

Applications of Toxicogenomics to Environmental Regulation

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Enhancing Risk Assessment

- **Toxicogenomics has potential to reduce many of uncertainties in risk assessment:**
 - **Dose response (low dose effects)**
 - **Animal to human extrapolation**
 - **Mode of action**
 - **Cumulative effect of environmental mixtures**
- **Toxicogenomics may reverse shift away from risk-based regulation due to uncertainty**
 - **cf. Senator Durenberger (1990) – “I would be glad to declare risk assessment dead.”**

High Throughput Screening

- **No pre-market testing requirements for chemicals other than pesticides and pharmaceuticals**
- **Only ~2,000 of 80,000 chemicals in commerce have been tested in rodent chronic bioassay**
 - **“Toxic Ignorance”**
 - **High Production Volume (HPV) Challenge**
 - **EU REACH Program**

High-Throughput Screening: Microarray Assays

- Gene expression profiling has potential to provide fast, inexpensive screen of chemicals
 - “We’ll be able to reduce the time it takes to test potential carcinogens from two to three years to a few days. And we’ll reduce the cost of such studies from \$2-3 million to less than \$500 dollars.”
 - Dr. Kenneth Olden, Director of NIEHS

Toxicogenomics and Cancer Classification: Hypotheticals

- **Chemical A tests negative in mice and rat carcinogenicity bioassay; but produces gene expression profile characteristic of a specific class of carcinogens**
- **Chemical B produces cancer in mice but not rats. It produces distinct gene expression pattern in mice not seen in rats and humans**
- **Chemical C causes cancer only at high doses in rodents. It produces no toxicologically significant changes in gene expression at lower level exposures in rodents or humans.**

High-Throughput Screening: Priority-Setting Opportunities?

- **Prioritizing chemicals for assessment in programs such as the Endocrine Disruptor Screening Program and the Voluntary Children's Chemical Evaluation program**
- **Safe Drinking Water Act Contaminant Candidate List**
- **Lists of chemicals included in various programs (e.g., Toxic Release Inventory)?**
- **Listing of hazardous waste sites on National Priorities List (NPL)?**

High-Throughput Screening: Potential Regulatory Applications

- **Amend TSCA to require gene expression assay to be included in pre-manufacturing notice (PMN)?**
- **Include genomic data in Screening information Data Set (SIDS)?**
- **Toxicity characteristic for identifying hazardous wastes?**
- **Evaluating need for 10-fold safety factor for children under FQPA?**
- **Defining categories of agents for FQPA cumulative risk requirement?**

Real-Time Surveillance and Monitoring

- Gene expression assays could be used for real-time monitoring of exposure and risk in residents near potentially hazardous sites
- Human and ecological risks could be evaluated
- Facilitate prioritization and effective early intervention



Potential Examples of Monitoring Applications

- **Microbial source tracking to determine sources of fecal contamination**
- **Oil spill damage assessment**
- **Superfund sites – before and after clean-up**
- **Water quality (designated uses)**
- **Early detection of health effects in high exposure communities (Environmental Justice)**
- **Need for beach closings**

Product Surveillance & Reporting Requirements



- Users of potentially hazardous products could be evaluated for gene expression changes

- Reporting obligations?

- TSCA §8(e) – “substantial risk of injury to human health or the environment”

- FIFRA §6(a)(2) – “unreasonable adverse effects”

Reference Dose

- EPA calculates “safe” level of non-carcinogens (RfD or RfC) by applying series of uncertainty factors to NOAEL or LOAEL
 - Gene expression response may result in lower NOAEL/ LOAEL
- Q: Are gene expression changes “adverse effect”?**
- Q: Should smaller uncertainty factors apply to gene expression effects than other adverse effects to account for reduced severity of effect?**

Clean Air Act Standards

- EPA sets ambient air quality standards at level that protects from “adverse effects” in susceptible subgroups with an adequate margin of safety
- Are gene expression changes “adverse effects”?
- Do gene expression changes trigger “adequate margin of safety”?
 - *Lead Industries Ass’n v. EPA* – “subclinical effects” of lead exposure – elevated erythrocyte protoporphyrin – were an “adverse effect”

Toxicogenomics: Challenges and Limitations

- **Distinguishing true toxicity from adaptive responses**
- **Standardization or compatibility of data from different microarrays**
- **Validation of results across different species, tissues, developmental stages, and time courses**
- **Data management, analysis and presentation**
- **Communicate with key stakeholders (Congress, media, citizen groups, etc.)**