Ten Ways Genomics Could Change Environmental Policy

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Genomics Can Help Fill Two Key Gaps in Risk Assessment

Current Approach:

- All individuals treated alike (uniform population)

Problem:

- People differ significantly in their response to toxic substances

Genomics Contribution:

- Identify genetic polymorphisms affecting susceptibility to toxics (toxicogenetics)

Current Approach:

- Rely on clinical disease to evaluate human toxicity

Problem:

- Need earlier, more sensitive, and more specific marker of toxicity

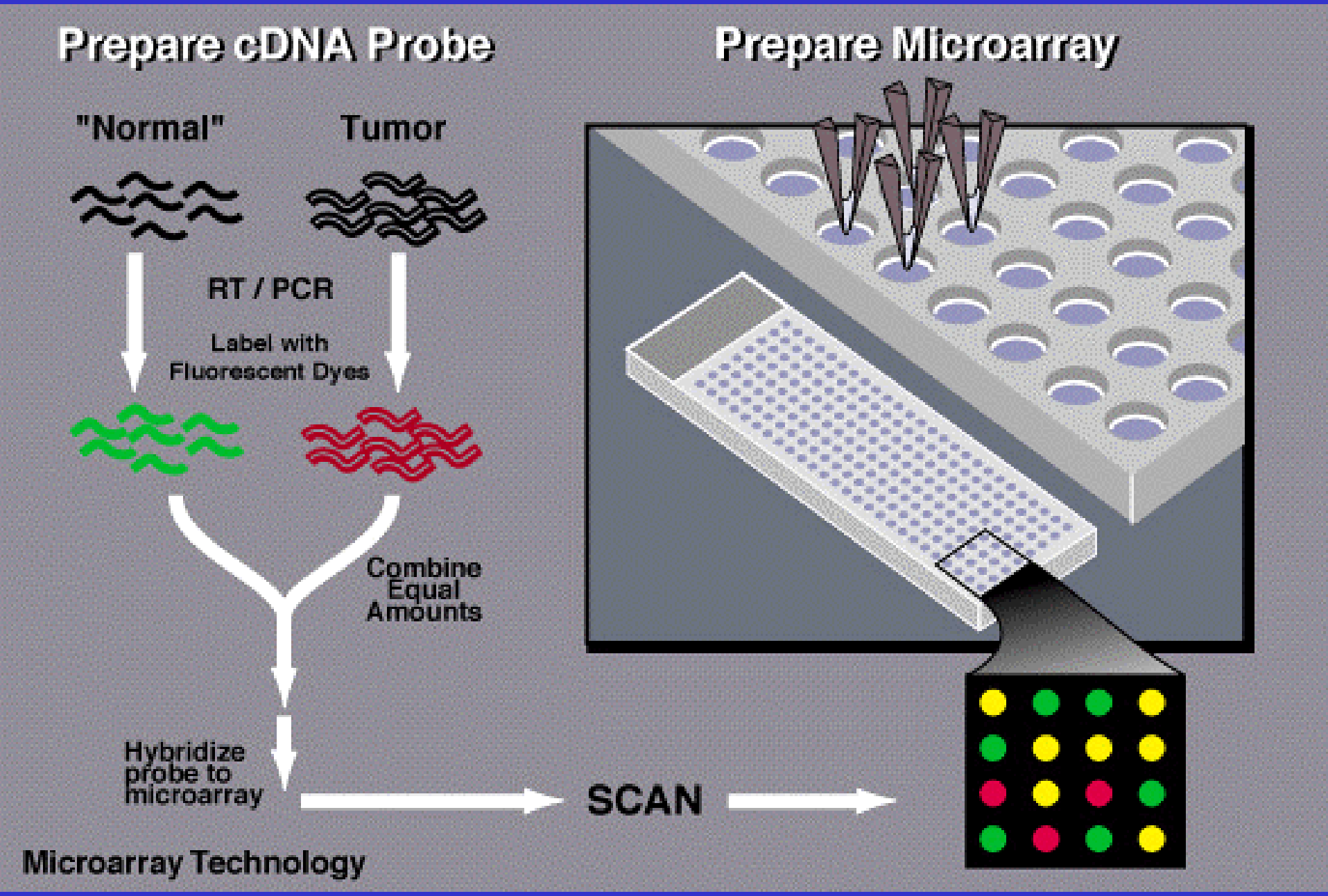
Genomics Contribution:

- Evaluate global gene expression in cells (toxicogenomics)

I. Toxicogenomics (Gene Expression Profiling)

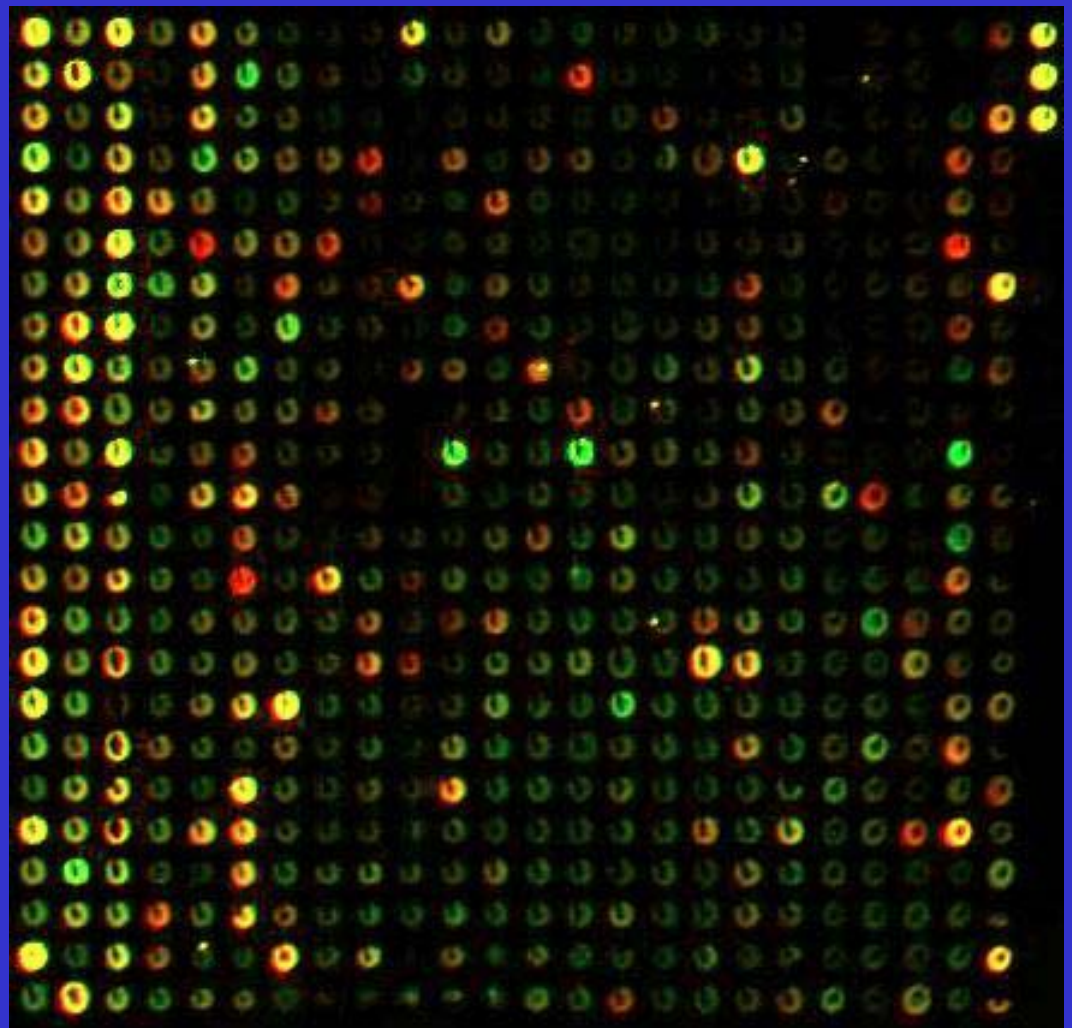
Toxicogenomics

- The scientific study of how genomes respond to environmental stressors/toxicants
- Toxicity almost always involves changes in gene expression
- Gene expression pattern may provide a "signature profile" of specific toxicant or mechanism
- Uses DNA microarrays (or "gene chips") to monitor global expression of genes involved in response to toxic agent

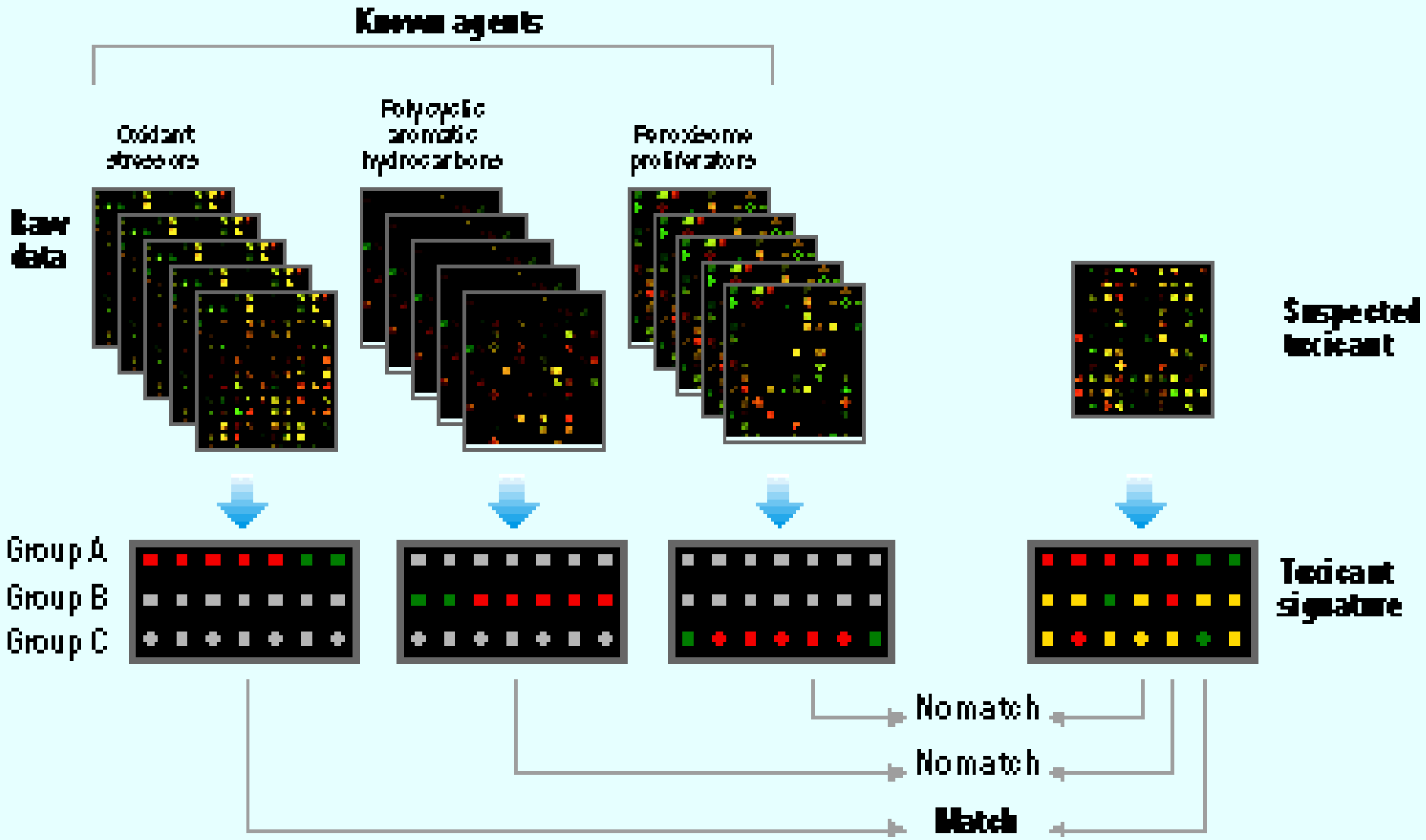


Source: NHGRI

Example of DNA Microarray



NIEHS "ToxChip"



Source: NIEHS

Advantages of Toxicogenomic (Gene Expression) Data

- Earlier biomarker of toxicity
  - do not need to wait for clinical disease
- More sensitive biomarker of toxicity
  - can detect toxic response in individuals who do not develop clinical disease
- More specific biomarker of toxicity
  - gene expression "fingerprint" may be more characteristic of specific agent than, e.g., tumor

Toxicogenomics: Promise or Hype?

- Microarrays provide "a tool of unprecedented power for use in toxicology studies."
  - Nuwaysir et al., 24 Molecular Carcinogenesis 153 (1999)
- "Unlike other new approaches or methods in toxicology that have been adopted slowly, genomic … methods are being evaluated and adopted rapidly by industry, academia and regulatory agencies."
  - Aardema & MacGregor, 499 Mutation Research 13 (2002)
- "Microprocessors have reshaped our economy, spawned vast fortunes and changed the way we live. Gene chips could be even bigger."
  - *Fortune*, March 31 (1997)

Toxicogenomics #1: Enhancing Risk Assessment

- Toxicogenomics has potential to reduce many of uncertainties in risk assessment:
  - 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."

Enhancing Risk Assessment: Some Hypotheticals

1. Chemical A induces tumors and characteristic gene expression changes in mice, but not in rats or cultured human cells.
2. Chemical B produces non-statistically significant increase in tumors in rats and mice, and induces gene expression changes characteristic of other known carcinogens.
3. Pesticide C produces similar gene expression changes in adult and neonatal rodents; human exposures are similar in adults and children.

Toxicogenomics #2: High Throughput Screening

- No pre-market testing requirements for chemicals other than pesticides and pharmaceuticals
- Only ~2,000 of 70,000 chemicals in commerce have been tested in rodent chronic bioassay
  - "Toxic Ignorance"
  - High Production Volume (HPV) Challenge
  - EU White Paper

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

High-Throughput Screening: Potential Regulatory Applications

- Amend TSCA to require gene expression assay to be included in pre-manufacturing notice (PMN)?
- Toxicity characteristic for identifying hazardous wastes
- Lists of chemicals included in various programs (e.g., Toxic Release Inventory)
- Listing of hazardous waste sites on National Priorities List (NPL)

Toxicogenomics #3: Real-Time Surveillance

- 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

Product Surveillance

- Users of potentially hazardous products could be evaluated for gene expression changes
- TSCA § 8(e) reporting requirement?

Toxicogenomics #4: 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?

Toxicogenomics #5: 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 microassays
- Validation of results across different species, tissues, developmental stages, and time courses
- Data management, analysis and presentation

II. Susceptibility Genes (Toxicogenetics)

Human Genetic Variation

- Human Genome Project – found variations at approx. 1/1000 base pairs
  - >1 million genetic differences between any two individuals
- >3 million candidate SNPs identified to date; estimated that there are ~11 million SNPs
- One estimate: 40-80 haplotypes for each of the ~31,000 genes, with wide variation between genes

Genetic Polymorphisms: Environmental Susceptibility

- Many genetic polymorphisms identified affecting response to xenobiotics
  - e.g., genes affecting metabolism, detoxification, DNA repair, receptors, cell cycle control, etc.
  - many genes increase risk from exposure, but some have protective effect
- Environmental Genome Project has identified ~ 500 genes with alleles exhibiting differential responses to environmental exposures

Loaded Gun Analogy

- "Conceptually, the relationship between genes and the environment is similar to that of a loaded gun and its trigger. A loaded gun by itself causes no harm; it is only when the trigger is pulled that the potential for harm is released or initiated. Likewise, one can inherit a predisposition for a devastating illness, yet never develop the disease unless exposed to the environmental trigger(s)."
  - Olden & Guthrie, *Mutation Research* 473: 3-10 (2001)

Examples of Polymorphisms Affecting Susceptibility

- Variant of several cytochrome p450 genes associated with increased lung cancer risk in smokers
  - e.g., *CYP1A1* - 10% of Caucasians have one such variant
  - another variant present only in African-Americans
- Deletion of one of glutathione S-transferase genes (*GSTM1*) associated with increased risk of bladder and lung cancer from exposure to several toxic substances (e.g., PAHs, aflatoxin)
  - 50% of Caucasians carry deletion

Susceptibility Genes #1: Health Standards

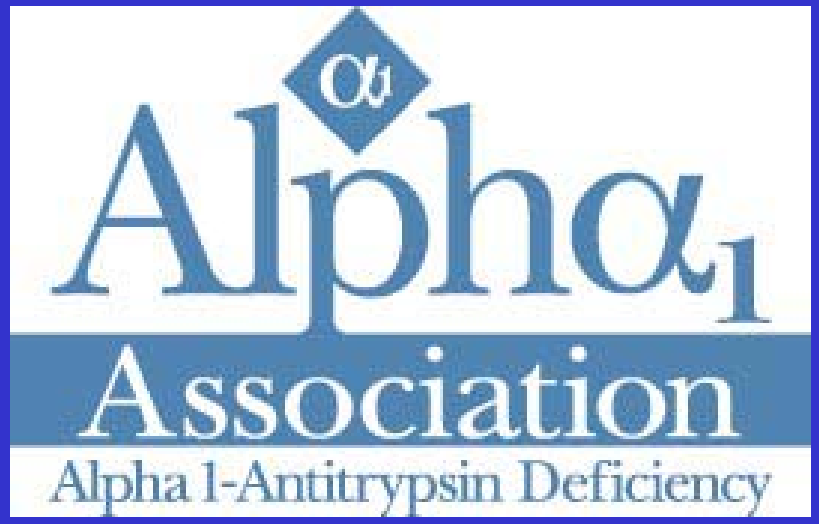
- Health-based standards (e.g., CAA) generally directed to protecting susceptible subgroups
  - D.C. Circuit – "NAAQS must be set at a level at which there is an absence of adverse effect on …. sensitive individuals." (*ALA v. EPA)*
- To date, the identified susceptible groups include asthmatic children, heavily-exercising workers
- Will standards have to be tightened with identification of genetically susceptible individuals?

EPA: 1979 Ozone Standard

- EPA focused "not only on the most sensitive population group, but also on a very sensitive portion of that group (specifically, those persons who are more sensitive than 99 percent of the sensitive group, but less sensitive than 1 percent of that group.").
  - 44 Fed. Reg. 8215 (Feb. 8, 1979)

Example: Alpha-1 Antitrypsin Deficiency

- 100,000 Americans have alpha-1 disease
- Predisposed to emphysema and other serious lung diseases from exposure to smoke or dust
- Zero (or background) level standard only protective option?



Safe Drinking Water Act: Susceptible Subgroups

- Directs EPA to conduct "a continuing program of studies to identify groups within the general population that may be at greater risk than the general population of adverse health effects from exposure to contaminants in drinking water."
  - limited to subpopulations that "can be identified and characterized"

Susceptibility Genes #2: Uncertainty Factors

- EPA applies a default 10X safety factor for non-carcinogens to account for inter-individual variation in susceptibility
- Identification of susceptibility genes creates potential to replace arbitrary generic default factor with data-based factor for each agent
- If there is a 20-fold difference in susceptibility between major genotypes in population, is 10X safety factor too big or too small?
- Is concept of population threshold still viable for genetically diverse population?

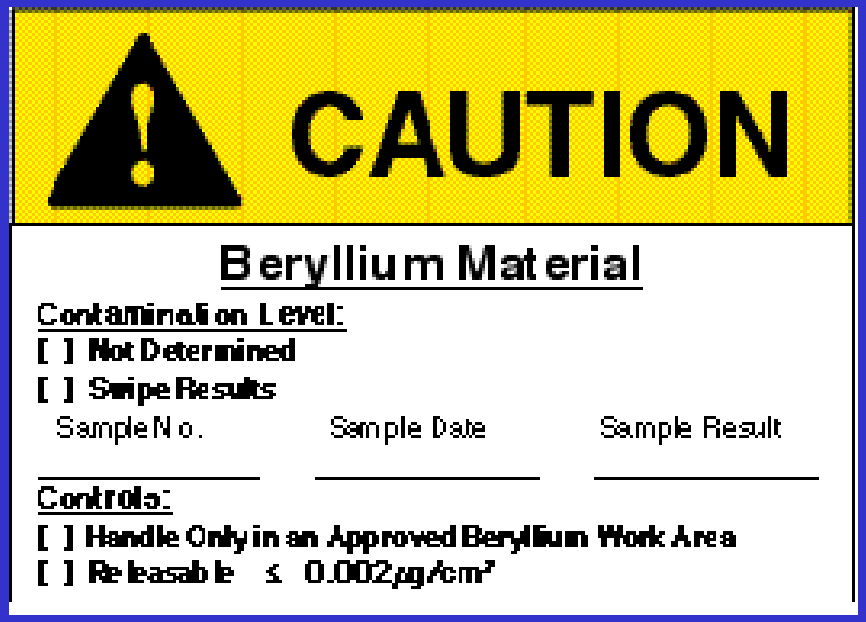
Susceptibility Genes #3: Self-Help Measures

- As individuals become capable of detecting their own genetic susceptibilities, they may become cheapest cost avoider
- Consumers make individualized decisions on whether they use products rather than population-based government regulation
  - "rescued" products that would otherwise be banned
- Question: What criteria should be used to shift primary responsibility from manufacturer/ discharger to individual consumer/citizen?

Self-Help: Consumer Products

- Diet sodas (containing aspartame) already carry warning for PKU
- What responsibility does manufacturer have for testing/ warning re: genetically susceptible subpopulations?
  - e.g., GlaxoSmithKline's Lymerix vaccine

Self-Help: Location



- Approx. 30% of population carries susceptibility gene (glu-69) for chronic beryllium disease
- Very low level of Be exposure may sensitize susceptible individuals
- Should residents near Be processing facilities be offered genetic test and relocation assistance?

Self-Help: Lifestyle

- Individuals with a variant of metabolic gene *CYP2E1* are more susceptible to solvents such as trichloroethylene (TCE)
- Enzyme is induced by ethanol, increasing risk
- Are warnings against alcohol consumption by such individuals an effective policy response?

Susceptibility Genes #4: Environmental Justice

- Can genetically susceptible sub-population file environmental justice complaint for disproportionate impact?
  - Does sub-population have to be geographically concentrated for EJ claim?
  - Does EJ apply to increased risk in absence of increased exposure?
  - Should "environmental justice" claims be limited to genetic susceptibilities disproportionately found in discrete racial or ethnic groups?

Susceptibility Genes #5: Americans with Disability Act

- ADA Title II requires that no person with a disability shall be denied the benefits of the services, programs, or activities of a public entity, or subjected to discrimination by any such entity
- Discrimination defined as failure to make "reasonable modifications in policies, practices, or procedures" to accommodate disabled persons, unless such modification would "fundamentally alter" the nature of program

ADA: *Save Our Summers v. Wash. Dep't of Ecology*

- **Lawsuit claimed that State violated ADA by allowing burning of wheat stubble under CAA, because it deprived two children (asthma, CF) from use of public facilities**
- **DOJ filed *amicus* brief arguing that CAA and ADA can be reconciled and both apply to environmental programs**
  - **DOJ suggested prior notice or limitations on burning may be appropriate accommodations**
- **Case settled prior to trial**

Susceptibility Genes: Challenges and Limitations

- Need for epi data stratified by genotype
- Gene-gene interactions
- Gene-environment (e.g., nutrition, health status, other exposures, etc.) interactions
- Dose-dependent effects
- Ethnic-dependent effects
- Privacy, discrimination, stigma, and psychological stress issues

Conclusion

“The future ain’t what it used to be.”

- Yogi Berra