

Incorporating Genetic Susceptibility Data Into Air Quality Standards

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National Ambient Air Quality Standards (NAAQS)

- Required for six Clean Air Act “criteria” pollutants (ozone, PM, SO₂, NO_x, lead, CO)
- Must be set at a level that is “requisite to protect the public health” with “an adequate margin of safety”
- Required to protect 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*)
- Cannot consider cost or feasibility

Reasons for Selection of NAAQS as a Case Study

- Nation's most important environmental regulations
- Statutorily-mandated focus on most susceptible subgroups
- Emerging evidence of genetic susceptibility to criteria air pollutants
- Raises two major categories of ELSI issues:
 - implementation and evidentiary issues
 - broader doctrinal, social and ethical issues

Genetic Susceptibility and Criteria Air Pollutants

- Substantial reproducible inter-individual variation in ozone response in healthy human volunteers
- Significant inter-strain differences in response to air pollutants in rats and mice
- Identification of candidate genes by quantitative trait loci approach
- Challenge studies involving genotyped human subjects
- No genetic epidemiology studies to date

Example of Human Volunteer Study

- 24 healthy nonsmokers performed 2-hr bike rides at ambient O₃ ranging from 32 to 103 ppb.
- Significant decrements in pulmonary function observed only at >80 ppb and only in *NQ01wt, GSTM1null* subjects
 - *NQ01* – *NAD(P)H:quinone oxidoreductase*
 - *GSTM1* – *Glutathione s-transferase 1*

Bergamaschi et al., Am. J. Respir. Crit. Care Med. 163:1426-1431
(2001)

Current Status:

Lancet editorial (Jan. 10, 2004)

- “We now have ways to identify individuals susceptible to air pollution and, because this sensitivity appears to be regulated by genetic and dietary factors, new approaches are emerging that might help protect these individuals from ambient pollution.”

EPA Draft PM Criteria Document (June 2004)

- “[A] handful of studies have begun to demonstrate that genetic susceptibility can play a role in the response to inhaled particles.... The extent to which genetic susceptibility plays as significant a role in the adverse effects of ambient PM as does age or health status remains to be determined.... Use of genomics, proteomics, and bioinformatics technologies will allow further characterization of the differences in susceptibility to PM.”

NAAQS Evidentiary Issues: Data Requirements

- Types of data
 - Strong preference for human data
- Number of studies
- Consistency of results
- Quantification of risk
 - **1977 lead standard – sickle cell and iron deficient individuals are potentially sensitive pop'ns, but “insufficient data to determine the effects threshold for such groups”**

NAAQS Evidentiary Issues: Threshold Issues

- Magnitude of susceptibility
 - Relative to other susceptible subgroups
- Size of susceptible group
 - EPA uses for deciding margin of safety
- Definition of susceptible subgroup
 - Heterogeneity within subgroup
 - Interactions with other susceptibilities
- Identification of susceptible individuals

How Protective Must Air Quality Standard Be?

- For 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)

How Protective?: 1970 Senate Report

- “In establishing an ambient standard ... reference should be made to a *representative sample* of persons comprising the sensitive group rather than to a *single person* in such a group. Ambient air quality is sufficient to protect the health of such persons whenever there is an *absence of adverse effect on the health of a statistically related sample of persons in sensitive groups* from exposure to the ambient air. . . . [A] statistically related sample is the number of persons necessary to test in order to detect a deviation in the health of *any person* within such sensitive group which is attributable to the condition of the ambient air.”

Implications of Genetic Susceptibility Findings

- NAAQS are likely to be based on genetic susceptibilities in foreseeable future
- Protecting most genetically susceptible subgroups with an adequate margin of safety may require zero or near-zero standards
 - e.g., O₃ and PM appear to be non-threshold pollutants
- Paradigm of setting air quality standards without consideration of costs or feasibility may be inconsistent with new genetic knowledge
 - Example of “unwanted knowledge”? Kavka, Midwest Stud. Phil (1990)

An Alternative Model For Air Quality Standards?

- Balance health benefits with costs, or reduce to lowest feasible level?
- But requires government effectively to conclude that we cannot afford to protect some genetically susceptible individuals from pollution
- Politically very difficult and undesirable decision

Ethics of Not Protecting Susceptible Subpopulations

- “Do we want to suggest that the most susceptible people in the community do not have sufficient moral standing to warrant protection, or that their standing to be protected is not equal to the healthy among us? Such implications seem unacceptable.”
 - Carl Cranor, *Envtl. Toxicol. & Pharmacol.* 4:239-245 (1997)

Relevant Analogies and Precedents

- Food allergies
- Multiple chemical sensitivity
- Very costly pharmaceuticals
- Other medical technologies in limited supply
- Rights-based environmental theories

Other Strategies: Targeted Interventions

- EPA Air Quality Index
 - “Unhealthy for Sensitive Groups”
- Dietary supplements (e.g., potassium, magnesium, vitamin C) may provide some protection against oxidative stress induced by pollutants
- Pharmacogenomic targeting
- Lifestyle changes
 - Reduce outdoor activities on high pollution days

Example of Targeted Interventions

- Group of children with asthma in Mexico City provided with oral antioxidant supplementation (vitamins C and E)
- Treatment reduced ozone-related decline in pulmonary function, but benefit limited to children who were *GSTM1null*, who also had the most significant response
 - Romieu et al., Thorax 59:8-10 (2004)

Options for Targeted Strategy Population

- All population
- Identifiable at-risk subpopulations (e.g., children, elderly)
- Symptomatic individuals (e.g., asthmatic children, COPD, individuals complaining of symptoms from air pollution)
- Individuals with at-risk genotypes
 - Requires genetic testing of population

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