
Summary of Papers and Research Recommendations of Working Group on Tropospheric Ozone, Health Effects Institute Environmental Epidemiology Planning Project

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This paper summarizes the themes and recommendations that emerge from the papers presented by the Working Group on Tropospheric Ozone. In terms of current knowledge, the following are considered of particular importance: *a*) lack of clear evidence for a human analogue of the terminal bronchiolar and proximal acinar changes observed in the lungs of ozone-exposed animals; *b*) lack of evidence for a connection between the acute respiratory effects of O₃ and possible chronic respiratory effects; *c*) need to better define the characteristics of O₃-susceptible individuals; *d*) the lack of adequate exposure assessment tools for reconstruction of lifetime O₃ exposure; and *e*) incomplete information on the role of other ambient environmental pollutants in the facilitation of O₃ effects or as a cause of effects attributed to O₃ in human populations. Based on the above, several recommendations for epidemiologic research on health effects of O₃ are offered. *a*) Studies to investigate the existence of chronic health effects of O₃ are essential, particularly those that include autopsied human lung tissue and biologic and physiologic response markers. *b*) Studies are needed to link acute responses with chronic effects and should include joint epidemiologic and controlled-exposure assessments. *c*) Studies are needed to identify susceptible subgroups. Such studies should include newly emerging biologic markers of O₃ exposure. *d*) Accurate and precise tools for chronic O₃ exposure assessment need to be developed for use in retrospective and prospective studies. *e*) Collaborative studies between epidemiologists and laboratory investigators are needed to develop and evaluate markers of O₃ exposure and to test O₃ exposure models. — Environ Health Perspect 101(Suppl 4):237-239 (1993).

Key Words: Ozone, health effects

This paper will summarize the themes and research recommendations that emerge from the papers presented by the Working Group on Tropospheric Ozone, of the Health Effects Institute Epidemiology Planning Project. The order of presentation of the themes and research recommendations is motivated by issues of coherence and is not intended to imply prioritization on the part of the working group. References to the individual papers that develop the themes are provided to assist readers who may choose to read this summary paper prior to the individual presentations.

Animal research has provided coherent evidence that the earliest effects of ozone (O₃) on the lung can be found in the terminal airways and acinus and are consistent with the changes (acute inflammation, fibrosis) and anatomic location that could be the antecedents for the occurrence of accelerated aging of the lung and chronic lung diseases.(1-3). Although human

dosimetry calculations and data from bronchial lavage studies are compatible with a comparable process in humans, there is no direct evidence that the early lesions observed in animals occur in man and that chronic lung disease can be attributed to O₃ exposure (1-4). Therefore, epidemiologic studies need to make use of methods that permit a direct test of the hypothesis that O₃ does produce changes in the lung that are compatible with the occurrence of chronic lung disease. The use of human postmortem lung specimens (1,2) and the parallel use of markers of biologic response (e.g., inflammation) and physiologic response (e.g., pulmonary function at the level of small airways) are considered to be essential elements in future epidemiologic studies of the health effects of O₃ exposure (1-5).

Most epidemiologic studies and all controlled exposure studies on the health effects of O₃ have focused on acute responses of one kind or another. The implicit assumption of such studies has been that there is some relationship between these acute responses and the subsequent occurrence of chronic disease (3-5). Nonetheless, this relationship has not been established firmly

(4). Moreover, the range of acute effects that can be attributed to O₃ exposure and the public health burden that they impose remain incompletely defined (4,5). The use of panel studies alone or nested within larger cross-sectional or longitudinal studies (4,6), the combining of traditional epidemiologic study designs with controlled exposure protocols, and the use of multiple biologic and physiologic response markers within a given study offer new possibilities to expand the current body of data with regard to the acute health effects of O₃ and their long-term consequences (3,4).

The need to define the diversity of individual and group susceptibility to the adverse health consequences of exposure to O₃ is a feature of each of the papers of the working group. The current database on the health effects due to O₃ exposure largely has ignored this issue, with the exception of the focus on asthmatic individuals and individuals with hyperactive airways as assessed by bronchoconstrictor challenge testing (4,5). The definition of the susceptible individual or group is complex: There is no uniform marker or set of markers that define(s) O₃-susceptibility either to acute or chronic effects (should they exist)

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(3), and susceptibility may be defined in terms of increased variance in response as well as in terms of the more traditional considerations of level of change (6). The later emphasis on individual variability in response imposes the need for the kind of repetitive measurements made in panel studies or more traditional longitudinal designs. Moreover, the issue of susceptibility is complicated by the fact that there may not be concordance between factors that define susceptibility to acute effects and those that define susceptibility to chronic effects (unpublished material) and, as noted above, there may not be a clear relationship between the occurrence of acute response to O₃ and the subsequent occurrence of chronic health effects. The identification of susceptible individuals and groups has implications for design choice, efficiency of epidemiologic studies, and analysis of data (3,4,6). To identify susceptible individuals, epidemiological studies will have to rely increasingly on biologic and physiologic response markers that more closely parallel the hypothesized effects of O₃ on the respiratory system (1-3). Currently, there are insufficient data on the validity, reproducibility (under conditions of known exposure), and specificity of the range of possible markers of O₃ susceptibility and exposure (3). Studies specifically designed to provide data on validity, reproducibility, and specificity should proceed in parallel with or, preferably, as an integral part of epidemiologic studies of the health effects of O₃ exposure.

Exposure assessment is an area of central concern for epidemiologic studies of O₃ effects (2,4). Epidemiologic studies that deal with chronic health effects must provide at least a semiquantitative estimate of O₃ exposure prior to the onset of the study (including longitudinal studies). To do so requires that available O₃ monitoring databases be used to estimate likely cumulative exposures that individuals have had prior to coming under direct observation (or prior to time of death in the case of autopsy studies). Such estimates depend upon detailed information on factors such as residential histories, typical activities (type, frequency, intensity), time spent indoors versus outdoors, etc. (2,4). Instruments need to be developed and validated for retrospective reconstruction of exposure history. Assessment of cigarette tobacco use and occupational exposures will have to be an integral part of such instruments. The use of such instruments also will be required for longitudinal studies, but the possibilities of conducting validation

substudies make the task here less daunting than for studies that will have to depend solely on retrospective exposure assessment. In this context, there is an obvious need for continued development and validation of O₃ exposure models. As is the case for markers, such studies should proceed in parallel with or as part of longitudinal epidemiologic studies. The continued development and application of technologies that permit direct monitoring of individuals (personal dosimeters) should be encouraged as part of epidemiologic studies (4).

Closely related to the issue of exposure assessment for O₃ is the role of other ambient environmental pollutants in the facilitation of O₃ effects or as the cause of effects that have been attributed to O₃ (2,4). Of particular interest is the role of acid aerosols and particulates of the PM10 fraction. Careful selection of study sites will be essential to control for these effects and should figure prominently in the design of epidemiologic studies of whatever type (2,4). If epidemiologic studies take place in a single geographical location, the location should be chosen to minimize the possibilities that other ambient pollutants are either modifying or confounding any health effects that are attributed to O₃ exposure. The advent of personal O₃ dosimetry or the identification of specific molecular markers of O₃ exposure would lessen the need for such a restriction (3,4).

Bates, in his lecture entitled "Health Indices of the Adverse Effects of Air Pollution: The Question of Coherence" (7), developed the concept of coherence of data from epidemiologic studies of air pollution. Bates defined coherence, in the context of air pollution health effects research, as the interrelationships between different indices of health. Coherence, in this context, is a central issue for epidemiologic studies that attempt to relate acute responses to O₃ exposure and chronic health effects (4), but the concept is relevant to all aspects of epidemiologic studies of the health effects of air pollution. Implicit in the concept of coherence is the explicit linkage of epidemiologic studies that address differing elements in the chain of relationships between O₃ exposure and health effects. The choice of study design(s), the location(s) of the studies, and the specific health effects to be investigated should form a series of studies that are planned as a logical unit that is designed to produce a set of data that can be evaluated as a logical unit (4). The nested study designs, (8) are the simplest examples employed to date.

The above synthesis forms the overall framework from which the following set of specific research recommendations are put forth (9).

Recommendations for Specific Epidemiologic Research

Epidemiologic studies specifically targeted to investigate the occurrence of chronic health effects due to O₃ are necessary. Innovative study designs that are based upon the use of autopsied human lungs and on the employment of combinations of biologic and physiologic response markers should be developed to test the hypothesis that chronic O₃ exposure can produce a respiratory bronchiolitis that is related to premature functional decline of human respiratory function. Studies that investigate the relationship between acute responses to short-term O₃ exposure and the occurrence of chronic respiratory tract symptoms and alterations of function should be undertaken. Such studies should employ traditional epidemiologic study designs in combination with panel studies and should provide samples that make population estimates feasible. Epidemiologic studies that investigate individuals who have recently moved (temporarily or permanently) from or to areas with markedly different O₃ and other pollutant profiles should be encouraged.

Epidemiologic studies of the full range of acute health effects that can be attributed to O₃ exposure are necessary. Epidemiologic studies of acute health effects should investigate the phenomenon of adaptation that has been observed in studies with controlled exposures and determine its role in the epidemiology of acute O₃-related health effects. Epidemiologic studies should be closely linked to controlled exposure studies in this regard.

Epidemiologic studies that investigate the role of other ambient air pollutants in the occurrence of O₃-related health effects are necessary. Collaborative epidemiologic studies over several regions that are chosen on the basis of their patterns of O₃ and other specific pollutants (e.g., acid aerosols) should be encouraged.

Epidemiologic studies to identify O₃-susceptible subgroups and individuals are necessary. Epidemiologic studies of the role of O₃ exposure as an etiologic factor for asthma and as a factor in increases in the morbidity and mortality of asthma should be undertaken. Such studies should include a combination of traditional epidemiologic study designs and controlled

exposure protocols both for the selection of subjects and the investigation of outcomes. Epidemiologic studies should be undertaken to provide data for estimation of the validity, specificity, and predictive values of new O₃ susceptibility markers that are under development in the laboratory. Close collaboration between epidemiologists and laboratory-based investigators for the development of markers that can be applied in epidemiology study protocols of O₃ health effects is to be encouraged. Epidemiologic studies of O₃, regardless of their design, should attempt to include repetitive measures of effect for individual subjects whenever feasible.

Epidemiologic studies to develop accurate and reliable (precise) tools for O₃ exposure assessment are necessary. The development of methods for retrospective reconstruction of cumulative O₃ exposure

in epidemiologic studies is of particular importance. There should be close collaboration between epidemiologists and investigators who are involved in the development and testing of exposure models.

Recommendations for Needed Studies in Support of Epidemiologic Protocols

There were a number of research recommendations considered by the working group that do not translate strictly into epidemiologic studies. However, the working group felt that developments in these areas were of sufficient importance to epidemiologic studies of O₃-related health effects that research into them should be supported in the context of an overall "Epidemiology Planning Project."

Laboratory investigations to identify sensitive and specific molecular, cellular,

and physiologic markers of O₃ health effects susceptibility are needed. Laboratory investigations to identify highly specific molecular and cellular markers of O₃ exposure also are desirable. Such efforts should occur in close collaboration with epidemiologic investigators, and studies to determine the validity, specificity, and predictive values of such markers in epidemiologic studies should be undertaken.

The further development and testing of models of O₃ exposure should be supported as a component of selected epidemiologic studies. Also, the further development, testing, and application of personal O₃ dosimeters should be supported as a component of selected epidemiologic studies, particularly those studies with an emphasis on the development of overall methods for exposure assessment. 

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