidative stress etc. Furthermore, such large scale microarrays allow the simultaneous profiling of gene expression events representing entire cellular pathways, facilitating a very detailed investigation of potential mechanisms of toxicity. Our laboratory is applying such platforms in many areas, including endocrine disruption, receptor biology, stress response, the effect of toxicants on immune function and in areas of biochemistry of relevance to particular compounds in development. Such approaches are an important part of the molecular toxicologist’s “toolbox” and can be particularly valuable when used in conjunction with more functional genomics approaches such as transgenic or knockout models. The challenge to researchers in mechanism-based toxicology is to utilize the technology in an appropriate manner, without generating confounding or potentially misleading data.

Classifying and understanding chemical toxicants using DNA microarray technologies

Russell Thomas[1,2], David Rank[1], Sharron Penn[1], Stevan Jovanovich[1], Kalyan Pande[2] and Chris Bradfield[2]
[1]Molecular Dynamics; [2]McArdle Laboratory, University of Wisconsin

One of the major objectives of toxicology is to understand the adverse health effects of chemicals in humans. This understanding could be aided by the ability to group chemicals that generally act the same or are believed to produce their toxic endpoints through similar mechanisms. For example, toxicologists tend to classify a number of chemicals as having 'dioxin-like' activity due to their ability to bind the aryl-hydrocarbon receptor (Ahr) and induce a defined change in the expression of a small population of genes (e.g., CYP1A1). Research related to this type of chemical classification has, to date, largely consisted of serially characterizing responses in a small number of genes, which allows only broad generalizations of toxicological behavior. However, with the advent of modern genomic technologies, parallel analysis of large numbers of genes is possible and could change the traditional toxicological models for classifying chemicals. These new tools provide a relatively quick and easy analysis of the chemically induced transcriptional changes in a cell and may be useful in defining classes of toxicants. In an attempt to identify these toxicologically relevant gene expression patterns, we initiated a survey of chemically induced changes in liver gene expression through the use of custom cDNA microarrays. These microarrays were constructed from cDNA clones derived primarily from chemically treated and control mouse livers. Five broad chemical classes were selected for study: phenobarbital-like, inflammatory, hypoxia-like, Ahr-like, and peroxisome proliferators. cDNA microarray analysis was performed on various chemicals within these groups and the results analyzed using various statistical techniques Using a Bayesian analysis, the classification of these treatments and time-points into their respective toxicological classes was very poor using expression changes from the microarray as a whole (47.8% accuracy based on leave-one-out cross-validation). However, using a forward parameter selection scheme, a 'minimal' set of 5 genes was identified that allowed 100% accuracy in classifying the treatments and an 'optimal' set of 12 genes which still provided 100% accuracy, but also gave more robust predictions. These results provide significant evidence that the classification of chemicals according to their gene expression profiles is possible and opens the door to a potentially new era of toxicological testing.

High Throughput Genotyping Using DNA Microarray Technology

Fred Kadlubar, Patricia Thompson, [1]Elena Martinez, [1]David Alberts, and [2]Michael Hogan
National Center for Toxicological Research, [1]Arizona Cancer Center, [2]Genometrix, Inc.

The Human Genome Project can be expected to have a major impact on our understanding of human cancer. A nearly complete sequence of the human genome has now been made available and forthcoming will be the identification of single nucleotide polymorphisms (SNPs) accounting for the genetic diversity of the human population. However, nearly 50 years ago, the renowned nutritionist, Roger J. Williams , reminded us that "every individual has his own inborn metabolic characteristics..., that every application of biochemistry must take these differences into account..., and that all diseases, such as cancer.... are related to biochemical individuality." Today, we realize that there are an estimated 3,150,000,000 DNA bases in the human genome. Of these, it appears that humans differ from each other by a frequency of 1/1000 nucleotides. Thus, these differences, or SNPs, involve about 3.15 million nucleotides. They can occur in both coding and non-coding regions of genes and their frequency may vary between genes (from 1/100 to 1/10,000), depending on their function and role in cellular maintenance and survival. Current data indicate that about 10-15% of these SNPs, or 300-500,000, are likely to be functional in determining the activity or the level of the protein expressed.

Accordingly, there is a clear and present need for high throughput (>1,000 samples/day) genotyping, so that one can characterize human tissue samples for 10-100 genes or alleles concurrently using small sample volumes and at low cost. DNA microarray technology would appear to be ideally suited for these needs. One can design oligonucleotide probes, fixed on glass surfaces or "chips" to conduct allele-specific hybridization of PCR-amplified DNA samples. After washing and activation of a fluorescent or other suitable signal, the information can be readily captured by image analysis and sorted by bioinformatics systems. Moreover, the rapid screening of these genes should allow the selection of genetically heterogeneous groups for inclusion in clinical trials and thereby increase our ability to protect public health.

To achieve these goals, we are developing a DNA microarray platform to genotype patients for all the major enzyme variants that would enable us to predict carcinogen susceptibility, adverse drug reactions, and perhaps chemotherapeutic drug efficacy. VistaMorph Arrays®, which are low-/medium-density microarrays formatted for very high throughput genotyping applications currently allow up to 250 oligonucleotide probes per array to be configured to interrogate single nucleotide polymorphisms (SNPs) or polymorphisms due to gene deletion or SNPs across hundreds of samples per day in a fully automated production facility. DNA genotyping microarray technology provides a means of rapid large-scale data/risk mining in population, and it will impact pharmacogenomics, pharmacogenetics, as well as SNPs associated with cancer susceptibility. At present, the VistaMorph Arrays includes *NAT1, NAT2, COMT, CYP1A1, CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5, GSTA1, GSTA2, GSTM1, GSTM3, GSTT1, GSTP1, GSTZ1, SULT1A1, MTHFR, NQO1, MPO, SOD, FMO3, HYL, UGT1A1, UGT1A6, UGT2B7, UGT2B15,* and *Ki-ras*. We are currently in the process of validation studies, comparing our standard methodologies of genotyping to automated, large-scale genotyping on a robotic workstation and have completed repeatability and validation studies for selected genetic variants. Our DNA chips have proven to be a very reliable for profiling of genotypes as demonstrated by a more than 99% concordance between the microarrays and conventional genotyping assays (PCR-RFLP), based on a mini-chip made so far (*ras, NAT2, and COMT*).

In a colon polyp prevention trial involving 1429 subjects, questionnaire information was used to assess potential exposure to heterocyclic amines. Using our high throughput DNA microarrays, 686 individuals who had undergone colonoscopy by year 3 were genotyped for all common *NAT2* alleles in one work-day. Only those in the highest tertile of red meat consumption who were rapid acetylators showed a significant increased risk and the odds ratios indicated gene-dose dependence. These data suggest that a one-third reduction in red meat consumption is in itself a sufficient preventive measure for colon polyp recurrence and thus should appreciably lower colon cancer risk.

Application of "Omics" to Predictive Toxicology: Toxicogenomics at NIEHS

Richard S. Paules, Toxicological Gene Expression Studies, NIEHS Microarray Center, National Institute of Environmental Health Sciences

A major challenge facing scientists is to assess the impact of environmental exposures on human health. In order to understand the impact of exposures to suspected toxicants, it is important to identify mechanisms of action underlying toxicity. The emerging area of toxicogenomics promises to contribute significantly towards accomplishing this goal. One aspect of toxicogenomics involves global gene expression profiling, which has been revolutionized by microarray technology. Microarray analysis allows one to study changes in genome-wide patterns of gene expression, analyzing the expression of thousands of genes in one experiment. Assuming that exposures to different classes of toxicants result in distinct patterns of altered gene expression, in addition to common changes associated with the subsequent toxic response, microarray technology can be utilized to categorize and classify compound effects through the direct comparison of gene expression signatures in exposed and control samples. Data

will be presented that support the principal hypothesis underlying our toxicogenomic strategy that chemical-specific patterns of altered gene expression can be revealed using high-density microarray analysis of RNA from exposed cells in culture or tissues *in vivo*. Analyses of these patterns can provide discrimination between classes of toxicants and as well as provide mechanistic insights into individual toxicants. In one study, analysis of gene expression in liver tissue derived from chemically exposed rats, revealed similarity in expression profiles between animals treated with different agents from a common class of compounds, peroxisome proliferators, which was distinct from the gene expression profile produced in animals treated with a compound from a completely distinct class, barbiturates. In addition, the data validated previously reported gene expression changes associated with these chemicals and revealed a substantial number of additional signaling events associated with exposure that provide new insight into potential mechanisms of chemical-mediated hepatotoxicity. Additional data will be presented that demonstrate the power of global gene expression analysis to provide insight into cellular responses to DNA damaging agents and ensuing toxicity before evidence of such toxicity is detectable.

Ecotoxicogenomics: The Challenge of Integrating Genomics into Future Ecological Risk Assessment of Chemicals

Jason R. Snape and Thomas H. Hutchinson, Brixham Environmental Laboratory, AstraZeneca Global Safety, Health & Environment

The impact of biotechnology on the biomedical and environmental sciences is moving at an ever increasing rate and has significant implications for future human and ecological risk assessments of chemicals. Exemplified by the high international profile of the Human Genome Project, rapid progress in the field of genomics (the study of how an individual's entire genetic make-up, the genome, translates into biological functions) is also pioneering new knowledge in a wide range of microbial, plant and animal species. In addition to the fundamental insights that genomics will provide towards biomedical advances and understanding of evolutionary biology, this rapidly developing discipline also promises to provide tools for understanding how chemicals may impact on human and ecosystem health. In many ways, scientific and regulatory efforts in the 20th century have sought to establish which chemicals are toxic to wildlife, whereas the challenge for the 21st century is to understand why such chemicals are toxic to different taxa. In the human context, the term '*toxicogenomics*' has been established to describe the sub-discipline that combines toxicology with genomics. Given the parallel implications for ecological (environmental) risk assessment, the new term *ecotoxicogenomics* is proposed to describe the integration of genomics into ecotoxicology. In this context, ecotoxicogenomics addresses both prokaryotes and eukaryotes. This presentation seeks to summarise some of the recent developments in genomic research and discusses challenges of and opportunities for effectively utilising this knowledge in future ecological risk assessments of natural and synthetic chemicals. Specific attention will be paid to: highlighting the short-, medium-, and long-term scientific challenges and benefits of applying genomics to ecotoxicology; the knowledge gaps that need to be addressed; concerns regarding data management and analysis; and the requirement for the chemical industry as a whole to collaborate with regulators and academia to ensure the development of common standards and the sharing of reference data-sets.

Methodologic Issues in the Design and Conduct of Epidemiologic Studies of Gene-Environment Interaction

Bob Millikan, University of North Carolina at Chapel Hill

A revolution is under way in molecular genetics that is rapidly changing, perhaps dominating, biomedical research. Comprehensive mapping of the human genome is nearly complete. Cloning the genes that are responsible for metabolic defects and those that contribute to chronic diseases such as cardiovascular disease and cancer is proceeding at a rapid pace. Genetic tests are available for many

diseases, and technological advances will soon allow large-scale population screening for many different disease-causing mutations. High throughput laboratory methods are now able to generate thousands of genotypes per day, including sequencing for rare mutations and allele discrimination assays for common variants (e.g. single nucleotide polymorphisms). The advent of the "genomics" approach suggests that researchers will embark on genotyping efforts using hundreds of genetics markers "without necessarily knowing in advance which pieces of information and which correlations will prove most important."

The intersection of genomics and epidemiology presents several methodologic issues. These include: (1) whether to study genotypes or phenotypes, (2) need for functional data on newly discovered genetic markers, (3) the problem of multiple comparisons, (4) population admixture, (5) study design challenges, (6) proper tests for interaction, and (7) reproducibility of results. Each of these issues will be dealt with in detail, accompanied by proposed solutions. One recommendation is a call for more "transitional" studies, investigations of the frequency, distribution, and functional characteristics of genetic markers prior to conducting association studies.

Challenges to Interpretation of Gene-Environment Research

Paul A. Schulte, Education and Information Division, National Institute for Occupational Safety and Health

Epidemiologists increasingly are presented with powerful new tools to piece together the roles of environmental/occupational and genetic factors in assessing disease risks. High throughput tools, such as microarrays and 2D gels, present new opportunities, but their utility for assessing disease risks in populations is still some time from being realized.

Making sense from population studies incorporating genes and environment has a rich history, but one fraught with problems. Despite notable examples to the contrary, the nature-nurture debate has given way to the fundamental realization that both genes and environment play a role in disease. Unfortunately, however, the degree of increased risk in exposed genetically susceptible individuals is highly dependent on the relationship between genes and exposure in terms of their effect on disease risk; and we seldom have had information about this. Depending on the type of model for gene-environment interaction, risks can vary dramatically. At least six different types of gene-environment interaction have been described. These have been generally considered with the dichotomous conditions, a single susceptibility genotype (present or absent), and a single environmental factor (present or absent). For example, in a paper by Khoury and Wagener, the risk to an exposed person with a rare (1% prevalence) susceptibility genotype ranges from 8% (under a multiplicative model of interaction) to 95.6% (when we assume that the exposure has no effect in susceptibles, but the genotype raises risk in unexposed as well as exposed persons).

Various study designs have been identified for the detection of gene-environment interaction. These include: case-only designs, case-control study designs using unrelated controls, case-control designs using related controls, case-control designs using relatives of cases and population- or hospital-based controls, twin-study designs, family-study designs, and combined segregation and linkage analyses.

There is currently a debate whether bias from population stratification (the mixture of individuals from heterogeneous genetic backgrounds) undermines the credibility of epidemiologic studies designed to estimate the association between genotype and risk of disease. However, Wacholder et al. found only a small bias from stratification in a well-designed case-control study of genetic factors that ignored ethnicity among non-Hispanic, U.S. Caucasians of European origin. When important confounding caused by population stratification does occur, it should be controllable by the usual design and analytical features employed by epidemiologists.

Existing and Potential Sources and Uses of Human Genetic Biomarker Data

Germaine M. Buck, Epidemiology Branch, Division of Epidemiology, Statistics & Prevention Research, National Institute of Child Health & Human Development

This talk is intended to inform the audience about potential opportunities for collaborative research for the fields of epidemiology, genetics and toxicology. A brief review of the epidemiologic method will be presented to provide the context for the collection, analysis and interpretation of biologic specimens utilized by practicing epidemiologists. Subsequent discussion will focus on existing data sources that may be appropriate for contemporary study. These resources include: newborn screening registries, military repositories, medical facilities, and research initiatives. The talk will conclude with a brief discussion of a potentially new data source for population-based epidemiologic studies focusing on human health.

Genetics, Workplace Medical Examinations and the Practical Value of Bioethics

Myron Harrison, Department of Safety, Health, and Environment, ExxonMobil Corporation

This presentation will use a case example to discuss:

- the types of medical examinations that are performed on the behalf of employers
- research on human subjects in industry
- the impact of genomics-related technologies upon these activities
- the practical value of bioethics for industry sponsored research

Medical examinations in a workplace setting are not generic. This discussion describes five different types of examinations distinguished by the intended uses of the information:

- fitness-for-duty exams
- medical surveillance exams
- medical screening exams
- clinical exams
- wellness exams

Information obtained in medical examinations is also used for research. It is important that industry based or sponsored research observes current ethical standards for research on human subjects.

The introduction of new genomic technologies will increase our understanding of disease processes. But, because this information is also potentially disadvantageous to an employee, there is significant public concern about possible abuses. This implies increased scrutiny of workplace policies and practices for medical examinations.

It is important that regulation does not prohibit intelligent uses of genetic testing by industry. Well-established bioethical principles provide guidance for employers who need to ensure that workplace examination programs are both scientifically and ethically sound.

Ethical, Legal, Social Issues (ELSI) and the Workplace

Mark A. Rothstein, Herbert F. Boehl Chair of Law and Medicine, Institute for Bioethics, Health Policy, and Law, University of Louisville

Ethical, legal, and social implications should be considered in evaluating all occupational health strategies, including the possible use of genetic information. There are two main ways in which genetic information could be used in the workplace: (1) using genetic information to promote occupational health, and (2) using genetic information to predict the future non-work-related health of the individual. Attempts to distinguish genetic information from other medical information for purposes of regulation have proved to be ineffective. A thoughtful, effective policy means reconsidering the physician-examinee relationship, restricting employer access to non-job-related medical information, and encouraging workers to make informed decisions about the acceptability of heightened workplace risks based on genetic factors.