Ozone, a Malady for All Ages

This summer, the U.S. Environmental Protection Agency (EPA) will begin the final phase in reviewing and potentially updating the current National Ambient Air Quality Standard (NAAQS) for ozone. To protect the nation's health, it is imperative that the EPA take action to issue a more stringent standard for ozone pollution.

Protecting the health of the nation's population is a clear mandate of the Clean Air Act. Over 150 million people residing in more than 240 counties across the United States today are exposed to ozone at unacceptable levels under the current ozone standard. We express our strong support for a revised primary 8-hour ozone ambient air quality standard at a level that will reduce the health risk confronted by the nation's population as the result of exposure to ozone air pollution. Numerous recent studies clearly demonstrate adverse health effects at ozone levels well below the current standard. The NAAQS must accurately reflect the state of the science and fulfill the Clean Air Act's mandate of protecting the public health, including those most vulnerable to the effects of air pollution, with an adequate margin of safety.

Among sensitive populations, children may be more at risk of the adverse effects of air pollution than adults for several reasons. First, children have a higher level of activity and a higher minute ventilation compared with adults, which increases the effective dose of inhaled pollutant (reviewed in Reference 1). Second, children spend more time outdoors than adults do, increasing exposure to ambient air pollutants (2). Third, lung development is a long-term process. Although the human lung needs to be sufficiently formed at birth to perform its primary function, gas exchange, lung growth continues for an extensive period (8–12 yr) after birth (3). During this time, there are multifold increases in overall lung size, active cellular differentiation, cell division, and alveolar formation. As a result, airways change in size and shape with maturation, altering deposition patterns. In addition, lung function also continues to change, increasing until late adolescence in both males and females, when it plateaus (4–6). This period of lung growth and development is a critical one in which a deficit in growth could be carried throughout life.

Increasing numbers of epidemiological studies suggest that ozone is detrimental to children's respiratory health, including increased hospitalizations, emergency room visits, and decreased pulmonary function (7–9). Current ozone levels in Canada's largest cities are associated with increased hospitalization for respiratory problems in neonates under 1 month of age (10). Ozone levels lower than current U.S. EPA standards have also been associated with difficulty breathing in infants (aged 3 mo to 1.5 yr), particularly in those with asthmatic mothers (11), and with increased use of rescue medication in children with asthma under 12 years of age using maintenance medication (12). The incidence of new diagnoses of asthma in children who exercise heavily is associated with average ozone levels of 55.8 to 69.0 ppb during the daytime (10 A.M. to 6 P.M.), levels below the current NAAQS (13). The effects of childhood exposure may be long-lasting. Decrements in small airways function have been reported in college freshmen who have grown up in polluted areas of California's South Coast Air Basin (14, 15).

Growing concern is emerging regarding the relative risks of increased morbidity and mortality among adults as well. A series of recently published meta-analyses and primary national-scale epidemiological studies have documented consistent associations between premature mortality and ozone exposures below the current 8-hour standard of 0.08 ppm (16). Controlled human exposure studies of healthy adults have demonstrated reduced lung function, increased respiratory symptoms, changes in airway responsiveness, and increased airway inflammation following 6.6-hour exposures to 0.08 ppm ozone (17, 18). Recent studies demonstrate that some of the individuals tested experience these adverse effects at concentrations of 0.06 ppm and below (19).

We are concerned that, throughout the public process of evaluating the available science, EPA senior political appointees have consistently overemphasized any "scientific uncertainty" surrounding the known health effects of ozone exposure. EPA senior appointees adopted a similar approach during the rule making for particulate matter, and ultimately, EPA administrator Stephen L. Johnson cited "scientific uncertainty" as a reason for the EPA not issuing a more protective particulate matter standard. It appears that the EPA may once again use scientific uncertainty as an excuse for failure to act decisively.

We find the EPA posturing over scientific uncertainty to be disingenuous, uncompelling, and, ultimately, in violation of the Clean Air Act. In drafting the Clean Air Act, Congress realized that "perfect" information about exposure–response relationships would not be available in setting NAAQS standards. The Clean Air Act is founded on the cautionary principle, and directs the EPA, in cases of scientific uncertainty, to err in favor of protecting the public health. The EPA again seems to be turning the precautionary principle on its head and using scientific uncertainty as justification for inaction.

Based on the strength of the scientific knowledge base regarding the adverse health effects of ozone air pollution, and the magnitude of public health impact such pollution has on the United States' population, especially on children, the American Thoracic Society has recommended that the EPA take action now to issue a stricter ozone standard of 0.060 ppm/8 hours (20). This recommendation is consistent with that of a number of other prominent expert scientific panels, including the EPA's own Children's Health Protection Advisory Committee and the Clean Air Scientific Advisory Committee. Any action less stringent than a 0.060-ppm standard will effectively represent a failure of the EPA to fulfill its mandate under the Clean Air Act.

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COPD and Lung Cancer Have Come a Long Way . . . Baby

A famous tobacco advertisement from the 1970s made the claim that women were biologically superior to men:

> We make Virginia Slims especially for women because they are biologically superior to men . . . . Women have two "X" chromosomes in their sex cells while men have only one "X" chromosome and a "Y" chromosome, which some experts consider to be the inferior chromosome . . . . In view of these and other facts, the makers of Virginia Slims feel it highly inappropriate that women continue to use the fat stubby cigarettes designed for mere men. Virginia Slims. Slimmer than the fat cigarettes men smoke . . . . You've come a long way, baby. (1)

Duplication of the X chromosome has obvious genetic advantages, but does this translate into resistance to the respiratory health effects of tobacco use, such as chronic obstructive pulmonary disease (COPD) and lung cancer? This duplication results in a variety of hormonal and enzymatic outcomes that, ultimately, make women and men different but also, potentially, confers sex-related differences in susceptibility to disease.

In recent years, COPD has become an "equal opportunity" disease with more women developing COPD and suffering COPD-related morbidity and mortality in high-income countries around the world (2–5). The increasing prevalence of COPD among women in high-income countries is due, in large part, to the historic increase in smoking among women in these populations. In low- and moderate-income countries, COPD prevalence remains lower in women compared with men and the risk factors for disease may also vary, with exposure to indoor air pollutants, poor diet, and poverty being more important than they are in high-income countries (6, 7).

In a similar way, lung cancer has also become a disease affecting an increasing number of women (8). Since the mid 1980s in the United States, more women have died annually of lung cancer than from breast cancer (9). By 1999, 4.6% of deaths among women and 5.1% of deaths among men were from COPD and 5.0% of deaths among women and 7.6% of deaths among men were from lung cancer (8). The link between COPD and lung cancer has been well established in several different cohorts, although the reasons for this association remain unclear (10–12). The question remains whether, all exposures being equal, women are more or less likely to develop COPD and lung cancer when compared with men.

The article by Ben-Zaken Cohen and colleagues in this issue of the *Journal* (pp. 113–120) (13) explores sex-related differences in the development of COPD and lung cancer and in the metabolism of tobacco smoke constituents. The authors acknowledge