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Impact of Genomics on Regulation of Chemicals and Drugs

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- I. Overview of Toxicogenomics
 - A. Toxicogenomics is an emerging science that studies the interaction among peoples' genetic makeup, chemicals in the environment, and disease. Toxicogenomics is the study of how genomes respond to environmental toxicants and other "stressors."
 1. Dramatic advances in genome sequencing projects and other advances taking place in genomic technologies for expression profiling of messenger RNAs (mRNAs) and proteins have accelerated the development of this evolving science.
 2. Advances in technology have also contributed greatly to this emerging science. Advances in bioinformatics (the science of managing biological data using advanced computer techniques) and computational toxicology are equally dramatic.
 - B. Toxicogenomics holds much promise in many areas of science, law, and policy. Key applications include:
 1. Predictive toxicology and screening.
 2. Identification of sensitive populations.
 3. Identification of biomarker of chemical exposure and effects.
 4. Definition of the relationship among multiple disciplines, including genetics, biology, and environmental stressors.



II. Regulatory Implications of Toxicogenomics Research

A. Potential Effects on Utilization of Uncertainty Factors in Risk Assessment

1. Quantitative methods of estimating human risk posed by chemicals are utilized in environmental and other public health laws to determine how chemicals to which persons may be exposed should be regulated. While regulatory standards in these laws vary, the use of quantitative risk assessment methods is common to most of them.
2. Examples include ascertaining risks under standards established by environmental protection laws administered by the United States Environmental Protection Agency (EPA), such as the Toxic Substances Control Act's (TSCA) provisions authorizing EPA to restrict or ban the manufacture of chemicals that are believed to present an unreasonable risk of injury to health or the environment; the "unreasonable adverse effects" standard in the federal pesticide statute, Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), applied in making pesticide registration determinations, and the Clean Air Act's (CAA) requirement to establish primary national ambient air quality standards (NAAQS) with an "adequate margin of safety" (Section 109(b)(1)) and to take into account health thresholds with an ample margin of safety in regulating hazardous air pollutants.
3. Quantitative risk assessments of chemicals under these statutes and programs often require the extrapolation from animal data alone, or animal data in combination with human data. When extrapolating risks from such data, uncertainty factors are employed to take into account the incompleteness of information.
4. The approach for estimating non-cancer human risks from animal studies that generally is utilized by EPA, as well as by other regulatory agencies, is exemplified by the methodology described in EPA's Integrated Risk Information System (IRIS). Under this methodology, the level of exposure at which a toxic effect of concern is



not expected to be observed in humans is typically determined in two steps. First, the no observed adverse effect level (NOAEL) (or other comparable dose-response benchmark) is determined from animal studies. The NOAEL is then divided by a 100-fold uncertainty factor. This uncertainty factor is comprised of two separate 10-fold uncertainty factors, one to account for the uncertainty in extrapolating from animals to humans and a second to account for variation in sensitivities within the human population. A number of studies have shown that these uncertainty factors are generally conservative.

5. Advances have been made in elucidating the source of some of the uncertainties which the 10-fold uncertainty factors are intended to address. For example, if data exist showing similarities between humans and laboratory animals with regard to absorption, distribution, metabolism, and excretion of a toxic compound (collectively known as toxicokinetic considerations), then such data may provide a basis for reduction in the default interspecies uncertainty factor of 10.
6. Toxicologists generally believe that toxicogenomics developments may have additional significant impact on, and refine, risk assessment methodologies thus allowing for the reduction of uncertainty factors. Toxicogenomics may accomplish these refinements by providing more data on the mechanism of a chemical's toxicity which, in turn, will increase the accuracy of extrapolation between animals and humans.
7. Risk assessments can also be enhanced by the promise of toxicogenomics to identify specific factors that make some humans more susceptible to a chemical than others. Such information possibly could help in the refinement and potential reduction of the uncertainty factor used to account for differences in susceptibility among different humans in the population.
8. It is unlikely that predictive models developed from toxicogenomics data will substitute in all cases for



animal testing. Toxicogenomics may be best used as part of a comprehensive multidisciplinary approach in toxicology.

B. Potential Implications for Exposure Assessment

1. Risk assessments required under various environmental, products, and public health regulatory programs generally must evaluate not only the levels of exposure at which humans may be at risk to the toxic effects of chemicals, but also which segments of the population are exposed and the magnitude of such exposures. For example, in evaluating whether pesticides pose “unreasonable adverse effects on the environment [including humans]” under FIFRA, it is necessary to relate estimated exposures resulting from the use of pesticides to the levels of exposure at which pesticides may cause toxic effects in humans.
2. The National Center for Toxicogenomics (NCT), the National Institute of Environmental Health Sciences’ Center devoted to understanding the genetic and biochemical pathways to disease, believes that toxicant specific gene expression “signatures” generated by toxicogenomics can serve as biomarkers that may make it possible to identify chemicals and the dose to which individuals or populations may be exposed. Accordingly, use of toxicogenomics data may prove to be an extremely useful tool in refining the exposure assessment component of risk assessment.

C. Implications of Toxicogenomics Technology on Chemical and Products Testing Requirements

1. Risks posed by a chemical requires a battery of tests to determine what adverse effects may be caused by the chemical after acute (short term), subacute or subchronic (medium term), and chronic exposures. Different types of tests are necessary to evaluate certain types of adverse effects, such as reproductive or developmental toxicity, carcinogenicity, neurotoxicity, or other health endpoints. Where relevant human data, such as epidemiological studies, do not exist, as is frequently the case, laboratory



animal tests, often involving a large number of test animals, are required.

2. Statutes such as FIFRA and the Federal Food, Drug, and Cosmetic Act (FFDCA) require testing before a product may be marketed or as a condition of continued product marketing.
3. TSCA provides a good example of EPA authority to require safety testing of chemicals which may be significantly impacted by toxicogenomics.
 - a. Under TSCA, EPA may require chemical manufacturers to test existing chemicals either through issuance of a test rule, as contemplated by TSCA Section 4, or through entering into an enforceable consent agreement (ECA) with manufacturers, a procedure governed by EPA regulations implementing TSCA Section 4.
 - b. EPA also may restrict or ban the manufacture or use of new chemicals for which Premanufacture Notices (PMNs) have been submitted pending development of new toxicology data, through issuance of orders under Section 5(e) or as is more commonly the case, by entering into a consent order with manufacturers.
 - c. In the 27 years since enactment of TSCA, few Section 4 rules or ECA's have been established for existing chemicals.
 - d. Under EPA's High Production Volume (HPV) Challenge Program, established in 1999, however, chemical manufacturers and importers have been encouraged to conduct testing of



chemicals on the HPV list of chemicals established by EPA.¹

- e. EPA intends to use its rulemaking authority under Section 4 to require testing of chemicals on the HPV list for which no companies volunteer to conduct testing.
4. Under the FFDCA, new drugs must go through a series of extensive and costly tests, beginning with animal toxicology testing, as one of the prerequisites for an investigational new drug (IND) application that permits a series of clinical trials to demonstrate sufficient safety.²
 5. Toxicogenomics technology could have an impact on testing requirements under these and other statutes and on chemical production and drug development in a number of ways.
 - a. By providing a quick screening method of identifying highly toxic chemicals or products early in the investigative stages, toxicogenomics may provide manufacturers of products subject to governmental approval, such as new chemicals under TSCA or new drugs, under FFDCA, with valuable information in deciding whether to proceed with product development before conducting more expensive toxicological tests on experimental animals.

¹ In response to findings in that toxicity data were not publicly available for a majority of the approximately 2,800 HPV chemicals manufactured or imported into the United States, EPA, in cooperation with the American Chemistry Council and Environmental Defense, established in 1999 the HPV Challenge Program.

² 21 C.F.R. §§ 312.20-312.23.



- b. The technology may provide EPA a valuable means of prioritizing for further testing the many chemicals for which there are insufficient toxicological data.
- c. The technology may provide useful information in determining whether and what testing should be required for new chemicals for which PMNs are submitted.
- d. Because of information which might be provided concerning mechanism of action and similarity of gene expression profiles to other chemicals with well-established toxicological information, toxicogenomics may reduce or possibly eliminate the traditional types of toxicological tests that might otherwise be required for a new or existing chemical or may reduce the number of animals needed to conduct a particular test.
- e. Toxicogenomics, by raising a red flag about the potential toxicity of a chemical, may increase the degree of testing that otherwise might be required, if the toxicogenomics data are insufficiently predictive.

D. Impact on Chemical Reporting Requirements

- 1. Certain environmental laws, notably TSCA and FIFRA, require manufacturers and others to report information regarding adverse effects associated with chemical exposure.
- 2. TSCA Section 8(e) requires any person who manufactures, processes, or distributes a chemical substance and who obtains information which reasonably supports the conclusion that such substance presents a “substantial risk of injury to health or the



environment,” must immediately inform EPA of such information.

3. EPA guidelines implementing this provision indicate that sources of substantial risk information include, among other things, controlled studies, epidemiological studies, environmental monitoring studies, and clinical studies. Toxicogenomics data that either establish that a chemical poses certain adverse toxicological risks or that demonstrate significant human exposures to chemicals of known toxicity may be subject to these reporting requirements, at least after the technology is further advanced and validated.

III. Legal and Ethical Implications of Toxicogenomics

A. Potential Implications in Toxic Torts Litigation

1. Toxicogenomics could significantly impact various aspects of toxic tort litigation, including the establishment of causation, theories of liability, and certification of classes in class actions. Implications for establishing causation are perhaps the most prominent.
2. Since the landmark decision *Daubert v. Merrell Dow Pharmaceuticals*,³ which redefined the standards for admissibility of expert scientific evidence and the court’s role as “gatekeeper” for the screening of such evidence, there has been a growing trend in court rulings to require human evidence to establish causation in toxic torts action.
3. More specifically, in toxic tort actions many courts have ruled that causation can only be established by epidemiological studies that demonstrate the substance in question resulted in a doubling or more of the risk of the disease or injury for which the plaintiff seeks relief.
4. The theory behind these rulings is that only such evidence is sufficiently reliable to show that the plaintiff’s illness more likely than not resulted from the

³ 509 U.S. 579 (1993).



exposure to the substance. Many courts have ruled that causation cannot be established by animal data alone or by epidemiological studies that show less than a doubling of risk.

5. Data generated from toxicogenomic technologies may facilitate the establishment of causation in toxic tort cases in several ways.
 - a. It is anticipated that this technology will be able to show whether an individual is highly susceptible to the toxic effects of a particular chemical. If the plaintiff is demonstrated to be highly susceptible to the effects of the substance on which the action is based, the task of establishing specific causation may be made easier. For example, courts that generally apply the epidemiological study doubling of risk rule may allow recovery even if the epidemiological data show a relative risk of less than two.
 - b. Application of toxicogenomic techniques may identify biomarkers that provide both qualitative and quantitative evidence of the plaintiff's exposure to the substance in question and therefore help establish the required showing of specific causation.
 - c. Data generated by toxicogenomics technology combined with animal data and other non-epidemiological data possibly may be sufficient to establish causation even in courts that generally adhere to the epidemiological evidence rulings. For example, if a gene expression profile for the substance in question shows a "fingerprint" very similar to that of another chemical shown by epidemiological evidence to cause the disease suffered by the



plaintiff, such information by itself or in conjunction with other data, such as animal toxicology data, conceivably may suffice to establish causation.

6. A number of other issues are raised by the availability of toxicogenomics technology with respect to toxic torts liability, including:
 - a. Whether a demonstration of wide variation in genetic susceptibility among a group of plaintiffs by toxicogenomics technology would preclude certification of a class pursuant to Federal Civil Judicial Procedure and Rules, Rule 23(b)(3), on the grounds of differences in issues concerning causation.
 - b. Whether the ready availability of toxicogenomic techniques to determine susceptibility to a manufacturer's product imposes a duty on the manufacturer to ascertain whether any significant groups are hypersusceptible to the product and to provide an adequate warning targeted at such groups.
 - c. Whether a defendant would be permitted to request a determination of hypersusceptibility in a plaintiff through toxicogenomic techniques and whether such a determination would provide a defense, particularly if the hypersensitivity is rare among the general population.
 - d. Whether the availability of toxicogenomics technology to ascertain biomarkers of exposure to a hazardous substance would impose a duty on an employer to test, or offer to test, potentially exposed employees.



B. Potential Implications of Toxicogenomics with Regard to Workplace Safety

1. As toxicogenomics develops and provides a greater ability to determine increased susceptibility of individuals to the toxic effects of exposure to chemicals, many legal, policy, and ethical issues will arise concerning the rights and obligations of employers and employees in the workplace.
2. At present, the legal framework at the federal level for addressing these issues is comprised largely of the Occupational Safety and Health Act (OSH Act)⁴ and the Americans with Disabilities Act (ADA).⁵
3. The OSH Act regulates toxic substances primarily through standards established under Section 6(b)(5)⁶ and the general duty clause in Section 5(a)(1).⁷ Section 6(b)(5) provides that the Occupational Safety and Health Administration (OSHA) shall set standards concerning toxic materials which adequately assure that “to the extent feasible . . . no employee will suffer material impairment of health or functional capacity.” The general duty clause requires that each employer furnish employees with employment and a place of employment “which are free from recognized hazards that are causing or are likely to cause death or serious physical harm.”
4. Occupational standards established under Section 6(b)(5) and other regulations apply to average workers and the OSH Act is not intended to protect highly susceptible individuals to the same degree as the normal or average worker.

⁴ 29 U.S.C. §§ 651 *et seq.*

⁵ 42 U.S.C §§ 12101 *et seq.*

⁶ 29 U.S.C. § 655(b)(5).

⁷ 29 U.S.C. § 654(a)(1).



5. In setting standards, courts have held that OSHA may take into account technological and economic feasibility as well as the Section 3(8) definition of standards as encompassing what is “reasonably necessary or appropriate to provide safe or healthful employment and places of employment.”
6. OSHA has not made special provision for susceptible workers in setting permissible exposure limits (PELs) under Section 6(b).
7. The Supreme Court has held, however, that OSHA can require monitoring and medical testing for employees exposed to levels below the standard and “in this way . . . could ensure that workers who were unusually susceptible . . . could be removed from exposure before they had suffered any permanent damage.”⁸
8. OSHA has issued a substantial number of standards that do not require medical examination and monitoring, but OSHA generally has not required specific tests.
9. Unless genetic testing is specifically required, employers are not required to conduct such testing, either under the existing standards or under the general duty clause.
10. Other questions arise as to how toxicogenomic technology could or should be utilized under OSHA. One issue is whether and the extent employers should be required to test their employees for hypersusceptibility.
11. Questions of the reliability of the tests and how they should be interpreted likely will be an issue in determining whether the tests should be required. Another issue is how the tests should be utilized. It could be impractical to require employers to lower exposure levels to the levels necessary to protect the most susceptible employees, particularly where the incidence of hypersusceptible individuals is very low.

⁸ *Industrial Union Dept., AFL-CIO v. American Petroleum Inst.*, 448 U.S. 607, 657-658.



12. The question remains as to what other steps should be taken to protect hypersusceptible individuals. It is unclear whether employers are required under the general duty clause to protect workers they know are hypersusceptible.
13. Other issues that might arise if employers conduct toxicogenomics tests on employees include how employers can be prevented from misusing such data and from unfairly discriminating against hypersusceptible employees, how employee confidentiality and privacy should be best protected, to whom toxicogenomics data should be made available, and what obligations and assumptions of risk should be assumed by employees provided with such data.
14. The ADA addresses many aspects of discrimination in the workplace based on disability.
 - a. To be subject to the protections of the ADA, an individual must be a “qualified individual with a disability.”⁹
 - b. While the Equal Employment Opportunity Commission (EEOC) in 1995 issued an interpretation that an employer that discriminates against an individual based on a predictive genetic test would be in violation of the ADA, the interpretation of the term “disabled” in recent U.S. Supreme Court holdings indicates that it is unlikely that a genetically susceptible person who is not actually disabled by illness would be covered by the protections of the ADA.

⁹ 42 U.S.C. §§ 12102(2), 12111(8), and 12112(a). “Disability” is defined by the ADA as “(A) a physical or mental impairment that substantially limits one or more of the major life activities of such individual; (B) a record of such an impairment; or (C) being regarded as having such an impairment.” *Id.* § 12102(2).



- c. For example, in *Sutton v. United Air Lines, Inc.*,¹⁰ the Court held that “[a] disability exists [under the ADA] only where an impairment ‘substantially limits’ a major life activity, not where it ‘might,’ ‘could,’ or ‘would’ be substantially limiting if mitigating measures were not taken.”
- d. Accordingly, a “person whose physical or mental impairment is corrected by medication or other measures does not have an impairment that presently ‘substantially limits’ a major life activity.”¹¹

IV. Potential Public Health Benefits of Toxicogenomics

- A. Toxicogenomics potentially will provide a number of significant public health benefits. The refinements in the risk assessment process, faster screening for toxicological effects of a large number of chemicals, and the identification of susceptible individuals in the workplace, as discussed above, are potential benefits that may result from toxicogenomics technology.
- B. Other public health benefits also may result. Toxicogenomics may allow for the identification of exposed individuals both in the workplace and among the general public to particular chemicals through biomarkers which may allow health intervention measures, such as increased health monitoring, preventive treatments, and preventive measures against further exposures.
- C. Further, the technology may facilitate the detection and therefore the taking of preventive measures for the protection of highly susceptible individuals both in the workplace and among the general public.
 - 1. Identification of highly susceptible individuals to potential toxic effects of certain consumer products may lead to measures that reduce the exposures of such individuals to the products in question.

¹⁰ 527 U.S. 471 (1999).

¹¹ 527 U.S. at 482; *see also Vaughan v. Murphy*, 527 U.S. 516 (1999).



2. Toxicogenomics likely will provide information on mechanism of action that in turn may lead to the development of more effective medical treatments or intervention measures for prevention of progression of disease processes initiated by exposure to chemicals or other toxicants.
- D. Further, toxicogenomics may allow for the use of highly useful, but potentially toxic, drugs while reducing the risks by identifying hypersusceptible individuals to whom the drug should not be administered.
 - E. Other potential benefits with regard to the use of therapeutic drugs or with regard to medical treatments also have been identified. For example, some experts have stated that toxicogenomics methods may be useful in predicting drug responsiveness in individual cancer patients and in identifying useful combination therapies.
 - F. Toxicogenomic methods could be used to measure a key parameter determining the usefulness of a drug -- the therapeutic index, which is a measure of the median toxic dose of a drug to the drug's median effective dose -- by providing data on both toxic and beneficial effects of a drug.
- V. Other Ethical/Legal Considerations
- A. The ethical, legal, and social ramifications of research in deciphering the human genome were recognized by the federal agencies involved in the Human Genome Project -- the National Human Genome Research Institute (NHGRI) within the National Institutes of Health (NIH) and the Department of Energy.
 - B. In 1990, those agencies established a program to evaluate the ethical, legal, and social implications (ELSI) of human genetics research, known as the ELSI Program.
 - C. Considerable research and analysis has been conducted under this program since 1990. Much also has been written about ethical issues concerning research and application of human genomics technology in academia and by other outside observers. The issues, however, which are complex, have evolved and have been viewed in ever changing contexts as the human genomics technology has progressed and as new



social and policy considerations and perspectives have come to light. Many of the issues, therefore, remain controversial and unresolved.

- D. While there is considerable overlap between ELSI issues concerning the Human Genome Project, and those concerning toxicogenomics methods and applications, the latter brings a plethora of new issues that are to be addressed within the NIH ELSI Program. Experts in the ELSI field have expressed the view that ELSI issues could profoundly affect the manner in which toxicogenomics is applied in the next few years.
- E. In evaluating the ELSI issues raised by genetics research and toxicogenomics applications, it is useful to consider why the development of human genetics information raises societal concerns that are different in kind from other types of information that may be obtained about individuals.
- F. Such information may concern not only health susceptibility information, but also possibly behavioral predispositions, issues of parentage, and reproductive options. Information contained in a person's DNA can be likened to the individual's "future diary," containing the most personal and private information about a person. The availability and future development of genomics and toxicogenomics methods also can make DNA samples taken from individuals a ticking time bomb, which, in the future, might release sensitive private information about the individual. If such information is not sufficiently safeguarded, harm to the individual may result from the unfair use of the information by employers, insurers, and others can exercise control over the individual's rights and freedoms.
- G. Some of the other key ELSI issues that have been identified in connection with human genomics and toxicogenomic issues include:
 - 1. How should unauthorized access to genetic samples contributed by individuals be prevented?
 - 2. How should the privacy and confidentiality of genetic information about an individual generated by toxicogenomics methodologies be protected?
 - 3. How should safeguards be implemented to restrict access to databanks containing toxicogenomics data concerning individuals?



4. How should toxicogenomics data be evaluated for accuracy, reliability, and utility and how should use of such data be regulated or restricted if it does not meet sufficient standards? How should uncertainties about susceptibility be dealt with where susceptibility to the disease in question is linked to multiple genes and/or multiple gene-environment interactions?
5. How should the potential for psychological impacts on persons tested be taken into account, particularly where testing may provide information about hypersusceptibility for which preventive or treatment measures are not available?
6. How should potential for stigmatization of individuals or definable groups, such as ethnic groups or races which show hypersusceptibility, be minimized? What protections are necessary to prevent discrimination against individual or minority groups that show hypersusceptibility?
7. Should there be restrictions or conditions on testing individuals for hypersusceptibility to diseases long before it is anticipated that effective medical interventions will be available?
8. How should informed consent principles be applied before subjecting individuals to toxicogenomics tests? What matters concerning risks and benefits should be explained, and by whom, before toxicogenomics tests are applied to individuals?
9. How should decisions be made on who should have access to toxicogenomics data concerning individuals and who should make the decision to disclose such data and to whom. For example, should employers have the right of access to protect hypersusceptible employees? Should the decision to supply such data be left with the employee? Even if the employee decides to be tested and provide the employer with hypersusceptibility data, what restrictions should be placed on the employer's use and dissemination of such data?



10. What protective measures should be provided to prevent misuse of toxicogenomics data, including discrimination, by employers, insurance companies, schools, and government?
 11. What additional protections are needed to protect individuals seeking health insurance from discrimination by insurance companies based on toxicogenomics data? To what extent should insurance companies offering other types of insurance, such as life insurance, have the right to require applicants to submit toxicogenomics tests?
- H. Federal law addresses genetic discrimination by providers of health insurance to a limited degree in the Health Insurance Portability and Accountability Act of 1996 (HIPAA). This law, however, applies only to employer-based and commercially issued group health insurance. No similar federal law affords similar protections to private individuals who seek health insurance in the individual market. Among other things, the HIPAA limits exclusions for preexisting conditions in group health plans to 12 months and expressly provides that genetic information in the absence of a current diagnosis of illness shall not be considered a preexisting condition.
- I. This legislation applies largely to insurance coverage for persons who change jobs. It does not, however, regulate new insurance premiums, which may be set at high levels based on genetic susceptibility.
- VI. EPA Regulatory Response
- A. EPA's 2002 Interim Policy on Genomics
1. On June 25, 2002, EPA Science Policy Council (SPC) released its Interim Policy on Genomics, <http://www.epa.gov/OSP/spc/genomics.pdf>. The Policy acknowledges the significance of genomic data and analyses, but notes that genomics "data alone are insufficient as a basis for decisions."
 2. EPA defines "genomics" broadly to encompass "scientific inquiry and associated technologies." A genome is the "sum total of all an individual organism's genes. Thus, genomics is the study of all the genes of a



cell, or tissue, at the DNA (genotype), mRNA (transcriptome), or protein (proteome) levels.”

3. According to Dr. Paul Gilman’s, EPA's Science Advisor to the Administrator and SPC Chair, memorandum transmitting the Interim Policy, “[g]enomics information will have an enormous impact on our ability to assess risks from exposure to stressors, elucidate mechanisms of action, and examine effects from combinations of stressors.”
4. In addition, such information “may prove to be predictive of subsequent adverse effects.” While there is much promise in these data, alone they are insufficient for EPA decision-making purposes, and “EPA will consider genomics information on a case-by-case basis.”
5. The Interim Policy goes on to state that before “such information can be accepted and used, agency review will be needed to determine adequacy regarding the quality, representativeness, and reproducibility of the data.”