Introduction to Working Group on Tropospheric Ozone, Health Effects Institute Environmental Epidemiology Planning Project

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The working group on tropospheric ozone of the Health Effects Institute has evaluated the need for epidemiologic studies on the health effects of ozone (O3) exposure. This paper summarizes current data and identifies possible research questions. The extent to which ozone exposure results in chronic health effects is largely undefined and is the central issue for epidemiologic studies. Most current data focus on transient endpoints; the link between acute changes in symptoms and/or lung function and possible chronic effects has not been established. Concepts of ozone-induced health effects have been extended to include processes of chronic disease (e.g., markers of ongoing inflammation and repair, markers of accelerated lung aging). Traditional epidemiologic studies performed have focused only on accelerated lung aging and are limited by a number of methodologic problems. Recent, very preliminary, studies suggest new opportunities for the use of human lung tissue and a variety of biological response markers as part of epidemiologic studies. The identification of sensitive subpopulations with regard to ozone-induced health effects has been studied incompletely and is important both in terms of study efficiency and mechanistic insight. Methodologic advances in the reconstruction of past ozone exposure are seen as essential, as is the incorporation of emerging markers of biologic response to ozone into traditional epidemiologic study designs. Finally, more data on the joint and independent contribution of other ambient air pollutants to putative ozone-induced health effects is warranted. — Environ Health Perspect 101(Suppl 4):205–207 (1993).

Key Words: Ozone, health effects

Background

An extensive body of data has been developed on the biologic, physiologic, and health effects of ozone. Two recent comprehensive reviews (1,2) summarize this information. From these reviews, it is clear that epidemiologic studies represent only a small part of the current knowledge base on ozone-induced health effects and that considerable opportunities exist for epidemiologic studies to fill in many of the gaps in the current state of knowledge about these effects.

The working group on tropospheric ozone has addressed Health Effects Institute’s (HEI’s) objectives with regard to needed epidemiologic research through the following steps: identification of general research questions with regard to ozone-induced health effects that the committee felt most needed to be addressed and formulation of these research questions in terms suitable for epidemiologic study designs. At each stage of this process, consideration was given to the theoretical and practical advantages of available study design alternatives and the need to consider new design approaches.

The remainder of this introduction is devoted to a brief summary of the working group discussions on the general research needs that guided the development of the papers that follow.

The extent to which ozone results in chronic health effects in humans remains largely undefined and is a central issue for epidemiologic studies. Data from primate exposure studies suggest that permanent or poorly reversible changes in the distal airways and proximal alveolar regions of the lung might be important consequences of prolonged ozone exposure (3,4). Recent chamber studies of the acute effects of ozone exposure on the dispersion of inhaled aerosol boluses support the possibility that similar small airway alterations occur in otherwise healthy humans (5) and could be precursor lesions to a more chronic process.

To date, most studies of ozone-induced health effects in humans have focused on specific transient endpoints (e.g., symptoms, change in lung function after acute exposure, one-time assessment of cellular and/or biochemical markers of inflammation and repair). Moreover, the link between current measures of acute symptomatic and/or functional responses to ozone (6,7) and the occurrence of chronic effects has not been established in humans, nor has it been established that the mechanisms that underlie acute effects (e.g., airways hyperreactivity (8), reflex neural alterations of measured vital capacity (9), inflammatory changes (10)) are the same as those that underlie chronic effects (e.g., loss of lung elastic recoil, deposition of excess collagen).

Analogous to studies of the natural history of the effects of cigarette smoke on lung function and the subsequent occurrence of chronic pulmonary disease (11), concepts of ozone-induced health effects have to be extended beyond the evaluation of specific endpoints to include processes indicative of chronic disease (e.g., markers of ongoing inflammation and repair, biochemical and/or physiological markers of accelerated lung aging, etc.). To date, traditional, population-based epidemiologic studies that have tried to address process (e.g., accelerated decline in lung function) have been restricted to the evaluation of a limited range of lung function measures. They also have been handicapped by a number of problems: a) large losses to follow-up (12,13), which on the surface do not appear to have affected validity; b) inadequate characterization of individual and group exposure to ozone prior to study onset; c) difficulties in obtaining detailed data on concurrent ozone exposure for large numbers of subjects; d) lack of data on modifying and/or confounding factors; and e) the relatively short duration of follow-up (12,13) or the purely cross-sectional nature of their evaluation (14). These

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studies have derived their epidemiologic appeal from a perceived need to have study samples from whom generalizations can be made to some population at large. These studies were considered to be of continued relevance for comprehensive policy analysis into the health and economic impact of exposure to ozone, but they were thought to be of less importance in terms of efficiency for studies aimed at the identification of acute and chronic health effects and chronic alterations of biological processes (e.g., premature aging of the lung). Epidemiologic studies in targeted populations (e.g., persons moving between localities with different ozone exposure characteristics, asthmatics) were considered as alternatives to provide valid data with greater efficiency for the determination of the extent to which acute and chronic health effects occur and for the characterization of such effects.

To address the issue of pathophysio-
logic process, innovative study designs that use new sources of data on the response of humans to ozone were considered in detail. Despite a number of significant limitations, the working group felt that the recent autopsy study of Sherwin and Richters (15), which reported an excess of severe respiratory bronchiolitis in the lungs of young accident victims who lived in Los Angeles, suggested important new opportunities for epidemiologic studies of chronic ozone-induced health effects. The development of well-designed autopsy studies and living population studies of inflammatory markers might provide a means to identify early pathologic changes that, by analogy to data for cigarette smoke (16,17), represent precursor lesions for more serious chronic effects and/or relate to acute and subacute functional changes in the lung. Study designs that utilize individuals who move, either temporarily or permanently, to and from areas with major differences in ambient ozone concentrations were seen as creative means to test hypotheses about functional changes in the lung and health effects in general (18).

The identification of sensitive subpopulations with regard to ozone-induced health effects (especially chronic effects) was considered to be important both for study design efficiency and for mechanistic (biologic) insight. Asthmatics, in particular, were singled out for consideration because of their increased reactivity to a variety of environmental stimuli. This approach was supported by population-based studies that demonstrated an association between acute asthma and other respiratory morbidity (emergency room visits) and other air pollutants (19).

The failure of controlled exposure studies to identify, unequivocally, asthmatics as a sensitive subpopulation was not seen as limiting in this context, since it may have been the result of a) inadequate exposures used in the controlled exposure studies that have been conducted to date (20), b) the inclusion of only milder asthmatics, c) the exclusion of asthmatics with acute respiratory illness or its exacerbation, and d) failure to simulate the complex mix of air pollutants to which such individuals may be exposed (13). Epidemiologic studies, in conjunction with additional controlled exposure studies (20,21), were considered essential to address the above problems and to identify more clearly other sensitive subgroups and the factors that define sensitivity to ozone. A recent study that indicates that ozone exposure may enhance lung airway responsiveness to aeroallergens (22) adds further impetus to this focus.

Standardized questionnaire assessment and measurement of forced expiratory volumes and flows have been the primary outcomes that have been used in controlled exposure and epidemiologic studies to identify individuals who respond to ozone exposure (e.g., report of a symptom(s) or a change in level of volume or flow after exposure). On a more limited basis, markers of lung inflammation, as assessed through analysis of the fluid and cellular phases of bronchoalveolar lavage, have been employed to expand the concept of response to ozone (23). Given the importance attached to the ozone-sensitive population in the working group's formulations, it was imperative that the studies of ozone-induced health effects include more proximate markers of biologic effect (damage, repair, etc.) and measures of pulmonary function that may be more sensitive markers of effect or may reflect a broader range of functional alteration (e.g., changes in the distribution of inhaled aerosols (5)).

Although not unique to epidemiologic studies of ozone-induced acute and chronic health effects, methodologic advances were seen as necessary for the retrospective reconstruction of past ozone exposure status (e.g., identification of suitable, long-term, air pollutant monitoring databases, development of indices of relevant past exposure, time-activity indices, etc.). It was felt that the need for valid and reproducible methods that assess retrospective and concurrent exposure that are suitable for epidemiologic studies is of sufficient importance to merit independent study. Moreover, the suitability of existing (24,25) and evolving (25) models to estimate individual ozone exposure in epidemiologic studies was considered to be in need of further definition, as were models that have utility for a wide variety of epidemiologic study designs.

In this context, ozone exposure indices need to account for the independent and joint effects of other air pollutants. The relationship of the distribution of ozone to other pollutants (e.g., acid aerosols) was seen as playing an important role in the selection of study locations and the integration of results from studies from a number of differing geographical locations.

While issues of statistical analysis were not the principal purview of the working group, statistical issues figured prominently in the discussions. In particular, the working group felt that study designs of ozone-related health effects need to be able to incorporate new approaches to the analysis of within- and between-subject variability in response to given ozone exposures. Moreover, this variability, particularly within individuals, was considered an important endpoint for study in its own right, especially given the evolutionary adaptation to ozone that has been observed in some controlled exposure studies (26,27).

**Research Questions for the Study of Ozone-Induced Health Effects**

The working group established a series of discrete questions to which the members have addressed their presentations. Within the framework of a particular question, a brief background is presented that is intended to provide a context for the discussion rather than a comprehensive summary of available research data. Where appropriate, issues of exposure assessment and the specification of a range of study designs are discussed or very specific designs are suggested (28,29). In these latter cases, the designs that are presented are done so because the working group felt that the illustration of a specific design best captured the research needs in question. Finally, while several of the papers discuss issues of analysis, the overall views of the working group have been synthesized in a single, more statistically oriented presentation (30).

The following questions reflect the synthesis of the working group's deliberation and the guideline for the articles in this volume.

**Chronic Effects and Processes**

What study (studies) is (are) required to determine whether ozone causes chronic health effects? How can population studies be utilized to determine if respiratory bronchiolitis is caused by ozone? Is premature aging of the lung related to this process (as a consequence
Acute Effects

What is the full range of acute outcomes due to ozone exposure, and which of these outcomes relate to specific chronic disease outcomes and chronic changes in physiological processes?

Sensitive/Susceptible Populations with Regard to Ozone Exposure

Are there sensitive subpopulations in relation to ozone exposure and how can they be identified? What laboratory-based endpoints are almost ready for use in epidemiologic studies? What new laboratory-based endpoints need to be developed for the identification of susceptible individuals in epidemiologic studies? What is the relationship of the epidemiology of asthma to ozone exposure?

Analytical Issues

What are the important (and new) issues required in the design and/or the analysis of epidemiologic studies of the health effects of ozone? What study designs most appropriately reflect the need to study biological variability in response to acute and chronic exposure to ozone?

The paper of the working group address each of these issues separately. A concluding paper (e.g.) will pull together common threads that appear throughout each of the sections to highlight the central research issues that will form the basis for specific recommendations.

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