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**Remarks of Lynn L. Bergeson
Before the American College of Toxicology
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November 3, 2003

Good afternoon. Welcome to Symposium II, *The Impact of Genomics on the Regulation of Chemicals and Drugs*. My name is Lynn Bergeson of Bergeson & Campbell, P.C., a law firm in Washington D.C., and I am your co-chair for this afternoon's session. Regrettably, Dr. Kathy Hudson, Director of the Genetics and Public Policy Center, here in Washington, D.C., was called out of town to assist an ailing family member. She regrets that she cannot participate in today's symposium, and has asked me to send you her regrets.

I will begin by providing background remarks on the role of genomics in various regulatory contexts. I will then turn the podium over to my colleague, Gary Callahan. Before joining Bergeson & Campbell, Gary served as General Counsel and Assistant Corporate Secretary for United Agri Products and its North American subsidiaries and operating divisions, a subsidiary of ConAgra Foods, Inc. Prior to UAP, Gary served as General Counsel to Inspiration Resources Corporation. Gary is a graduate of the University of Kentucky Law School, where he also obtained his Masters and Bachelors degrees. Gary is a seasoned litigator who is well versed in toxic tort litigation. He has published extensively and lectures often on toxic tort, products liability, and related topics. Gary will discuss the litigation framework within which genomic data may be used and/or misused in the years ahead.



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We will then have a short break and begin the second portion of our symposium featuring the Honorable Paul Gilman, Assistant Administrator of the Office of Research and Development at the United States Environmental Protection Agency (EPA). Sworn into service as Assistant Administrator in April 2002, Dr. Gilman previously was Director of Policy Planning for Celera Genomics in Rockville, Maryland. Prior to joining Celera, Dr. Gilman was the Executive Director of the Life Sciences and Agricultural Division of the Natural Research Council (NRC) of the National Academy of Sciences and Engineering (NASE), which provides independent advice to the government in matters involving science and engineering. Prior to joining the NRC, Dr. Gilman was the Associate Director of the Office of Management and Budget (OMB) for Natural Resources, Energy, and Science, where he coordinated budget formulations, regulatory and legislative activities among agencies such as the EPA, the National Science Foundation (NSF), USDA, and the Department of Energy, and with the Executive Office of the President. Dr. Gilman received his undergraduate degree from Kenyon College and his Ph.D. in ecology and evolutionary biology from Johns Hopkins University.

My remarks focus on some of the regulatory issues inspired by the use of toxicogenomic data. The various regulatory agencies with which I interact as a lawyer and advocate on a day-to-day basis -- EPA, FDA, OSHA -- are at an embryonic stage of addressing the complex legal, science, and policy issues that the use of toxicogenomic data invite, and are just now beginning to formulate policies and directives regarding whether, how, and under what



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circumstances genomic data should be and legally can be used and relied upon for regulatory purposes. EPA in particular is to be complimented for issuing last year its Interim Policy on Genomics, in which EPA notes that it will consider genomic data cautiously and on a case-by-case basis. I will also identify a number of regulatory applications where toxicogenomic data may be used in the future, and ask a number of questions that might reasonably be expected to arise in connection with each such application.

The explosion of information from advances in the area of genetic technology portends major changes in fundamental concepts of environmental regulation and risk assessment. Traditional concepts of environmental protection are premised on the notion that pollution standards should protect large groups of people from known environmental and human health harms. Traditional principles of risk assessment have sought to protect sensitive subpopulations through the application of risk factors without knowing who precisely is included in the group of sensitive subpopulations.

This is changing -- and rapidly. As researchers learn more about genetic variations, it may be that traditional paradigms of risk assessment will not be adequate in all cases. In the future, for example, sensitive subpopulations may well lose their anonymity, and no longer be nameless, faceless entities whose genetic sensitivity to toxicants is addressed through the application of uncertainty factors. Identifying what level of protection such people



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may reasonably be expected to be provided under health and safety standards will be a challenging endeavor for policy and lawmakers.

The emergence of toxicogenomic biomarkers for disease and/or exposure to toxicants or environmental stressors is also of great interest to scientists and lawyers, particularly toxic tort lawyers. When scientists start using expressions like “signatures” for “pathways” of toxicity, as the literature in this area is prone to do, toxic tort lawyers are drawn to the area like bees to honey.

The utility of genomic data to improve drug administration techniques is significant. In the not too distant future, doctors will have the capability to screen for genetic information to avoid adverse drug reactions and prescribe patient-specific tailored medications and dosages. Doctors will be able to avoid adverse side effects to chemotherapy drugs, allergic reactions to penicillin, and drug resistance problems.

Genetic testing will also be used to screen certain patients and prevent them from being prescribed drugs that may be ineffective due to their unique metabolism, or to adjust the dosage and schedule for drug administration to optimize the drug’s effectiveness. All of these tools are within striking distance, and these breakthroughs are very encouraging.



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The significant knowledge gained through these advances is, however, very much a double edged sword. Knowledge that a particular subgroup of individuals is more adversely affected by exposure to a particular chemical raises complex legal, ethical, regulatory, and science policy issues and places great burdens on regulators to address this new information under existing laws.

Likewise, knowledge of a person's sensitivity to an environmental toxicant offers the possibility of more effective prevention and treatment. Such information also, however, could be used wrongly to classify people and subject them to illegal discrimination and stigmatization. The implications of the use of genetic testing in the health insurance area are, for example, truly daunting.

Before discussing areas of the law where the application of certain types of toxicogenomic information might be relevant, I offer a word about the technology platform that will be used for many of these examples. As Dr. Ray Tennant, Director of the National Institute of Environmental Health Sciences (NIEHS) National Center for Toxicogenomics describes, genome-based technology has created the opportunity to array large numbers of individual gene fragments on small matrices (chips) that can be hybridized to mRNA (or cDNA) and then assess the effects, both good and bad, that specific chemicals can cause. The gene expression, which is the gene activation or deactivation caused by exposure to a chemical, pharmaceutical, or other



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stressor, produce mRNA, which acts as a template for the production of a particular protein. These advances have led to the development of toxicogenomics, as we know it today, which applies both mRNA and protein expression technologies to the study of chemical effects in biological systems.

The thought that changes in gene activity are precursors to other symptoms of harm is what is at the crux of the flurry of legal and science policy commentary. These advances in gene expression technology have many potential applications in (i) regulatory standard setting; (ii) risk assessment; (iii) adverse effects reporting; (iv) chemical screening; and (v) employment law settings. Here are a few illustrations in each area.

Standard Setting -- Quantitative methods of estimating human risk posed by chemical exposure are utilized in environmental and in other public health laws to determine how chemicals should be regulated. The specific regulatory standards set forth in these laws vary greatly. Under Clean Air Act (CAA) Section 109, EPA must establish primary National Ambient Air Quality Standards (NAAQS) for criteria pollutants with an “adequate margin of safety.” EPA must under CAA Section 112 take into account health thresholds with an “ample margin of safety” in regulating hazardous air pollutants (HAPs). In discharging its statutory obligation under Section 109, EPA must protect against adverse effects caused by exposure to air pollutants.



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The question then becomes what is an adverse effect? Are gene expression changes that are typical of a known toxicological endpoint at levels considerably below an existing NAAQS for lead, for example, sufficient to constitute an adverse effect for CAA standard setting purposes? As EPA grapples with “residual risk” under Section 112 of the CAA, will data that suggest exposure to a particular HAP induces gene expression changes at levels below existing National Emission Standards for Hazardous Air Pollutants (NESHAP) limits be sufficient to warrant enhanced regulation? The answers to these questions are not known.

Risk Assessment -- Genomic data will also have a profound influence on risk assessment -- the art and science of using observations about what is known to make predictions about what is not known and thus to abate a risk of harm.

The risk assessment approach EPA uses for estimating the non-cancer human risk based on animal studies is exemplified by the method described in EPA’s Integrated Risk Information System (IRIS). 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 of extrapolating from animals to humans, and the second to account for variation



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in sensitivities within the human population. A number of studies have shown that these uncertainty factors can be quite conservative.

Genomic data may in the future replace/refine greatly the application of these uncertainty factors. For example, if data exist showing similarities between humans and laboratory animals with regard to the absorption, distribution, and excretion of a toxic compound, then these data may provide a basis for a reduction in the default interspecies uncertainty factor 10 to, perhaps, 3 or some lower number.

Gene expression technology may also result in data that eliminate safety factors that are applied due to uncertainties regarding life stage differences relevant to chemical exposures. For example, under the Food Quality Protection Act (FQPA), EPA must apply an additional 10-fold safety factor for the protection of infants and children in regulating pesticides unless "reliable data" show that a different margin of safety is appropriate. If gene expression data show there is no meaningful difference in the response of adults and children to a particular pesticide, it is possible that these data may be considered "reliable" for purposes of eliminating the FQPA 10-fold safety factor that otherwise might apply under FQPA. The availability of such data would be welcome news to agricultural chemical producers who now fear the application of these safety factors are in some instances overly conservative and may thus unnecessarily limit the application of otherwise efficacious food chemicals.



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Adverse Effects Reporting -- The use of genomic data raises sticky questions in the area of adverse effects reporting, which is required under both the Toxic Substances Control Act (TSCA) and FIFRA and analogue state laws. For example, if studies show that a chemical induces gene expression changes at levels well below the existing NOAEL, should these changes be considered “adverse” and be reported to EPA under TSCA Section 8(e)? Should these data be relied upon for purposes of changing the NOAEL? Dr. Gilman may address this topic in more detail. My own view is the TSCA Section 8(e) reporting provision must be considered when analyzing gene expression data. EPA’s Interim Genomics Policy states that the “... relationships between changes in gene expression and adverse effects are unclear at this time and may likely be difficult to elucidate. Nonetheless, EPA believes that some of these changes may prove to be predictive of subsequent adverse effects.”

Chemical Screening -- Chemical screening is another area where toxicogenomic data will have a significant influence. New chemical product development, whether industrial, agricultural, or pharmaceutical requires the completion of a battery of tests to determine what adverse effects the chemical product might cause. These include tests to assess the impact of acute, sub-acute, and sub-chronic, and chronic exposures to the chemical. New product development is extremely expensive and time consuming, spanning many years and costing millions of dollars. Where relevant human data, such as epidemiological data, do not exist, as is frequently the case, laboratory animal tests often involving large numbers of animals are



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required. Additionally, statutes such as FIFRA and TSCA often require testing as a condition of continued product approval.

Gene expression assays may allow for an expedient, cheap, reliable, and effective high throughput screening tool for a much wider range of genotoxic and nongenotoxic responses that could provide a useful methodology for the systematic toxicity screening of new and existing chemicals. For example, DNA microassays could provide an inexpensive, accurate, and quick characterization of the extent and mechanism of a chemical's toxicity for purposes of the TSCA new chemicals program. Even if not required, chemical manufacturers may in the future rely on such data more routinely to eliminate chemical candidates that are not commercially promising due to their tox baggage.

European chemical companies are going to be in need of reliable, inexpensive, useful screening mechanisms when the European REACH system is in full throttle, which will be in a few short years. Under this program, thousands of chemical substances will need to be tested to ensure that their continued use and marketing do not pose adverse human health or environmental affects. Whether any genome-based technology will be standardized for these purposes is unclear, but the technology holds much promise for application in this area.



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Other regulatory applications include, for example, the use of DNA microassays to identify hazard characteristics under the Resource Conservation and Recovery Act (RCRA). EPA's Office of Solid Waste and Emergency Response has been stymied over the years in expanding the range of characteristics that could be considered for testing materials when disposed to determine whether they are RCRA hazardous. DNA microassay screening may provide an inexpensive and reliable test to evaluate whether a chemical waste stream induces a gene expression profile that is characteristic of a known toxicity mechanism.

Susceptibility Genes

I would like now to address briefly advances in susceptibility genes and their relevance in various regulatory contexts. One of the many data points emerging from the sequencing of the human genome is the identification of genetic variations, and the role of these variations in genetic susceptibility to environmental health risks. Although much progress has been made, there still is a great deal of work that must be done to define an individual's genetic susceptibility potential. Even when a susceptibility genetic marker is found, its effects can vary greatly from individual to individual. Some increases in susceptibility are dose dependant. Other associations are thought to be ethnic dependant. In short, few definitive statements can be made regarding susceptibility genes. That being said, there is a growing body of genomic data



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that is helping identify groups of people or life stages that are genetically susceptible to certain harms caused by toxicants.

The regulation of chemical exposure based on susceptible subgroups is specifically countenanced in certain regulatory programs. For example, under the CAA Section 108, EPA must provide federal, state, and local regulators information on measures that may be employed to reduce the impact on public health or protect the health of sensitive or susceptible individuals or groups. The protection of susceptible subgroups is a factor in establishing NAAQS. In the years ahead, how EPA will discharge its CAA obligations to protect susceptible subgroups, and how it will use genetic information that suggests defined groups of people are more vulnerable to some types of toxicity than others is one of the many challenges EPA and other agencies face.

Similarly, the Safe Drinking Water Act Amendments of 1996 (SDWA) require EPA to identify subgroups within a general population that may be at “greater risk than the general population of adverse health effects from exposure to contaminants in drinking water.” EPA has correctly concluded that genetic influences are complex and inadequately understood. It is unclear to what extent certain individuals with heightened sensitivities to environmental stressors must or should be considered under the SDWA. The Act itself is silent on whether and how EPA should apply data on susceptible subpopulations, and how and under what



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circumstances these data should be used for regulatory decisions pertinent to drinking water contaminants.

Genomic data could also be used to identify at what life stage people may be more vulnerable to toxicants. EPA's *Supplemental Guidance for Assessing Cancer Susceptibility Resulting From Early-Life Exposure to Carcinogens* concludes that exposure in early life to gene mutating carcinogens poses a greater risk of eventually getting cancer than adult exposure. Genomic data could be used to pinpoint specific cancer-causing chemicals and thus adopt regulations that better protect children, and exclude other compounds that are found not to have a detrimental effect when exposures are at early life stages.

Product Labeling

Another area where genomic data is expected to impact is product labeling. People who may be more genetically susceptible to a particular constituent in a product or chemical raises questions regarding how best to protect people with a genetic predilection to harm from a chemical. Many pharmaceuticals have never made it to the market because of the potential for adverse effects in a small percentage of the population. If most of these adverse effects occur in a definable segment of the population that carries a particular genetic coding, it may be possible to prevent adverse effects simply through product labeling.



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Employment Implications

Genomic data will also have a profound impact in the area of employment law. The legal framework at the federal level for addressing the rights, duties, and obligations of employers whose workplaces invite chemical exposures is defined by the Occupational Safety and Health Act and the Americans with Disabilities Act (ADA). The availability of genomic data will force many, many issues, including:

Whether and to what extent employers should be required to test employees for hyper-susceptibility; How is an employee's privacy and confidentiality to be protected? What risk assumptions do employees make in selecting certain employment opportunities? How should unauthorized access to genetic samples be prevented? Is a genetically susceptible person who is not actually disabled by illness covered under the ADA, which addresses many aspects of discrimination in the workplace based on disability? How should informed consent principles be applied before subjecting persons to genetic testing? I have many more questions than answers.

IQA Implication

I would like to note in closing another legal component that must be considered in assessing genomic information generally. The utility of these data must be considered within the



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framework of the Information Quality Act (IQA), passed as an amendment to the OMB's Appropriations Bill in 2000. Under the IQA, OMB was required to establish by September of 2001 government-wide guidelines for ensuring and maximizing the quality, objectivity, utility, and integrity of information disseminated by federal agencies. Each affected federal agency was required to have its own IQA guidelines in place by October of last year. OMB's Information Quality Guidelines, which apply to all federal agencies subject to the Paperwork Reduction Act, set forth goals that are especially relevant for purposes of the dissemination of scientific and statistically information traditionally issued by such agencies as EPA, FDA, NIEHS, and OSHA. The burden on these agencies is significant given the higher burden on federal agencies when disseminating information deemed "influential." Influential information is designated under OMB guidelines as scientific, financial, statistical information that, if disseminated, would have a "clear and substantial impact" on important public policies or private sector decisions. Many rulemakings, policies, and guidance documents involved in the science/policy arena fall within the ambit of influential information and thus require a high degree of integrity, reliability, and transparency when disseminated. Dr. Gilman will provide more information on EPA's efforts in this regard. A host of interesting legal issues arise in this context. For example, how are genomic data to be validated? Should test protocols be standardized? How much genetic data will suffice to demonstrate a causal link between a chemical exposure and an adverse effect for regulatory purposes? What kinds of data are "reliable" for purposes of satisfying a particular statutory



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standard? These are just a few of the questions that will require thoughtful consideration before government policies on the use of genomic data can be implemented.

I will stop here and turn the podium over to Gary Callahan. Gary will continue the discussion of the use of genomic information in a different type of legal context, namely in litigation, and discuss the evolving relationship between genomics and toxic torts.

Thank you.