

in increasingly larger numbers of individuals. Symptomatic and pulmonary function responses follow a similar time course during an acute exposure and the subsequent recovery, as well as over the course of several days during repeated exposures. As with pulmonary function responses, the severity of symptomatic responses varies considerably among subjects. For some outdoor workers or active people who are highly responsive to ambient O₃, respiratory symptoms may cause reduced productivity, may curb the ability or desire to engage in normal activities, and may interfere with maximal exercise performance.

(iii) *Increased airway responsiveness.* Increased airway responsiveness is an indication that the airways are predisposed to bronchoconstriction, with a high level of bronchial responsiveness being characteristic of asthma. As a result of increased airway responsiveness induced by O₃ exposure, human airways may be more susceptible to a variety of stimuli, including antigens, chemicals, and particles. Because enhanced response to antigens in asthmatics could lead to increased morbidity (*i.e.*, medical treatment, emergency room visits, hospital admissions) or to more persistent alterations in airway responsiveness, these health endpoints raise concern for public health, particularly for individuals with impaired respiratory systems.

(iv) *Increased susceptibility to respiratory infection.* When functioning normally, the human respiratory tract, like that of other mammals, has numerous closely integrated defense mechanisms that provide protection from the adverse effects of a wide variety of inhaled particles and microbes. Evidence that inhalation of O₃ may break down or impair these defense mechanisms comes primarily from a very large number of laboratory animal studies with generally consistent results. One of the few studies of moderately exercising human subjects exposed to 0.08 ppm O₃ for 6.6 hours reported decrements in alveolar macrophage function, the first line of defense against inhaled microorganisms and particles in the lower airways and air sacs. While no single experimental human study or group of animal studies conclusively demonstrates that human susceptibility to respiratory infection is increased by exposure to O₃, taken as a whole, the data suggest that acute O₃ exposures can impair the host defense capability of both humans and animals, potentially resulting in a predisposition to bacterial infections in the lower respiratory tract.

(v) *Hospital admissions and emergency room visits.* Increased summertime hospital admissions and emergency room visits for respiratory causes have been associated with ambient exposures to O₃ and other environmental factors. Numerous studies consistently have shown such a relationship, even after controlling for modifying factors, as well as when considering only O₃ concentrations < 0.12 ppm. Individuals with preexisting respiratory disease (*e.g.*, asthma, chronic obstructive pulmonary disease) may generally be at increased risk of such effects, and some individuals with respiratory disease may have an inherently greater sensitivity to O₃. On the other hand, individuals with more severe respiratory disease are less likely to engage in the level of exertion associated with provoking responses to O₃ exposures in healthy humans. On balance, it is reasonable to conclude that evidence of O₃-induced increased airway resistance, nonspecific bronchial responsiveness, susceptibility to respiratory infection, increased airway permeability, airway inflammation, and incidence of asthma attacks suggests that ambient O₃ exposure could be a cause of increased hospital admissions, particularly for asthmatics.

(vi) *Pulmonary inflammation.* Respiratory inflammation can be considered to be a host response to injury and indicators of inflammation as evidence that respiratory cell damage has occurred. Inflammation induced by exposure of humans to O₃ may have several potential outcomes: (1) Inflammation induced by a single exposure (or even several exposures over the course of a season) could resolve entirely; (2) repeated acute inflammation could develop into a chronic inflammatory state; (3) continued inflammation could alter the structure and function of other pulmonary tissue, leading to disease processes such as fibrosis; (4) inflammation could interfere with the body's host defense response to particles and inhaled microorganisms, particularly in potentially vulnerable populations such as children and older individuals; and (5) inflammation could amplify the lung's response to other agents such as allergens or toxins. Exposures of laboratory animals to O₃ for periods ≤ 8 hours have been shown to result in cell damage, inflammation, and increased leakage of proteins from blood into the air spaces of the respiratory tract. In humans, the extent and course of inflammation and its constitutive elements have been evaluated by using bronchoalveolar

lavage (BAL) to sample cells and fluid from the lung and lower airways. Several such studies have shown that exercising humans exposed (1 to 4 hours) to 0.2 to 0.6 ppm O₃ had O₃-induced markers of inflammation and cell damage, with the lowest concentration of prolonged O₃ exposure tested in humans, 0.08 ppm for 6.6 hours with moderate exercise, inducing small but statistically significant increases in these endpoints. Thus, it is reasonable to conclude that repeated acute inflammatory response and cellular damage is potentially a matter of public health concern; however, it is also recognized that most, if not all, of these effects begin to resolve in most individuals within 24 hours if the exposure to O₃ is not repeated. Of possibly greater public health concern is the potential for chronic respiratory damage that could be the result of repeated O₃ exposures occurring over a season or a lifetime.

b. Potential Effects of Long-term O₃ Exposures

Epidemiologic studies that have investigated potential associations between long-term O₃ exposures and chronic respiratory effects in humans thus far have provided only suggestive evidence of such a relationship. Most studies investigating this association have been cross-sectional in design and have been compromised by incomplete control of confounding variables and inadequate exposure information. Other studies have attempted to follow variably exposed groups prospectively. The findings from such studies conducted in southern California and Canada suggest small, but consistent, decrements in lung function among inhabitants of the more highly polluted communities; however, associations between O₃ and other copollutants and problems with study population loss have reduced the level of confidence in these conclusions. Other epidemiologic studies have attempted to find associations between daily mortality and O₃ concentrations in various cities around the United States. Although an association between ambient O₃ exposure in areas with very high O₃ levels and daily mortality has been suggested by these studies, the data are limited.

In a large number of animal toxicology studies, "lesions" ²⁵ in the

²⁵ Differing views have been expressed by CASAC panel members regarding the use of the term "lesion" to describe the O₃-induced morphological (*i.e.*, structural) abnormalities observed in toxicological studies. Section V.C.8 of the Staff