



Environmental Compliance & Litigation *Strategist*

Volume 16, Number 11

April 2001

SCIENTIFIC METHODOLOGY

The Brave New World of Toxicogenomics

By **Todd M. Hooker**

Lawyers have long lamented the disconnect between science and law. The two disciplines sometimes appear to operate in different universes, each having its own set of assumptions and methodologies. Lawyers demand certainty from scientists, while scientists can offer only a snapshot of their understanding of available data that is likely, or certain, to change.

Environmental and mass tort lawyers in particular confront this disconnect on a regular basis, in the litigation context of proving or disproving the cause of disease with expert testimony, and in the regulatory context whenever governmental agencies establish discharge, emissions or exposure guidelines.

A new and emerging scientific subdiscipline called "toxicogenomics" is poised to alter this paradigm drastically and give lawyers far more certainty with respect to these

Todd M. Hooker is an environmental attorney with Lowenstein Sandler PC in Roseland, N.J. Telephone: (973) 597-2500. He wishes to acknowledge the scientific expertise and editorial assistance of Peter G. Amanatides, M.S., director of quality systems for Celera Genomics.

issues. But will the new science be used correctly or misused to support political or litigation objectives?

Toxicogenomics combines the traditional scientific field of toxicology (the study of the nature and effects of substances in living organisms) with the rapidly emerging scientific field of genomics (the investigation of the way the genome translates into biological forms and functions). This new field of science is a direct result of the successes that have been made in sequencing and characterizing the human genome and advances in scientific testing methodologies.

The well-celebrated race to the finish to complete the mapping of the human genome resulted in the publication of the complete human genome map and sequence earlier this year by Celera Genomics, a biotech firm in Rockville, Md., in the journal *Science*, and by the government-sponsored Human Genome Project in the journal *Nature*. The sequence shows that the human genome consists of only about 30,000 to 35,000 genes.

The publication of the human genome was an important first step and developments are expected to flow quickly. Understanding the structure of the human genome

allows scientists to identify and characterize sequence variations in genes that respond to chemicals, pharmaceuticals, dietary supplements and other environmental agents.

Toxicogenomics promises to allow scientists to discover why genes behave the way they do, how they interact with other genes in the body, and why differences in genes may mean an increased risk of cancer for one person and not for another.

Recent technical advances in testing methodologies have set the stage for such research. Two related techniques have been developed to allow thousands of genes to be analyzed at one time. These techniques are referred to as microarrays or DNA chips. Microarrays and DNA chips contain thousands of known DNA sequences that will bind to complementary strands of DNA. DNA chip technology allows for the culturing of cells (which contain DNA) in both the presence and absence of a substance, such as chemicals, pharmaceuticals or cosmetics, to determine whether genes are activated or deactivated by such exposure. The activation or deactivation of a gene is what scientists refer to as gene expression.

When genes are activated, they

produce a nucleic acid called messenger RNA (mRNA) that acts as a template for the production of a particular protein. Microarrays and DNA chips are capable of measuring the amount of mRNA expressed before and after exposure to a substance. The theory behind analyzing gene expression data is that changes in gene activity are precursors of other more visible symptoms of harm, like tumors. Scientists also believe that gene tests will be more sensitive to lower doses of a substance than is currently required in animal testing.

Effect of Toxicogenomics On Environmental Issues

Toxicogenomics is expected to have an impact on regulatory, toxic tort, public health and chemical safety issues. On Dec. 7, the National Institute of Environmental Health Sciences (NIEHS) established the National Center for Toxicogenomics. (See www.niehs.nih.gov.) The new center's mission is to coordinate research in the field of toxicogenomics, and to develop a database containing comprehensive toxicological gene expression data that can be used to aid in predictive toxicology and toxicant risk assessment.

The results of NIEHS research is likely to be used by governmental agencies to conduct risk assessments for purposes of establishing new regulatory guidelines, such as limitations on air emissions and wastewater discharges, or cleanup requirements for contaminated sites. Worker exposure guidelines may also be drastically altered as a result of such research. In theory, toxicogenomics should support better, but not necessarily more or less stringent, regulatory standards. However, it already appears that environmental groups

are likely to use NIEHS data to urge that certain chemicals be banned or more strictly regulated.

Information from the NIEHS database is also likely to affect toxic tort lawsuits. Again, in theory, toxicogenomics should support better science in assessing causation between exposure and disease, and not necessarily favor plaintiffs or defendants. However, the environmental group Friends of the Earth recently issued a report titled "Crisis in Chemicals," which argues that genetic research would make it easier to link chemicals to disease, thereby increasing the chances of winning liability lawsuits. (See www.foe.co.uk/campaigns/safer_chemicals/pdf/crisis_inchem.pdf.)

To be sure, NIEHS scientists believe that microarray and DNA chip technology ultimately can help identify how environmental agents cause disease. However, scientists do not yet fully understand how to interpret the significance of activating a gene. Many factors influence whether a gene will be activated, including dose and duration of exposure. Indeed, at this early stage, there is little understanding of the relationship between gene expression and dose dependent induction of toxicity. Thus, the use of gene expression data in hazard identification or risk assessments, especially in the absence of a correct interpretation of the toxicological significance of the data, is premature. Basic questions of relevance still need to be addressed. For example, how many and which genes should be measured to characterize a toxic response, and how will scientists distinguish such a response from physiologically adaptive responses that are not linked to toxicity? Many

questions regarding the reliability of toxicogenomics have yet to be addressed by the scientific community.

What Does the Future Hold?

The future promises a new era in which science may be moving faster than the law. The mapping of the human genome will allow scientists to collect new data faster than it can be interpreted. In the next few years, toxicogenomics will probably reshape the scientific community's understanding of how chemicals and other environmental agents perturb biological systems. Unfortunately, in the short run, we may see toxicogenomic data interpreted incorrectly or used to establish unsound or junk public and regulatory policy or to expand private liability.

In the long run, toxicogenomics has the potential to impose the burden on regulators and plaintiffs lawyers to prove their positions with documented, confirmed findings at the human genome level. Substances that do not activate genes whose activation is necessary (albeit rarely sufficient) to induce a particular toxic endpoint may be exonerated. Courts may be unwilling to accept opinions of experts on causation issues in toxic tort litigation if toxicogenomic analysis is lacking or contradictory to the proposition asserted. Finally, a better understanding of the dose-response relationship at the gene level may finally put to rest concerns about extremely low dose exposures, and may result in substantial improvements in the establishment of safe levels of contaminants in air, water and food.

