A Theoretical Basis for Investigating Ambient Air Pollution and Children's Respiratory Health

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Acute respiratory health effects in children from exposure at current ambient levels of ozone are well documented; however, evidence for acute effects from other criteria pollutants such as nitrogen dioxide and respirable particles is inconsistent. Whether chronic effects result from long-term exposure to any of these pollutants during childhood is an important unresolved question. Establishing whether acute or chronic effects result from childhood exposure and identifying sensitive subgroups may require integration of biologic mechanisms of lung defenses, injury, and response into the study design and statistical models used in analyses. This review explores the theoretical basis for explaining such adverse effects in light of our contemporary understanding of mechanisms of lung injury and response at the cellular and molecular levels. The rapidly evolving understanding of the effects of air pollution on cellular and molecular levels presents an opportunity to develop and refine innovative biologically based hypotheses about the effects of childhood exposure. We hypothesize that children with low fruit and vegetable intake, low antioxidant levels, high polyunsaturated fat intake, or who have inherited certain alleles for genes involved in lung defenses and immune response regulation may be at increased risk for adverse effects. Because responses to air pollutants of interest are complex and involve a number of pathophysiologic processes, the magnitude of main effects of dietary factors, genes, and gene–environment interactions may be modest for individuals; however, each may make an important contribution to the population burden of preventable respiratory diseases. *Key words*: air pollution, children, nitrogen dioxide, ozone, particulates, respiratory health epidemiology. — *Environ Health Perspect* 107(suppl 3):403–407 (1999).
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The health effects of air pollution on children's respiratory health are of clinical, public health, and regulatory concern. Although a large number of chemical species occur in ambient air, ozone (O_3), nitrogen dioxide (NO_2), acid vapors and respirable particulates (PM_{10} and $PM_{2.5}$), sulfur dioxide (SO_2) and acid aerosols have been identified as presenting the greatest hazard to human populations (*1*). Acute exposures to high levels of ambient pollutants can have severe effects including substantial increases in mortality, as observed during pollution episodes in the Meuse Valley in 1930, Donora, Pennsylvania, in 1948, and London in 1952 (*2,3*). In the United States and Western Europe, regulatory efforts make such episodes a remote possibility; however, acute respiratory effects in children exposed at current ambient levels of O_3 are well documented (*1*). Whether acute effects result from exposures to ambient levels of NO_2, SO_2, acids, and respirable particulates or whether chronic effects are produced by long-term exposures is unresolved.

Although the concentrations of respiratory toxins in ambient and indoor air are generally low, the large volume of air inhaled each day by a child may deliver substantial doses of these toxins to the respiratory tract. Children spend more time outdoors, are generally more active, and have higher ventilation rates than do adults (*4*). For example, the timing of high O_3 levels may increase the exposure and dose for children relative to adults. Children spend more time outside during high O_3 periods in the afternoon, on weekends, and during the summer months (*4*). Furthermore, children are more likely to engage in vigorous physical activity while outside and are less likely to report exposure-related symptoms. Such characteristics may increase the delivered dose of pollutants to the distal lung, which may be more sensitive to damage because it has thin or patchy respiratory extracellular lining fluid (RELF) as a protective barrier. The large doses that children experience may be particularly detrimental because growing lungs may be most vulnerable to permanent adverse effects.

Studies have established that adverse health effects occur in some groups of children exposed to ambient levels of O_3, particulates, and NO_2 common in developed nations, and have provided a limited amount of suggestive evidence for chronic health effects (Table 1) (*1*). Much of the research on the acute effects of air pollution has focused on short-term exposures to O_3 and NO_2. Studies using controlled human exposures have documented that O_3 inhalation of as little as 0.08 ppm for several hours is associated with reproducible dose-dependent (concentration, duration, and minute ventilation) effects that are enhanced by exercise (*1*). NO_2 also has acute effects, but only at levels exceeding 2.0–4.0 ppm (*1*). The effects include decrements in forced expiratory volume in 1 sec (FEV_1) and forced vital capacity, cough and chest discomfort, lung injury and inflammation, and changes in airway responsiveness (*5–8*). Changes in pulmonary function have also been observed in children at summer camp and athletes exposed to ambient air pollution during outside activities (*6,9*). The O_3-induced acute changes in pulmonary function appear to be reversible, resolving within 24 hr. The reversibility of the acute changes in lung function either with anesthetic or with time indicates this mechanism may not be responsible for chronic effects (*10–13*). Airway hyperreactivity persists after O_3-induced changes in FEV_1 resolve and the degree of reactivity is not associated with the magnitude of spirometric changes, suggesting an independent mechanism for hyperreactivity (*14*). Increased reactivity may be involved in the pathogenesis of chronic lung disease because increased airway reactivity to nonspecific stimuli such as methacholine is a characteristic of chronic

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Table 1. Acute and chronic effects of ambient air pollution on children's respiratory health.

Acute effects	Chronic effects (putative)
Increased respiratory symptoms	Impaired functional lung growth
Increased respiratory illnesses	Earlier onset and increased rate of decline in lung function with aging
Asthma exacerbations	Increased lifetime risk for chronic respiratory diseases including chronic obstructive pulmonary disease, asthma, and lung cancer
Increased health care utilization	Altered lung structure including metaplasia of the respiratory epithelium in respiratory bronchioles, mononuclear peribronchiolar inflammation, localized deposition and alteration in collagen, and remodeling of the peribronchiolar airspace
Excess cardiorespiratory mortality	
Respiratory tract inflammation	
Increased airway reactivity	
Altered host defenses including oxidant defenses, mucociliary clearance, macrophage function, and immune response	

Adapted from Bascom et al. (*1*).

respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD). The inflammatory response involves increased numbers of macrophages, neutrophil infiltration, increased cellular protein permeability following the production of a broad range of inflammatory cytokines, and increased arachidonic acid metabolites (*8,15–18*). In addition to the inflammatory response, a large body of evidence suggests that acute NO_2 exposure at environmental levels may adversely affect other aspects of immune function including macrophage function, resulting in decreased airway clearance and increased risk of infection.

Air pollution may also increase the risk of chronic respiratory diseases by adversely affecting lung growth in children. Lung growth continues throughout childhood into early adulthood, reaching a plateau and then declining with increasing age (*19*). It has been hypothesized that the risk for chronic respiratory diseases such as COPD is associated with maximum lung size, length of the plateau, and rate of decline in function (*20*). Under this hypothesis, exposures such as O_3, NO_2, PM_{10}, and $PM_{2.5}$ may reduce maximum lung size by affecting the rate of lung growth during childhood and thereby increase the risk for chronic respiratory disease in adulthood.

A Theoretical Basis for Adverse Respiratory Effects

Investigating the acute and chronic respiratory effects of air pollution is a challenging task because of the complex temporal and spatial patterns of exposure and the limited understanding of the cellular and molecular pathogenesis of associated respiratory effects. The lack of a detailed and well-accepted mechanistic understanding of chronic effects from air pollutants has limited our ability to specify biologically based hypotheses. Statistical approaches that use the data to direct analyses were appropriate in the past, given what was known about the mechanism of lung injury. However, the pitfalls associated with using nonbiologically based statistical models that implicitly assume some underlying form of biologic interactions are well known. The rapidly evolving understanding of the effects of air pollution on cellular and molecular levels presents an opportunity to develop and refine innovative biologically based hypotheses about the effects of childhood exposure.

Developing testable hypotheses requires a theoretical framework that relates exposures to air pollutants with acute and chronic respiratory effects. We propose that respiratory effects in children from exposure to gaseous air pollutants (O_3, NO_2, acids) and particulates (PM_{10} and $PM_{2.5}$) result from chronically increased oxidative stress, alterations in immune regulation, and repeated pathologic inflammatory responses that overcome lung defenses to disrupt the normal regulatory and repair processes (Figure 1). In this theoretical framework, the effects of O_3, NO_2, PM_{10}, and $PM_{2.5}$ are mediated by complex, interacting, and self-enhancing processes of oxidative, radical, and enzymatic attack on the RELF, epithelial cells, and macrophages. These processes are coupled to a persistent inflammatory response that produces tissue damage, decreased ventilatory capacity, increased airway reactivity, decreased macrophage clearance, and altered immune functions. The inflammatory response, if not properly regulated, may produce tissue damage from the activity of secreted proteases, oxidants, and radicals. Inactivation of protease inhibitors by oxidant air pollutants may further enhance the damage from proteases released during neutrophilic inflammation.

Because airway defenses to inhaled oxidants are complex interacting systems, a number of biologic factors may contribute to children's responses to air pollutants. In the following sections, dietary factors that may affect responses to air pollutants are identified based on contributions to lung defenses and the airway inflammatory response (*21–36*). The intensity of the airway inflammatory response is likely to be influenced by genetic factors as well. Candidate susceptibility genes are proposed based on involvement in the pathogenesis of persistent lung damage (e.g., lung oxidant defenses, inflammatory responses, repair) and on the existence of functional polymorphisms for the genes (*27–45*). Genotypes that result in higher

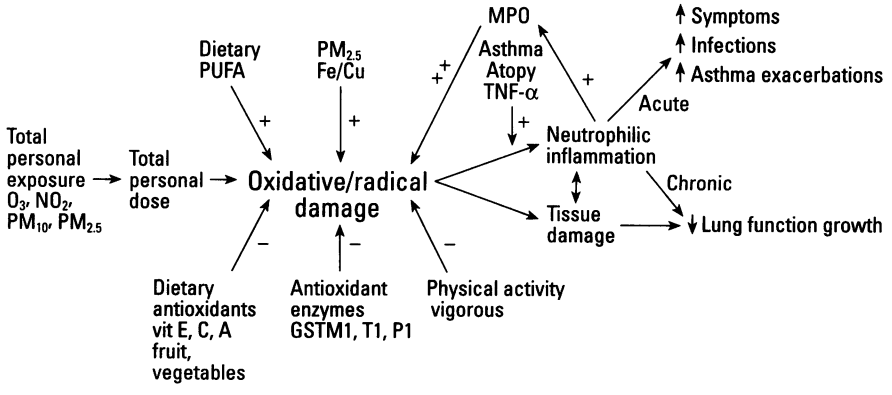

Figure 1. Biologic impact pathways of ozone, nitrogen dioxide, particulates on acute and chronic respiratory effects and susceptibility factors. Cu, copper; Fe, iron; GST, glutathione *S*-transferase (M1 T1 P1 polymorphic); MPO, myeloperoxidase (polymorphic); PA, physical activity; PUFA, polyunsaturated fatty acids; TNF-α, tumor necrosis factor α; vit E, C, A, vitamins E, C, A.

intensity inflammatory responses may be associated with increased susceptibility to respiratory effects from acute and chronic exposure to air pollutants.

Because pollutants may interact with specific components of the lung defenses, our framework also suggests a path for developing methods to summarize exposure data over time using biologic rationales. An in-depth discussion of biologically based exposure metrics is beyond the scope of this review. Asthma incidence is an important adverse event; however, it is not considered in detail in this framework because asthma appears to involve a distinct pathogenesis.

Role of Dietary and Enzymatic Antioxidants in Lung Defenses for Air Pollution

Constituents of the RELF provide an important first line of lung defenses for air pollutants. Inhaled doses of pollutants are largely delivered to the RELF. For gases and soluble liquid droplet aerosols, clearance occurs by dissolution and reactions with RELF components (e.g., antioxidants, lipids, proteins) or absorption into epithelial cells. O_3 is highly reactive with unsaturated lipids, antioxidants, proteins, and mucopolysaccharides. On inhalation, O_3 is delivered to the air/RELF interface. Where the RELF is thin (< 0.1 micron) or patchy, cellular damage may be directly caused by O_3 reactions with components of the membranes of the airway epithelial cells. If deposited where the RELF covers the airway surface, O_3 is completely consumed in reactions with components of the RELF including unsaturated lipids, proteins, and small antioxidant molecules. Insoluble particles are cleared from the proximal airway by the mucociliary elevator (*46*). Particles in the distal airways and alveoli are dissolved or cleared by alveolar macrophages, but some may be deposited around small airways. It appears that some ultrafine metallic particles are retained for long periods in the distal lung. Retained particles may contribute to adverse effects by enhancing radical production in these regions (*47*).

Because the RELF is the barrier between the delivered pollutants and respiratory epithelial cells and contains high concentrations of antioxidants such as vitamin C and enzymatic antioxidants such as glutathione *S*-transferases (GST), the RELF plays a key role in defenses to oxidant and radical gases and aerosols. Dietary intake of fruits and vegetables may therefore be important in protecting the airway from oxidant and radical air pollutants (*48–51*). Epidemiologic studies have shown that a high intake of fruits and vegetables is associated with increased lung function and decreased respiratory symptoms (*48–51*). One mechanism for these effects is the protection of the lung from damage from air pollution (*48–51*). Inadequate intake of antioxidants, radical scavengers, and trace metals may increase susceptibility to oxidant and radical air pollutants. Antioxidants (vitamin C) and radical scavengers (vitamin E) are present in the RELF and in cellular membranes (*31,52*). Low dietary intake of these nutrients results in lower levels in the RELF and in cells that diminish defenses against oxidative and radical attack from air pollutants. Polyunsaturated fats are a class of prooxidant nutrients that may increase susceptibility to oxidant and radical attack. Dietary fat intake affects the lipid composition of cell membranes. High intake of polyunsaturated fats increases the amount of unsaturated lipids in the RELF and cell membranes, making the airways more susceptible to oxidant damage.

Genetic Factors for Oxidant and Inflammatory Damage from Air Pollutants

The reproducibility of acute responses in humans suggests that a stable host characteristic may be a determinant of sensitivity to air pollution. Marked variation in response to O_3 has been observed among the homogeneous groups of healthy volunteers selected for chamber studies (*1,6*). The pulmonary function decrements from O_3 inhalation are reproducible within an individual but show marked interindividual variation (*14*). The determinants of O_3 sensitivity are unknown; however, chronic disease does not appear to explain the variation because subjects with asthma, COPD, advanced age, or those who smoke do not show larger responses to O_3. Animal studies also are consistent with a genetic etiology (*53*). For example, among rat strains, Wistar rats have the greatest neutrophil influx, but Fischer rats have the greatest epithelial cell damage. Although the inflammatory response is a complex trait that may have contributions from several loci, Kleeberger et al. identified the *inf* locus that confers susceptibility to O_3-induced neutrophilic inflammation in mice (*53*). The genes at the *inf* locus have yet to be identified.

Because genes involved in responses to air pollutants have not been identified, a practical approach to identifying genetic factors is studying associations with candidate genes. Several criteria must be satisfied in selecting and establishing useful links between polymorphisms in candidate genes and adverse respiratory effects. First, the product of the candidate gene must be significantly involved in the pathogenesis of the adverse effect of interest, often a complex trait with many determinants. Second, polymorphisms in the gene must produce a functional change in either the protein product or in the level of expression of the protein. Third, in epidemiologic studies, the issue of confounding by other genes or environmental exposures must be carefully considered. The GST superfamily of genes are candidate genes for susceptibility to air pollution (*39*). GSTs are peroxidases as well as transferases and appear to be involved in repairing lipid peroxidation products from oxidative and radical attack from tobacco smoke and oxidant and radical air pollutants. Enzymes that function as glutathione peroxidases (GPxs) are important enzymatic antioxidants because they can detoxify hydroperoxides formed by radical attack or secondary ozonation products using the high concentrations of reduced glutathione (GSH) found in RELF (*54–56*). Two types of GPx are found in the RELF (*54–56*). The majority of RELF GPx activity is due to a nonselenium-dependent peroxidase. GSTs appear to account for the majority of the nonselenium-dependent GPx activity in RELF.

Several GST families have common, functionally important polymorphic alleles that significantly reduce expression of function in the lung (homozygosity for the null allele at the GST M1 and T1 loci, and homozygosity for the A105G allele at the GSTP1 locus) (*38,45,57*). GST genes are inducible by oxidative stress. Exposure to radicals and oxidants in air pollution induces decreases in GSH that increase transcription of GSTs (*58*). Individuals with genotypes that result in enzymes with reduced or absent peroxide activity are likely to have reduced oxidant defenses and increased susceptibility to inhaled oxidants and radicals.

Myleoperoxidase (MPO) is another candidate gene for response to air pollution. Levels of MPO, released by activated neutrophils, are increased in the RELF during O_3-induced inflammation. MPO produces potent oxidants that can damage lung tissue and macrophages. Increased level or dysregulation of expression may contribute to susceptibility to respiratory

effects from air pollution. The MPO gene has a polymorphism in its promoter region (G to A at position -463 of the MPO gene). The A allele (MPO A) results in decreased expression of MPO compared to expression of the G allele (MPO G (common allele) (*18,42,43,59–61*).

Tumor necrosis factor (TNF)-α is a third candidate for susceptibility to air pollution. Induction of inflammation, which involves both neutrophils and macrophages, following air pollutant exposure may be mediated by the production of reactive oxygen species, which activate nuclear factor-κB (NF-κB) (*62*). NF-κB regulates a number of cytokines including TNF-α. Polymorphisms in TNF-α may contribute to the neutrophil response and to enhanced oxidant damage to respiratory epithelial cells and macrophages. TNF-α appears to be involved in the pathologic inflammation in COPD. Patients with COPD show increased numbers of neutrophils and concentrations of TNF-α in the RELF compared to smokers or nonsmokers (*63*). The association may stem from a polymorphism in the 5′ region of the gene that modulates expression. COPD is also associated with inheritance of one TNF2 allele. These findings suggest that TNF2 modulates neutrophilic inflammation and is involved in the pathogenesis of this tobacco-related disease. Because some effects of air pollutants are mediated by neutrophilic inflammation, inheritance of one TNF2 allele may increase the likelihood of acute or chronic respiratory effects following exposure to ambient air pollutants.

Lung growth, immune function, and chronic respiratory diseases are complex multifactorial processes. The etiologies of these and other adverse respiratory health effects are probably not fully explained by allelic variation at one locus. In the population at large, the occurrence of respiratory effects and diseases is more likely to result from a complex interplay of multiple genetic and environmental factors that evolves through time. Because the traits of interest are complex and clearly involve a number of physiologic processes, we anticipate that the magnitude of main effects of genes and gene–environment interactions, as well as dietary factors, may be modest for individuals. Because these genetic and dietary factors are common, each may make an important contribution to the population attributable risk. To be successful, studies of genes with high population attributable risk, but with modest individual effects, need detailed exposure assessment, careful end point measurement and classification, and include a large enough sample size to obtain precise and accurate estimates of modest effects. The possibility of gene–gene interactions must also be considered, especially for metabolic genes with overlapping substrate specificities and immune regulatory genes involved in common pathways.

Conclusion

A major unresolved air pollution research goal is to determine whether air pollution causes chronic respiratory disease or reduced lung growth, and if so, to determine the independent and joint effects of specific pollutants. An essential element is identifying groups in the population that are more sensitive to any chronic effects from exposure to ambient levels of air pollution. The evolving understanding of the interactions of air contaminant exposures, causal mechanisms that reflect pathophysiologic pathways, and multilocus genetic variation provides a basis for focused research, identification of sensitive individuals, and improved prevention strategies. Fruitful lines of future investigation for the chronic effects of air pollution include the roles of dietary intake of antioxidants, variation in physical activity, and polymorphisms in genes that modulate free radical damage. Children with low fruit and vegetable intake, low antioxidant intake, or who inherited certain alleles for cytokine genes or free radial damage repair may be such a sensitive group. As the complete human genome is described over the next decade, innovative strategies will be needed to assess genotype–phenotype relationships, allowing genetics to be fully integrated into air pollution research.

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