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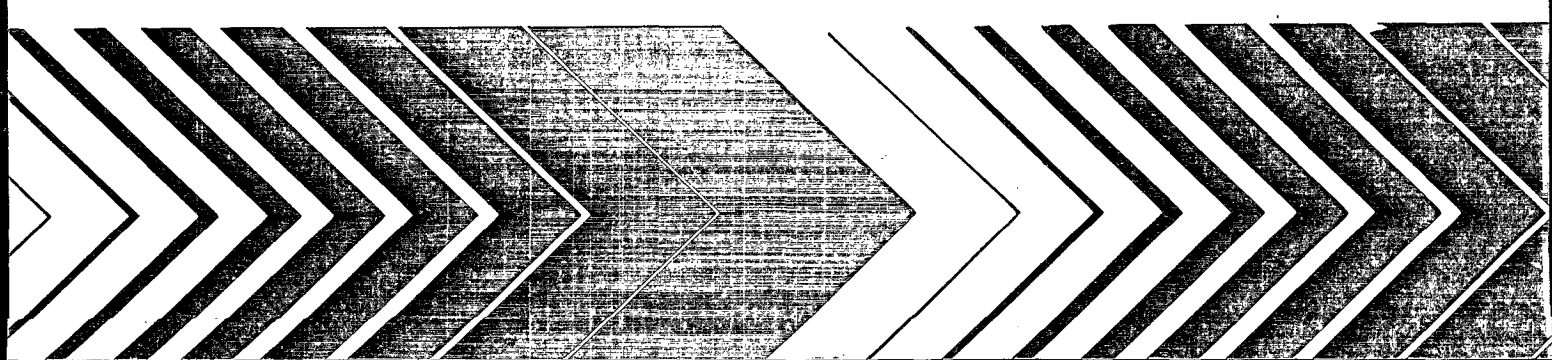

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SUMMARY OF SELECTED NEW INFORMATION ON EFFECTS OF OZONE ON HEALTH AND VEGETATION

Supplement
to
Air Quality Criteria for Ozone
and Other Photochemical Oxidants

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Office of Research and Development
Research Triangle Park, NC 27711

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ABSTRACT

Since completion of the 1986 air quality criteria document for ozone, additional information has become available that warrants consideration by the U.S. Environmental Protection Agency (U.S. EPA) in its review of the National Ambient Air Quality Standards (NAAQS) for ozone. This summary reviews and evaluates selected literature published from 1986 through early 1989 on the vegetation and health effects resulting from exposure to ozone. Emphasis has been placed on evaluation of key human health effects literature and other data most pertinent to determination by U.S. EPA of the appropriate level and form of the primary NAAQS and the appropriate form of the secondary NAAQS.

AUTHORS

Dr. Daniel L. Costa, Health Effects Research Laboratory, OHR, ORD, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711.

Dr. Lawrence J. Folinsbee, C. E. Environmental, Inc., Suite 200, 800 Eastowne Drive, Chapel Hill, North Carolina 27514.

Mr. James A. Raub, Environmental Criteria and Assessment Office, MD-52, OHEA, ORD, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711.

Ms. Beverly Tilton, Environmental Criteria and Assessment Office, MD-52, OHEA, ORD, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711.

Dr. David T. Tingey, Environmental Research Laboratory, OEPER, ORD, U.S. Environmental Protection Agency, 200 S.W. 35th Street, Corvallis, Oregon 97333.

CONTRIBUTORS AND REVIEWERS

Dr. Robert S. Chapman, Dr. Timothy R. Gerrity, Dr. Carl G. Hayes, Dr. Donald H. Horstman, Dr. Hillel S. Koren, Dr. William F. McDonnell, Dr. Frederick J. Miller, and Dr. John H. Overton, Health Effects Research Laboratory, OHR, ORD, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711.

Dr. Lester D. Grant and Dr. Judith A. Graham, Environmental Criteria and Assessment Office, OHEA, ORD, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711.

Dr. Milan J. Hazucha, Center for Environmental Medicine and Lung Biology, The University of North Carolina, Chapel Hill, North Carolina 27514.

Dr. William Hogsett, Environmental Research Laboratory, OEPER, ORD, U.S. Environmental Protection Agency, 200 S.W. 35th Street, Corvallis, Oregon 97333.

Dr. Allan Marcus, Battelle-Applied Statistics, 200 Park Drive, P.O. Box 12056, Research Triangle Park, North Carolina 27709.

Dr. James H. Ware, Harvard University, School of Public Health, Department of Biostatistics, 677 Huntington Avenue, Boston, Massachusetts 02115.

1. SUMMARY OF SELECTED NEW INFORMATION ON EFFECTS OF OZONE ON HEALTH AND VEGETATION

1.1 INTRODUCTION

The U.S. Environmental Protection Agency (U.S. EPA) document, *Air Quality Criteria for Ozone and Other Photochemical Oxidants*, completed in August 1986 provided comprehensive evaluation of the relevant scientific literature on ozone published through mid-1986 (U.S. Environmental Protection Agency., 1986). The criteria document was prepared by the Office of Research and Development for use as the scientific basis for decision making by the Agency regarding retention or revision of primary and secondary National Ambient Air Quality Standards (NAAQS) for ozone.

Since completion of the 1986 document, additional information has become available that warrants consideration by the Agency in its review of the NAAQS for ozone. As a supplement to the 1986 document, this summary reviews and evaluates published literature concerning exposure- and concentration-response relationships observed for vegetation effects and for health effects in humans and experimental animals. Emphasis has been placed on evaluation of new human health effects literature and other data most directly pertinent or useful for determining the appropriate level and form of the primary standard and the appropriate form of the secondary standard. Selected important data on dosimetry and on experimental animal studies that elucidate concentration $\times$ time (duration) exposure-response relationships have also been included. As required by the Clean Air Act, an earlier external review draft of this Supplement (U.S. Environmental Protection Agency, 1988) was publicly peer-reviewed by the Clean Air Scientific Advisory Committee (CASAC) of U.S. EPA's Science Advisory Board (McClellan, 1989).

The publications reviewed and evaluated in this supplement were selected from approximately 500 new articles and abstracts on the health effects of ozone and from about 300 new articles and abstracts on the vegetation effects of ozone that appeared as peer-reviewed journal publications or as proceedings papers from 1986 through early 1989. Since

the time of review by CASAC, several of the abstracts and articles previously cited in the draft supplement as "in press" or "submitted for publication" have been published. In such cases, the citation has been updated in this final version of the supplement, including several revised citations of 1989 (and a few later) publications.

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2. EFFECTS OF OZONE ON VEGETATION

2.1 STUDIES RELEVANT TO SELECTION OF THE AVERAGING TIME FOR THE SECONDARY NAAQS FOR OZONE

A review by Hogsett et al. (1988) discusses the biological, environmental, and exposure-dynamic factors (e.g., concentration, duration, frequency, threshold, respite time) that influence the magnitude of the biological responses of plants. These factors contribute to observed variability in responses, and thus become considerations in measures of exposure that best describe plant response to pollutant exposure. The various types of exposure indices that have been used historically to describe pollutant exposure were also evaluated. The ultimate goal of investigations of factors influencing plant response is to develop exposure indices that account for all of the variation in the exposure-response relationship. However, a second and more practical goal is that of developing or specifying indices useful for standard setting. An index for a standard should be simple, not site-specific, and as generic as possible.

Musselman et al. (1986) examined the influence of two different patterns of ozone (O_3) exposure on beans. The studies were conducted in a greenhouse and the plants were exposed to either a simulated ambient or a uniform O_3 concentration. The simulated ambient exposures followed the ambient exposure patterns of Riverside, CA (O_3 concentration range: 0.058 to 0.40 ppm; peak exposure duration: 0.5 to 1.5 h; and total exposure duration: 6 h). The uniform distribution was selected to match the total dose and peak concentration of the simulated ambient exposure (O_3 concentration: 0.30 or 0.40 ppm; exposure duration: 2.3 h). Exposures occurred weekly, and the plants received one, two, or three exposures before being harvested 6 days after their last exposure. Both O_3 exposures induced foliar injury and reduced plant growth; and the effects of the two distributions were not statistically different. Consequently, if the maximum concentrations and "total doses" are equal, peak shape appears not to be an important variable.

Kohut et al. (1988) examined the effect of peak concentration and exposure frequency on the responses of kidney beans to O_3. The plants were exposed to one of four O_3 exposure regimes: (1) constant exposure to 0.05 ppm daily; (2) fluctuating exposure to 0.08 ppm on

alternate days (Monday, Wednesday, and Friday); (3) cluster exposure to 0.08 ppm on three consecutive days (Wednesday, Thursday, and Friday); and (4) exposure to 0.12 ppm on two consecutive days (Thursday and Friday) or charcoal-filtered air. The exposure duration was 4 h and yielded weekly mean concentrations between 0.05 and 0.06 ppm. The test plants were grown in pots and exposed to O_3 in open-top chambers under field conditions. Plants were harvested weekly throughout the study. Although there were two replicates of each O_3 treatment, the experiment was not replicated in time. In the early harvests, the plants receiving the peak exposures were significantly impaired. By the final harvest (12 weeks), however, there were no significant effects of O_3 on any of the plant growth or yield parameters. The authors concluded that the plants integrated the impacts, and, consequently, that "...the response of the plants was related to the mean rather than the peak concentration of exposure." This conclusion is difficult to substantiate with the data, as none of the O_3 exposures produced a significant effect at the final harvest. It is therefore not possible to determine whether the various treatments differentially affected plant response.

Heagle et al. (1986) studied the responses of soybeans to chronic doses of ozone applied in two different ways. Plants were grown in the field using standard National Crop Loss Assessment Network (NCLAN) methodology except for the way in which the O_3 was dispensed. In one set, various constant amounts of O_3 were added to the ambient air for 7 h/day; for the second set, the O_3 was increased above the ambient air by proportional amounts. Although there was a constant addition of O_3 to the ambient air, in the constant-addition treatments, the resultant exposure regime was not "square wave" because the O_3 concentration in the ambient air varied throughout the exposure. The principle effect of the constant addition or proportional addition treatments was to create various levels of exposures. The O_3 concentrations were expressed as the 7-h seasonal means. The authors concluded that the two different types of exposure regimes produced identical responses. Several trends in the data, however, cast doubt on the validity of this conclusion. The authors clearly state that the proportional additions caused the more frequent occurrence of elevated concentrations, but their exposure index (the 7-h seasonal mean) failed to characterize or reflect this elevated exposure. In fact, the 7-h means for the proportional additions were lower than those for the comparable constant-addition treatments. The authors also reported that the slope of the "dose-response curve" for the proportional additions was

greater than for the constant additions. The authors speculated that an extension of the dose range might have shown significant results. The failure of the 7-h seasonal mean to adequately characterize the higher concentrations is not surprising because a previous paper (Cure et al., 1986) from the same group states that the 7-h seasonal mean was selected specifically because it was less sensitive to variations in O_3 patterns. Consequently, the conclusions of the authors must be viewed with skepticism.

Heagle et al. (1987) also evaluated the influence on tobacco yield of daily O_3 exposure duration and fluctuations in concentrations. Plants were grown in the field using standard NCLAN methodology except for the O_3-dispensing protocol. In one set of studies, various constant amounts of O_3 were added to the ambient air for 7 h/day; to the second set, the O_3 was increased above the ambient air by proportional amounts. In addition, the study compared the effects of 7- and 12-h exposures on tobacco yield. The O_3 concentrations were expressed as the 7- and 12-h seasonal means. Yield was reduced to a greater extent by 12-h than by 7-h exposures. The authors concluded that the two different types of 7-h exposure regimes (7-h constant and 7-h proportional) produced identical responses.

Additional analyses of the soybean (Heagle et al., 1986) and tobacco (Heagle et al., 1987) data sets were carried out by Rawlings et al. (1988) to evaluate various exposure indices and the influence of exposure duration on plant response. The results from the soybean data and the 12-h studies with tobacco suggested that the peaks should be given greater weight. In contrast, the 7-h studies with tobacco suggested that the arithmetic mean was sufficient and that the peaks did not require additional weighting. Rawlings et al. acknowledged that these results must be viewed with caution, because the differences in exposure profiles between the constant and proportional O_3 additions were relatively small, thus limiting the power of the experiment for determining the "best" exposure index. This same caveat also applies to the conclusions reached by the authors of the soybean (Heagle et al., 1986) and tobacco (Heagle et al., 1987) studies. The analysis of exposure duration found that 12-h exposures caused greater effects than 7-h exposures (Rawlings et al., 1988). The negative impact of the exposures did not increase linearly with exposure duration (i.e., the decrease in yield loss was not directly proportional to the increased length of exposure).

In a study by Adomait et al. (1987), white beans (*Phaseolus vulgaris*) were grown in field plots throughout southern Ontario, Canada. Plants at each location were treated with a

chemical protectant, ethylenediurea (EDU), to reduce or eliminate the impact of O_3 on yield, which was determined as the difference between the yields of EDU and non-EDU treated plots at each location. Ozone exposure was expressed as the cumulative O_3 concentrations above a threshold of 0.08 ppm for the month of August. Yield decreased as the cumulative O_3 concentration increased. The addition of temperature and rainfall to the regression equation, in an attempt to approximate O_3 flux into the plant, significantly improved the fit of the regression equation to the data. To express the experimental results, the authors assumed that the elevated O_3 concentrations (peaks) were important and that the impact was the cumulative result of multiple exposures.

Data used in a study by Cure et al. (1986) were generated using standard open-top chamber NCLAN protocols. The study did a three-way comparison of relationships among the 7-h seasonal mean, the 1-h seasonal mean, and the 1-h maximum for the season. For two of the three comparisons, the 7-h/1-h ratio was essentially constant, suggesting that these two variables differed by a constant. For the other comparison, the ratio was less stable. The authors concluded, however, that the 7-h and 1-h seasonal means were surrogates for each other. The ratio of the 1-h maximum to the 7-h seasonal mean was highly unstable, which suggests that the maximum was poorly related to the long-term mean. The authors selected a seasonal mean for two reasons: (1) They assumed that crop yield reductions resulted from an accumulation of daily O_3 effects over the growing season; and (2) the seasonal means were much less sensitive to peak variations in yearly O_3 patterns, especially at concentrations near the current ambient levels.

In a study by McCool et al. (1986), plants grown in a standard soil were exposed to a range of O_3 levels in closed-top exposure chambers and the yields were determined. The authors developed yield-loss functions that related decreased crop yield to a cumulative exposure index for 12 crops. Ozone exposure was characterized as the cumulative concentrations greater than 0.10 ppm. The concentration threshold (0.10 ppm) was chosen because it was the California state O_3 standard. A threshold concentration for O_3 was used to avoid giving equal mathematical weight to the numerous low concentrations and to ignore the low nighttime background in calculating the exposure.

In a field study using closed-top exposure chambers, McCool et al. (1987) assessed the impact of O_3 on four vegetables (turnip, beet, onion, lettuce). The exposure-response

functions were best described as a linear function with increasing exposure. Both the sum of the concentrations >0.10 ppm and the 12-h seasonal mean concentration were used in developing the exposure-response functions. Neither exposure index was uniformly best.

A 3-year field study was conducted by Smith et al. (1987) in which the effects of O_3 on foliar injury and yield were assessed using the chemical protectant EDU. Ozone exposure was characterized as the 7-h seasonal mean and as the cumulative exposure (using various concentration thresholds). The EDU treatment did not significantly enhance crop yield. Yield and foliar injury, respectively, were similar among cultivars and over years. Although the ambient O_3 exposures between 1983 and 1984 were substantially different, as indicated by the various cumulative statistics, this difference was not reflected in the 7-h seasonal mean. These data are another example of the lack of sensitivity of the mean to temporal variations in O_3 exposures.

Open-top chambers were used by Wang et al. (1986a) in a field study to examine the effects of ambient O_3 on the growth and foliar injury of three tree species. Ozone was characterized as the number of daily occurrences above 0.08 and 0.12 ppm. The authors concluded that O_3 significantly impaired the growth of hybrid poplar in the absence of visible foliar injury. There were 20 days when O_3 exceeded 0.08 ppm and 1 day when the concentration exceeded 0.12 ppm. In a 3-year study with quaking aspen, Wang et al. (1986b) found that plant growth was reduced 12 to 24%. In only one of the years was the current National Ambient Air Quality Standard for O_3 exceeded. The observations that growth reductions can occur in the absence of the ambient O_3 concentration exceeding the level of the current standard are consistent with the recent analysis of Lee et al. (1989), which forecast significant effects on crop yield when the standard was not exceeded.

Only a limited number of studies have been conducted with the specific objective of developing or evaluating various exposure indices; several studies have reanalyzed existing exposure-response data to evaluate a range of exposure indices. The results of these retrospective analyses have provided useful concepts and their conclusions are in general agreement. Because the experiments analyzed were not specifically designed to evaluate various indices, the differences among the actual exposure treatments (frequency of O_3 occurrences) may be relatively small. Consequently, the power of these studies is less than desirable.

Reanalysis of several NCLAN data sets (soybean and wheat from Argonne, IL; cotton from Shafter, CA; and alfalfa from Corvallis, OR) was performed by Lee et al. (1987) using various mean and cumulative peak-weighted exposure indices (e.g., concentration threshold and functional peak weighting). Exposure indices that included all the data (24 h) performed better than those that used only 7 h of data. The 7-h seasonal mean was never "best" and was near optimal in only 5 of 14 cases. From a modeling standpoint, the exposure indices that emphasized peaks performed better than those that gave equal weighting to all concentrations; indices that accumulated the exposures performed better than those that averaged the exposures.

In a more extensive retrospective analysis of NCLAN data, Lee et al. (1988) fit 24 common and 589 general phenologically weighted, cumulative-impact (GPWCI) exposure indices to the response data from seven crop studies (2 years of data for each). The "best" exposure indices were those that displayed the smallest residual sums of square error when the yield response data were regressed on the various O_3 exposure indices using the Box-Tidwell model. The "best" exposure index was a GPWCI with sigmoid weighting on concentration and a gamma weighting function as a surrogate for changes in plant sensitivity over time. Cumulative indices (with concentration thresholds) performed as well as the GPWCIs, whereas mean indices did not perform as well. The general conclusions of the authors were, "While no single index was deemed "best" in relating ozone exposure to plant response, the top-performing indices were those indices that (1) cumulated the hourly ozone concentrations over time, (2) used a sigmoid weighting scheme which emphasizes concentrations of 0.06 ppm and higher, and (3) phenologically weighted the exposure such that the greatest weight occurs during the plant growth stage. These findings illustrate the importance of the duration of exposure, the importance of repeated peaks, and the time of increased sensitivity in assessing the impact of ozone on plant growth." Although peak concentrations should be given greater weight, the authors suggested that lower concentrations should also be included but given lesser weight in the calculation of an exposure index.

The paper by Tingey et al. (1989) is essentially a condensation of the paper by Lee et al. (1988) and therefore the conclusions are basically the same. However, the paper does show the importance of exposure duration in influencing the magnitude of plant response and the limitation of the seasonal mean to specifically incorporate varying exposure durations.

For example, the mean cannot distinguish among exposures to the same average concentrations over different durations (e.g., for 10, 50, or 100 days).

Wheat and soybean data sets (Kohut et al., 1987, 1986) collected using standard NCLAN protocols at Ithaca, NY, were reanalyzed by Lefohn et al. (1988a) to compare exposure indices. The authors used the 7-h mean and cumulative statistics with thresholds, or peak weighting. The data were fit with both linear and Weibull response models. No one exposure statistic was best for all data sets or response models. The linear model showed no strong tendency to fit any exposure index; however, a peak-weighted statistic and the number of occurrences >0.08 ppm or the sum of the concentrations >0.08 ppm had a higher R^2 than the 7-h seasonal statistic. When the Weibull model was used, the cumulative statistics performed better than the seasonal means. The authors also concluded that a sigmoid peak-weighted scheme was better than a threshold approach because it included the effects from the concentrations below the selected threshold concentration but gave them less weight.

The paper by Lefohn et al. (1988a) has engendered discussion in the literature about the interpretation of the data (Runeckles, 1988; Parry and Day, 1988). Both groups of respondents thought that the paper contained insufficient data and evidence to support the conclusion that peak-weight exposure indices should be used in developing exposure-response functions. However, Runeckles tempered his criticism with the observation that peak-weighted indices performed at least as well as mean indices. Also, the respondents criticized the compilation of the 2 years of wheat data into a single model when the exposure durations were markedly different. In response, Lefohn et al. (1988b) stated that the wheat data support the need to include a cumulative component in an exposure index. They concluded that, "The cumulative index is more relevant to use in the standard-setting process than seasonal means, which ignore the length of the exposure period."

Musselman et al. (1988) conducted a retrospective analysis of crop loss data originally collected by Oshima et al. (1976) (see U.S. Environmental Protection Agency, 1986). The analysis was based on data for five crops, but those data were not replicated in time. The plants were grown in pots in standardized soil and were provided with adequate water and nutrients. The plants were placed at 9 to 12 sites along an ambient O_3 concentration gradient in the Los Angeles Basin. The crop loss data were originally summarized by Oshima et al.

(1976) on the basis of the cumulated concentration above 0.10 ppm for the growing season. In this study, the authors tested (1) various peak indices, (2) daily mean indices, and (3) indices based on subsets of a 24-h day. No single exposure index was "best" for the five crops. Ozone indices utilizing a concentration threshold level performed well for most crops, but the optimum threshold level varied with the particular index calculated. Some of the "better" indices were (1) seasonal mean of concentrations above 0.09, 0.12, or 0.14 ppm; (2) mean of all daily peak concentrations; (3) sum of the daily peaks squared above a concentration of 0.15 ppm; and (4) total number of seasonal peaks above 0.12 ppm. The 7- or 12-h seasonal means were not among the better-performing indices.

Larsen et al. (1988) evaluated 14 O_3 exposure indices for their ability to predict crop yield loss. The second highest daily maximum concentration and 13 other indices, including the effective mean O_3 concentration and the summer daytime average (M7), were calculated for 80 "agricultural" National Aerometric Data Bank sites and for multiple years, for a total of 320 site-years. In contrast to other retrospective analyses, separate exposure-response functions were not derived from biological data for each exposure index. Larsen et al. (1988) used ambient air monitoring data to derive correlations between the effective mean and other air quality indices. These correlations (based only on ambient air monitoring data) were used to express the plant response data in terms of the different indices (i.e., the lognormal model that expressed crop reduction as a function of the effective mean concentration [Larsen and Heck, 1984] was used to generate crop loss estimates for the 320 site-years of ambient data). Because there was no biological variation in the data, correlations between the exposure indices and estimated crop reductions were, in fact, measures of association between the (transformed) effective mean and the other indices. Consequently, no evidence that the mean indices were better correlated with plant response than other indices can be inferred from the analysis of Larsen et al. (1988).

Larsen et al. (1983) developed an exposure-response model that relates O_3 impact on plants to a cumulative index that they denoted as the total impact. A 75-day exposure for 7 h/day was originally assumed for calculating the estimated crop reduction for soybean (this may not be representative of the phenological life span of soybean). In the original analysis, the effective mean was not calculated from the hourly O_3 concentrations for the NCLAN studies but was estimated by multiplying M7 by 1.15 for charcoal-filtered and nonfiltered

exposures (and supplementing the nonfiltered exposures with the constant additions for other exposures). Further, treatment means rather than chamber means were used in estimating the lognormal model. Consequently, this lognormal model is inaccurate and needs to be estimated more precisely for use in the selection of exposure indices for use as a O_3 standard. The adequacy of the lognormal model using other exposure indices must also be determined.

Reich and Amundson (1985) have reviewed a series of field and controlled-environment studies to assess the impact of O_3 on photosynthesis. The authors stated, "...it may be inappropriate as well as difficult to compare directly the response of the species on the basis of a mean O_3 exposure concentration. However, when the responses are compared on the basis of a unit dose of O_3, the results are more easily interpreted." A unit dose of O_3 as defined by the authors means cumulative exposure (i.e., total parts per million). The O_3-induced decrease in growth was directly related to reduced photosynthesis, which was decreased by the cumulative O_3 exposure.

2.2 SUMMARY AND CONCLUSIONS: VEGETATION EFFECTS

Recent literature concerning the appropriate averaging time for an exposure index for O_3 effects on vegetation was evaluated in relation to (1) the role of exposure duration, (2) the role of peak O_3 concentrations, (3) comparison of exposure indices, and (4) evaluation of the 7-h seasonal mean.

2.2.1 Exposure Duration

Increasing the duration in the exposure index from a 7-h seasonal mean to a 12-h seasonal mean caused a greater decrease in yield. A comparison of 7- and 24-h exposure indices showed that 24-h indices provided an even better statistical fit to the exposure-response data. Although plant effects increased with exposure duration, the study of Rawlings et al. (1988) showed that the increase in plant response was not proportional to the increase in exposure duration.

All the recent studies that used impaired plant growth or yield as an adverse effect specifically selected exposure indices that might reflect the cumulative impact of effects throughout the growing season. For example, Cure et al. (1986) stated that crop yield

reductions result from an accumulation of daily O_3 effects over the growing season. Reich and Amundson (1985) stated that the O_3-induced decrease in growth was directly related to reduced photosynthesis, which was impaired by the cumulative O_3 dose. These data can be interpreted to mean that growth and yield are reduced by repeated O_3 episodes, because that is how O_3 occurred in the studies and how it occurs in nature.

These studies support the conclusion that a cumulative O_3 exposure index is needed that reflects the total exposure that the plant experiences. This conclusion is consistent with the 1986 U.S. EPA criteria document (U.S. Environmental Protection Agency, 1986), which states, "When plant yield is considered, the ultimate impact of an air pollutant on yield depends on the integrated impact of the pollutant exposures during the growth of the plant." By inference or deduction, then, a mean of unspecified time (days or months) is inappropriate because the lack of specification of "time" results in a variable duration of O_3 accumulation.

2.2.2 Peak Concentrations

Most of the recent studies, except for papers reporting results of the NCLAN program, selected exposure indices that cumulated the exposure and preferentially weighted the peaks. Three main peak-weighting approaches have been used: (1) a concentration threshold approach, in which the concentrations above the selected threshold are summed or in which the number of days or hours above the concentration threshold are summed; (2) an allometric or exponential weighting, in which all concentrations are raised to a specific exponential power; and (3) a sigmoid weighting, in which all concentrations are weighted with a multiplicative weighting factor (which depends on concentration).

The threshold weighting approach assumes that only the concentrations above the selected concentration threshold are biologically active. Recent studies have shown that the concentrations below the selected concentration threshold or cutoff may also have biological importance. It is also likely that the appropriate concentration threshold differs between species, with environmental conditions, and with endpoint measured.

Functional weighting approaches using either an allometric or sigmoid weighting are preferred to the concentration threshold approach. These approaches do not censor concentrations, but rather give weight, although not equal, to all concentrations in eliciting a

biological response. Specific comparisons of the functional weighting to the threshold approaches showed that they yielded better statistical fits to the data. Also, the sigmoid weighting functions appeared to perform better than the allometric weighting approach.

The conclusions found in recent literature regarding the importance of cumulative peak concentrations in causing vegetation responses are consistent with the data and conclusions presented in the 1986 criteria document (U.S. Environmental Protection Agency, 1986).

2.2.3 Comparison of Exposure Indices

There have been several studies (Lee et al., 1987, 1988, 1989; Lefohn et al., 1988a; Musselman et al., 1988) conducted that were retrospective analyses of existing plant-response data sets. These authors evaluated the relative efficacy of existing and proposed exposure indices, using a large number of crop data sets. The exposure indices included various means and cumulative statistics using both threshold and functional concentration weighting. The authors concluded that there was no single exposure index that was best for all crop species or for all data sets. These studies are all in agreement, however, that (1) mean indices are not among the best indices and (2) the preferred (yielded best statistical fit to the data) exposure indices cumulated the exposure impact over the growing season and preferentially weighted the peak concentrations.

2.2.4 Evaluation of the 7-Hour (or 12-Hour) Seasonal Mean

The 7-h seasonal mean is the most commonly used exposure index in the literature reviewed in the 1986 U.S. EPA criteria document (U.S. Environmental Protection Agency, 1986), and it continues to be used by investigators. Mathematically, the mean contains all hourly concentrations making up the exposure period and treats all concentrations equally, thus implying that (1) all concentrations of O_3 (across the range of concentrations to which plants are exposed in a growing season) are equally effective in causing a response, and (2) the contributions of the peak concentrations to the response are minimal. The mean treats low-level, long-term exposures the same as high-concentration, short-term exposures, a scenario that the literature does not support (e.g., the 1986 U.S. EPA criteria document). An infinite number of hourly distributions, from those containing many peaks to those containing none, can yield the same 7-h seasonal mean. Cure et al. (1986) reported that mean

characterizations of O_3 exposure were much less sensitive than the daily 1-h maximum to variations in yearly O_3 patterns. Also, Reich and Amundson (1985) stated, "...it may be inappropriate as well as difficult to compare directly the response of species on the basis of a mean O_3 exposure concentration. However, when the responses are compared on the basis of a unit dose of O_3, the results are more easily interpreted."

The use of a mean exposure index for characterizing exposures implies certain assumptions.

1. A seasonal mean assumes that crop yield reductions result from the accumulation of daily O_3 effects over the growing season (Cure et al., 1986).

2. A mean assumes that the distribution of hourly O_3 concentrations (over the averaging time) are not highly skewed and that the distribution is unimodal. In the ambient, the O_3 concentration distributions are frequently skewed toward the higher concentrations.

3. The mean weights all concentrations within the selected averaging time equally.

4. The mean does not specifically include an exposure duration component; it cannot distinguish between two exposures to the same concentration but of different durations (e.g., 50 or 100 days).

5. The mean assumes that the selected time interval, over which the concentrations are averaged, is the period of highest hourly occurrences of O_3 or any other pollutant being examined.

6. The mean index assumes that peak events do not need to be given special consideration. This is not consistent with results showing that short-term peak concentrations are important in determining vegetation response (see, e.g., the 1986 U.S EPA criteria document).

The correlation between the 7-h seasonal mean (M7) and the second-highest daily maximum 1-h concentrations (i.e., HDM2, the current O_3 standard) was low ($r = 0.54$) due to the insensitivity of peak concentrations in the M7 calculation (Lee et al., 1989). A wide range of temporal distributions with HDM2 between 0.06 and 0.24 ppm was found at sites with M7 values between 0.036 and 0.048 ppm. Temporal distributions of ambient O_3 data at 83 nonurban sites showed large spatial differences across these sites, with the HDM2 ranging

from 0.06 to 0.24 ppm. In contrast, the 7-h seasonal mean (M7 calculated from May to September) across the 83 sites showed small differences (i.e., 90% of the sites had M7 values between 0.03 and 0.06 ppm).

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3. EFFECTS OF OZONE ON HEALTH

3.1 HEALTH STUDIES RELEVANT TO SELECTION OF THE PRIMARY NAAQS FOR OZONE

3.1.1 Human Clinical Studies

The strongest and most quantifiable concentration-response data on the acute health effects of ozone (O_3) are provided by the controlled human exposure studies, in which significant decrements in pulmonary function have been reported (U.S. Environmental Protection Agency, 1986). In most of these studies, the greatest attention has been focused on decrements in forced expiratory volume in 1 s (FEV_1) because this measure of lung function represents a summation of changes in both lung volume and resistance. At the lower O_3 concentrations of interest for standard-setting (≤0.12 ppm), however, the observed decrements in FEV_1 primarily reflect decrements in forced vital capacity (FVC), with little or no contribution from changes in airway resistance. These changes in FEV_1 are caused by a reduced inspiratory capacity that most likely results from sensitization or stimulation of airway irritant receptors.

Scientific evidence presented in the 1986 U.S. EPA criteria document (U.S. Environmental Protection Agency, 1986) established that pulmonary function decrements are generally observed in healthy adults after 1 to 3 h of exposure as a function of the level of exercise performed and the O_3 concentration inhaled during the exposure. Decrements in lung function have been reported to occur in some groups of healthy adults at the current level of the standard (0.12 ppm) or somewhat higher. Also, pulmonary function decrements have been observed in children and adolescents at concentrations of 0.12 ppm and 0.14 ppm, respectively, with heavy exercise. At the lower O_3 concentrations in the range 0.12 to 0.16 ppm, the average group mean changes in lung function are generally small (≤6%), and the medical significance of these changes is a matter of controversy. Some individuals, however, are intrinsically more responsive to O_3 than others and exhibit noticeably larger-than-average pulmonary function decrements than the rest of the group. Such larger (>10%) decrements in lung function may be of some medical significance to the affected individuals.

More recent controlled human exposure studies appearing after the completion of the 1986 criteria document have further confirmed and extended the above types of findings, as well as demonstrating some additional new types of effects. The most pertinent of these newer studies are summarized in Table 3-1. The newer studies noted in Table 3-1 add most extensively to our knowledge concerning pulmonary function decrements associated with acute O_3 exposures near the current 1-h NAAQS for O_3. The newer pulmonary function decrement findings are summarized in Table 3-2 in relation to the earlier such findings previously discussed in the 1986 criteria document.

Two of the more recent studies, by Linn et al. (1986) and Avol et al. (1987), add to the information reviewed in the 1986 U.S. EPA criteria document (U.S. Environmental Protection Agency, 1986) on lung function changes occurring in healthy children and young adults exposed to low concentrations of O_3 while exercising at moderate to heavy loads. Data presented by Linn et al. (1986) in a controlled human study of healthy young adults exercising intermittently at heavy work loads have added more detailed concentration-response information at low O_3 concentrations ranging from 0.08 to 0.16 ppm. The O_3 responsiveness of subjects in this study falls somewhere between that of subjects studied by McDonnell et al. (1983) and of those studied by Kulle et al. (1985) under similar exposure conditions (see Table 3-2). These subjects were also less responsive than the group previously studied by Avol et al. (1984), who were exposed to similar concentrations of O_3 but with continuous exercise for 1 h. Although the authors of this report could not offer a definitive explanation for differences among these studies, they pointed out that individual biological factors such as the presence of asthma or clinical respiratory allergies and bronchial reactivity in individual subjects, as well as external factors such as ambient exposure history or differences in controlled exposure conditions during the study, might contribute to differences in cohort responsiveness to O_3. It is obvious that more research is needed to better define the possible reasons for the large variations in responsiveness to O_3 in individuals and the variations in group mean responsiveness across studies.

Avol et al. (1987) presented data from a laboratory field study of healthy children (8 to 11 years old) exercising continuously for 1 h in ambient air containing a mean O_3 concentration of 0.11 ppm. The same authors (Avol et al., 1985a,b) previously studied adolescent subjects (12 to 15 years old) under a similar protocol, although the

TABLE 3-1. CONTROLLED HUMAN EXPOSURE LABORATORY STUDIES RELEVANT TO REVIEW OF THE 1-HOUR NAAQS FOR OZONE (O_3)

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Exposure Duration and Activity[a]	No., Sex, and Age of Subjects	Observed Effects[b]	Conclusions	Reference
0 221	0.00 0.113[c]	1 h, CE ($\dot{V}_E$ = 22 L/min) 33 °C and 43% rh	66 children 33 males, 33 females 8 to 11 years old	Forced expiratory function and symptoms in the group showed no statistically significant responses to 0.113 ppm O_3 in ambient air when compared to purified air; there were no gender differences. Regression analysis of individual data indicated a significant ($p < 0.05$) trend toward decreased forced expiratory function with increasing O_3 concentration.	The responsiveness of children to ambient O_3 exposure is qualitatively similar to that of adolescents and adults, although definitive comparisons among age groups were not possible because of differing ambient exposure levels and large intersubject variability in responsiveness to O_3	Avol et al. (1987)
0 882	0.00 0.45	2 h, IE (20/20) $\dot{V}_E$ = 26 L/min 3 exposures	8 males, 8 females 51 to 76 years old	Group mean changes in FVC were similar for the three exposures (-4.6, -5.8, -4.2%), but individual responses were variable.	In older subjects, O_3 responsiveness may be variable from time to time.	Bedi et al. (1988)
0 882	0.00 0.45	2 h, IE (20/20) $\dot{V}_E$ = 25 L/min	8 males, 8 females 51 to 76 years old 8 males, 8 females 19 to 26 years old	Decreases in spirometry were slightly greater in older women (FVC = 7.1%, FEV_1 = -7.0%) than in older men (-3.5%, -4.2%) despite higher average $\dot{V}_E$ in men. Ratio of exercise $\dot{V}_E$ to FVC was larger in women (9.5) than men (6.3). Older subjects (FVC = -5.3%; FEV_1 = -5.6%) had less response than young subjects (FVC = -14.1%; FEV_1 = -17.8%) under same exposure conditions.	Spirometry effects in older subjects are smaller than in younger subjects for similar O_3 exposure.	Drechsler-Parks et al. (1987) Drechsler-Parks et al. (1989)
0 784	0.0 0.4	2 h, IE ($\dot{V}_E$ = 30 L/min/m^2, ≈53 L/min)	10 normal 18 to 35 years old	Subjects were exposed to O_3 with no medication, placebo, or indomethacin prior to exposure. Changes in FVC were -19.1, -12.6, -6.8%, respectively. In previous study with the same protocol (Kreit et al., 1989), FVC change was -9.4%. Spirometry changes in this group of normal subjects were greater than in the asthmatics. Indomethacin reduced FVC change but did not alter change in airway response to methacholine.	Indomethacin partially blocks O_3-induced restrictive pulmonary function changes, but not changes in airway responsiveness.	Eschenbacher et al. (1989)

TABLE 3-1 (cont'd). CONTROLLED HUMAN EXPOSURE LABORATORY STUDIES RELEVANT TO REVIEW OF THE 1-HOUR NAAQS FOR OZONE (O_3)

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Exposure Duration and Activity[a]	No., Sex, and Age of Subjects	Observed Effects[b]	Conclusions	Reference
0 235	0.00 0.12	6.6 h, IE ($\dot{V}_E$ = 40 L/min); (6) 50-min exercise periods + 10-min rest, 45-min lunch; 18 °C and 40% rh	10 males 18 to 35 years old	Forced expiratory and inspiratory spirometry measured before exposure and after each exercise period showed a progressive fall in lung function during 6.6-h exposure to 0.12 ppm O_3; FEV_1 decreased 13.6%, FVC decreased 8.5%, and $FEF_{25-75\%}$ decreased 17.4% by the end of exposure. FIVC and $FIV_{0.5}$ decreased 12.6% and 20.7%, respectively. No changes observed with clean air exposure. Increases in symptom ratings of cough and pain on deep inspiration observed with O_3 exposure but not with clean air. Airway reactivity to methacholine more than doubled following O_3 exposure.	Prolonged exposure to 0.12 ppm O_3 at moderate exercise levels results in a marked increase in airway reactivity to methacholine and progressive changes in respiratory function and symptoms.	Folinsbee et al. (1988)
0 686	0.00 0.35	1 h, CE ($\dot{V}_E$ = 40 L/min)	18 females 19 to 28 years old	Post-O_3 exposure FVC = -14%; FEV_1 = -22%; $FEF_{25-75\%}$ = -32%; small residual effects were present 18 h later, FVC = -3%, FEV_1 = -4%. Airway responsiveness to methacholine increased after O_3 exposure.	Minor effects in spirometry following O_3 exposure may persist for 18 h.	Folinsbee and Hazucha (1989)
0 784	0.00 0.40	1 h, CE ($\dot{V}_E$ = 40 L/min)	20 males 18 to 35 years old	V_T decreased 25% and f_b increased 45% with ozone exposure. FVC (-13%) and FEV_1 (-18%) also decreased. Change in breathing pattern caused reduction in lower respiratory tract (LRT, -17%) O_3 uptake.	Decreased LRT uptake was due to decreased tidal volume.	Gerrity and McDonnell (1989)
0 196 392 784	0.00 0.10 0.20 0.40	nasal, mouth, and oronasal breathing @12 and 24 bpm	18 males 18 to 35 years old	Removal of O_3 by extrathoracic (nose and mouth) airways and intrathoracic airways was measured during nasal, mouth, and oronasal breathing at 12 and 24 bpm at O_3 concentrations of 0.1, 0.2, and 0.4 ppm. Overall, 39.6 $\pm$ 0.7 (SEM)% of inspired O_3 was removed by extrathoracic airways and 91.0 $\pm$ 0.5% of the remaining O_3 removed by intrathoracic airways. Significant effects of breathing frequency, mode of breathing, and O_3 concentration were of little biological significance.	This study provides information on the distribution of inspired O_3 in the respiratory tract of humans that will contribute to (1) better definition of O_3 dose-response relationship and (2) potential extrapolations of chronic pulmonary effects of O_3 from laboratory animals to humans.	Gerrity et al. (1988)

TABLE 3-1 (cont'd). CONTROLLED HUMAN EXPOSURE LABORATORY STUDIES RELEVANT TO REVIEW OF THE 1-HOUR NAAQS FOR OZONE (O_3)

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Exposure Duration and Activity[a]	No., Sex, and Age of Subjects	Observed Effects[b]	Conclusions	Reference
0 235 392	0.00 0.12 0.20	Competitive conditions: CE ($\dot{V}_E$ = 89 L/min) for 1 h followed by CE ($\dot{V}_E$ = 150 L/min) until exhaustion @ 31 °C and 38% rh	17 endurance cyclists 15 males 2 females 24 ± 3 years old	$\dot{V}_E$ (89 L/min), $\dot{V}O_2$ (51 mL/min/kg), work load (260 W), and work time (57 min) were similar for all exposures during submaximal exercise at 70% $\dot{V}O_2$ max; during maximal exercise, significant reductions in peak $\dot{V}_E$ (18%), $\dot{V}O_2$ (16%), tidal volume (22%), work load (8%), and ride time (30%) occurred at 0.20 ppm O_3 compared to filtered air. Significant post-exercise decrements in FEV_1 averaged 5.6% and 21.6% at 0.12 and 0.20 ppm O_3, respectively. Respiratory symptoms were mild at 0.12 ppm O_3 but intensified to limit maximal performance in 13 subjects at 0.20 ppm O_3. Histamine airway responsiveness increased in 9 subjects after exposure to 0.20 ppm O_3 as compared with 1 subject at 0.12 ppm.	Exposure of heavily exercising endurance athletes to 0.20 ppm O_3 for 1 h in a hot environment leads to impairment of maximal exercise performance large decrements in FEV_1 (21.6%) and FVC (19.1%), increase in airways responsiveness to histamine, and potentially limiting O_3-related respiratory symptoms. Exposure to 0.12 ppm O_3 does not limit exercise performance despite mild symptoms and small decrements in FEV_1 (5.6%) and FVC (7.6%).	Gong et al. (1986)
0 157 196 235	0.00 0.08 0.10 0.12	6.6 h, IE (20/20) $\dot{V}_E$ = 40 L/min	21 males 18 to 33 years old	Significant increases in airway responsiveness to methacholine were observed after exposure to all levels of O_3; $PD100_{AIR}/PD100_{03}$ were 1.56, 1.89, and 2.21 at 80, 100, and 120 ppb. $FEV_{1.0}$ decreases averaged 7, 7, and 12.3%, respectively. Small but significant increases in respiratory symptoms also occurred.	Long duration exposure to O_3 levels as low as 80 ppb causes spirometry decrements and increased airway responsiveness.	Horstman et al. (1988, 1989)
784	0.4	30 min, CE ($\dot{V}_E$ = 30 L/min)	11 males, 6 females healthy 18 to 31 years old	No significant differences in mean decrements in FVC (4.5%), FEV_1 (5.9%), or respiratory symptoms were found between the two modes of inhalation (oral vs. nasal).	No differences in pulmonary function or respiratory symptoms were found between oral and nasal breathing of O_3.	Hynes et al. (1988)

TABLE 3-1 (cont'd). CONTROLLED HUMAN EXPOSURE LABORATORY STUDIES RELEVANT TO REVIEW OF THE 1-HOUR NAAQS FOR OZONE (O_3)

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Exposure Duration and Activity[a]	No., Sex, and Age of Subjects	Observed Effects[b]	Conclusions	Reference
0 784	0.0 0.4	2 h, IE ($\dot{V}_E$ = 67 L/min) @15 min intervals	8 males 20 to 30 years old	Increased respiratory symptoms (cough and chest tightness) and SR_{aw} (71%), decreased FVC (14%), after 2 h exposure to O_3 when compared to exposure in clean air. Pulmonary clearance of ^{99m}Tc-DTPA, measured 75 min after exposure, was increased in 7/8 subjects with a group mean increase from 0.59 to 1.75% min. There was no relationship between O_3-induced change in lung function and increased radiolabeled DTPA clearance.	Ozone exposure causing decrements in lung function and increased respiratory symptoms also caused an increase in respiratory epithelial permeability, as measured by radiolabeled DTPA clearance.	Kehrl et al. (1987, 1989)
0 235 353	0.00 0.12 0.18	40 min (30 rest, 10 exercise) @ $\dot{V}_E$ = 33 L/min	4 males, 9 females healthy 14 to 19 years old 8 males, 8 females asthmatic 11 to 19 years old	No difference between air and O_3 exposure at 0.12 ppm. R_T increased after 0.18 ppm in both healthy and asthmatic subjects. FEV_1 did not change significantly.	No differences between healthy and asthmatic subjects.	Koenig et al. (1987)
0 235	0.00 0.12	1 h, IE ($\dot{V}_E$ = 33 L/min)	5 males, 7 females healthy 12 to 18 years old 9 males, 3 females asthmatic 12 to 18 years old	In the asthmatics, $\dot{V}$50% VC decreased -4.5% after air exposure, -11% after O_3 exposure, and -4% after O_3 + NO_2 (0.12 ppm) exposure. Changes in FVC and FEV_1 were similar with air or O_3 exposure. No significant changes in healthy subjects.	A small but significant effect of O_3 was observed in adolescent allergic asthmatics exposed to 0.12 ppm for 1 h.	Koenig et al. (1988)
0 784	0.00 0.40	2 h, IE (15/15) $\dot{V}_E$ = 70 L/min	11 males 18 to 35 years old	FEV_1 decreased 960 mL. Postexposure (18 h) BAL revealed 8× increase in PMN; 2× increase in albumin, protein, and IgG; 6× increase in fibronectin; and 2× increase in PGE_2 and C3a. Preliminary evidence suggests increased PMNs after 6.6 h of 0.01 ppm O_3 exposure.	Ozone causes inflammation, increased permeability, and stimulation of fibrogenesis. Inflammation persists for at least 18-h postexposure.	Koren et al. (1988a,b; 1989a,b)

TABLE 3-1 (cont'd). CONTROLLED HUMAN EXPOSURE LABORATORY STUDIES RELEVANT TO REVIEW OF THE 1-HOUR NAAQS FOR OZONE (O_3)

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Exposure Duration and Activity[a]	No., Sex, and Age of Subjects	Observed Effects[b]	Conclusions	Reference
0 784	0.00 0.40	2 h, IE ($\dot{V}_E$ = 30 L/min/m^2, ≈53 L/min)	5 females, 4 males healthy 19 to 31 years old 5 females, 4 males asthmatic 18 to 34 years old	Normal subjects FVC (-9.4%) and FEV_1 (-13.2%) decreased after O_3. Asthmatic responses were larger [FVC (-14.8%); FEV_1 (-24.0%)]. Change in SR_{aw} (corrected for air exposure) was 0.98 units in normals and 4.2 units in asthmatics. (Ratio of % SR_{aw} increase in air to % SR_{aw} increase with O_3 was approximately 2 for both normals and asthmatics.) The SR_{aw} and FEV_1 responses were significantly larger in asthmatics than normals. Both groups had similar increases in methacholine responsiveness.	Asthmatics have larger changes in airway resistance (obstruction) than normals, but not greater changes in airway responsiveness or in the restrictive (i.e., lung volume) component of O_3-induced decrement in spirometry (i.e., FVC).	Kreit et al. (1989)
0 120-140 245-260	0.00 0.06-0.07 0.12-0.13	16-28 min progressive maximum exercise ($\dot{V}_E$ = 30-120 L/min)	12 males, 12 females young	Maximum performance time was reduced for tests conducted during O_3 exposure. In female subjects exposed to 0.13 ppm performance was reduced 11%. Minimal, inconsistent changes were seen in FEV_1. Increase in symptoms of irritation, cough, etc., after tests in O_3.	Brief high intensity exercise during O_3 exposure may be associated with slight decrements in indices of physical performance.	Linder et al. (1988)
0 157 196 235 274 314	0.00 0.08 0.10 0.12 0.14 0.16	2 h, IE ($\dot{V}_E$ = 68 L/min) @15 min intervals 32 °C and 38% rh	24 males 18 to 33 years old	Forced expiratory function and symptoms in the group showed no statistically significant changes after exposure to 0.08 to 0.14 ppm O_3; mean FEV_1 increased 1.1% and decreased 2.3% following 1 and 2 h of exposure to 0.16 ppm O_3, respectively, without respiratory symptoms. Two individual subjects responded at 0.14 ppm O_3, and one of them also responded at 0.12 ppm O_3.	Only a mild irritant response was found in a group of young subjects intermittently exercising at heavy work loads during exposure to 0.16 ppm O_3 for 2 h. The subjects were well-conditioned and free of asthma or clinical respiratory allergies and bronchial reactivity, possibly accounting for the observations.	Linn et al. (1986)

TABLE 3-1 (cont'd). CONTROLLED HUMAN EXPOSURE LABORATORY STUDIES RELEVANT TO REVIEW OF THE 1-HOUR NAAQS FOR OZONE (O_3)

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Exposure Duration and Activity[a]	No., Sex, and Age of Subjects	Observed Effects[b]	Conclusions	Reference
0 353	0.00 0.18	2 h, IE ($\dot{V}_E$ = 35 L/min/m^2)	5 males, 7 females responders 19 to 40 years old 8 males, 5 females nonresponders 18 to 34 years old	Responders (R) and nonresponders (NR) were selected after O_3 exposure of 59 subjects in spring 1986. R had more atopic and asthmatic subjects and ΔFEV_1 averaged -12.4%. NR were all normal and had no change in FEV_1. After summer O_3 session, R experienced smaller changes in FEV_1. Reduced response persisted for several months, but responsiveness returned in spring 1987. NR remained nonresponsive throughout the study.	Frequent ambient O_3 exposure may result in persistent reduction in O_3 responsiveness of O_3-sensitive subjects.	Linn et al. (1988) Avol et al. (1988) Hackney et al. (1989) Hackney and Linn (1989)
0 353	0.00 0.18	2 h, IE ($\dot{V}_E$ = 64 L/min) @15 min intervals	26 males with allergic rhinitis 18 to 30 years old	Increased ($p < 0.01$) respiratory symptoms (cough, shortness of breath, and pain upon deep inspiration) and SR_{aw}, decreased FVC, FEV_1, and $FEF_{25-75\%}$, after 2 h exposure to O_3 when compared to exposure in clean air (CA). Airway reactivity to histamine (PC_{50}) also increased ($p < 0.01$) following O_3. After 60 min recovery in CA, significant decrements in lung function and increased symptoms were still present; some of these persisted for as long as 165 min after exposure. There were no differences in FRC, V_T, f_b, or $\dot{V}_E$ during exposure or recovery. Correlation coefficients between baseline PC_{50} and lung function/symptoms were not significant.	Allergic rhinitis subjects without history of asthma-like symptoms not more reactive to histamine than subjects without rhinitis and had similar responses to O_3, with exception of modest increase in bronchoconstriction. Baseline airway reactivity to histamine in this group not associated with the magnitude of responses to O_3, as measured by lung function and respiratory symptoms.	McDonnell et al. (1987)
0 392 588	0.0 0.2 0.3	1 h (mouthpiece), IE ($\dot{V}_E$ = 29 L/min for males, 23 L/min for females)	9 males, 10 females 55 to 74 years old	R_T increased 13% in female subjects at 0.3 ppm ($p < 0.027$); no significant changes in males; no significant changes in symptoms.	Older, healthy subjects are no more susceptible to O_3 than are healthy adolescents.	Reisenauer et al. (1988)

TABLE 3-1 (cont'd). CONTROLLED HUMAN EXPOSURE LABORATORY STUDIES RELEVANT TO REVIEW OF THE 1-HOUR NAAQS FOR OZONE (O_3)

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Exposure Duration and Activity[a]	No., Sex, and Age of Subjects	Observed Effects[b]	Conclusions	Reference
0 235 353 470	0.00 0.12 0.18 0.24	1 h (mouthpiece), CE ($\dot{V}_E$ = 86.6 L/min) 30-min warm-up + 30-min endurance 23-26 °C and 45-60% rh	10 males endurance athletes 19 to 29 years old	All subjects completed filtered air exposure, but significant increase in inability of subjects to complete competitive simulations with increasing O_3 concentration. That is, 1, 5 ($p < 0.10$) and 7 ($p < 0.05$) subjects did not complete the 0.12, 0.18, and 0.24 ppm O_3 exposures, respectively. Significant decreases ($p < 0.05$) in FVC (7.8 and 9.9%) and FEV_1 (5.8 and 10.5%) following the 0.18 and 0.24 ppm O_3 exposures, respectively. No significant O_3 effect on exercise respiratory metabolism or ventilatory patterns, but the number of respiratory symptoms significantly increased with 0.18 and 0.24 ppm O_3 exposures.	This study demonstrates that significant impairment of exercise performance and pulmonary function occurs along with increased respiratory symptoms following exposure of well-trained endurance athletes to O_3 levels $\geq$ 0.18 ppm while engaged in 1 h exercise protocol simulating competition.	Schelegle and Adams (1986)
0 686	0.00 0.35	1 h (mouthpiece), CE ($\dot{V}_E$ = 60 L/min)	14 males 18 to 34 years old	Pretreatment with indomethacin, a prostaglandin synthetase inhibitor, significantly ($p < 0.05$) reduced O_3-induced decrements in FVC and FEV_1. Exercise V_T and respiratory symptoms also reduced.	Cyclooxygenase products of arachidonic acid may play a role in the development of O_3-induced pulmonary function decrements.	Schelegle et al. (1987)
0 784 1,176	0.0 0.4 0.6	2 h, IE (83 W for women, 100 W men) @15 min intervals 71.5 °C, 55% rh	10 adults 3 females, 7 males 23 to 41 years old	Increased airway reactivity to methacholine (MCh) at 0.4 ppm ($p < 0.025$) and 0.6 ppm ($p > 0.01$). Increased neutrophils in BAL of O_3-exposed subjects, particularly those with increased MCh airway reactivity. Also prostaglandin E_2, $F_{2\alpha}$, and thromboxane B_2 increased in lavage fluid 3 h after O_3 exposure.	Ozone-induced airway reactivity to methacholine is associated with neutrophil influx into the airways and changes in cyclooxygenase metabolites of arachidonic acid.	Seltzer et al. (1986)

[a]Activity level: CE = continuous exercise, $\dot{V}_E$ = minute ventilation, rh = relative humidity, IE = intermittent exercise, bpm = breaths per minute, W = watts.
[b]FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 s, $\dot{V}_E$ = minute ventilation, FEF = forced expiratory flow, FIVC = forced inspiratory vital capacity, $FIV_{0.5}$ = forced inspiratory volume in 0.5 s, V_T = tidal volume, f_b = breathing frequency, SEM = standard error of the mean, $\dot{V}O_2$ = maximal oxygen uptake, $PD100_{AIR}$, $PD100_{O_3}$ = provocative dose of bronchoconstrictor producing a doubling of baseline specific airway resistance after exposure to air and O_3, respectively, SR_{aw} = specific airway resistance, ^{99m}Tc-DTPA = radiolabeled diethylene triamine pentacetic acid, R_T = total respiratory resistance, $\dot{V}50\%VC$ = maximum expiratory flow at 50% of vital capacity, NO_2 = nitrogen dioxide, BAL = bronchoalveolar lavage, PMN = polymorphonuclear leukocyte, IgG = immunoglobulin G, PGE_2 = prostaglandin E_2, C3a = complement fraction, FRC = functional residual capacity.
[c]Ozone concentration of ambient air.

TABLE 3-2. KEY HUMAN STUDIES DEMONSTRATING LUNG FUNCTION DECREMENTS NEAR THE CURRENT 1-HOUR NAAQS FOR OZONE

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Measurement Method[a,b]	Exposure Duration	Activity Level ($\dot{V}_E$)[c]	Percent Change in FEV_1[d]	Number, Sex, and Age of Subjects	Reference[e]
0 157	0.00 0.08	UV, UV	1 h	CE (57)	+0.6 +1.7 (ns)	42 male 8 female (26.4 ± 6.9 years)	Avol et al. (1984)
0 157 196 235	0.00 0.08 0.10 0.12	UV, UV	2 h	IE (68)	+1.0 +2.4 (ns) +1.7 (ns)	24 male (18-33 years)	Linn et al. (1986)
0 157 196 235	0.00 0.08 0.10 0.12	CHEM, UV	1 and 2 h of 6.6 h study	CE (40)	-1.5 (1 h) -1.0 (2 h) -0.4 (ns) -1.1 (ns) -1.3 (ns) -1.3 (ns) -0.5 (ns) -2.7 (ns)	21 male (18-33 years)	Horstman et al. (1988)
0 196	0.00 0.10	UV, UV	2 h	IE (68)	+1.5 +1.1 (nd) range: +10 to -4	20 male (25.3 ± 4.1 years)	Kulle et al. (1985)
0 196	0.00 0.10	CHEM, NBKI	2 h	IE (67)	-0.3 -2.6 (ns)	10 male (18-28 years)	Folinsbee et al. (1978)
0 216	0.00 0.11[f]	UV, UV	1 h	CE (22)	-2.7 -2.9 (ns)	33 male 33 female (8-11 years)	Avol et al. (1987)
0 235	0.00 0.12	CHEM, UV	2 h	IE (68)	-1.0 -4.5 ($p = 0.016$)[g] range: +7 to -16	22 male (22.3 ± 3.1 years)	McDonnell et al. (1983)
0 235	0.00 0.12	CHEM, UV	2 h	IE (39)	-0.5 -3.4 ($p = 0.03$) range: +5 to -22	23 male (8-11 years)	McDonnell et al. (1985a,b)

TABLE 3-2 (cont'd). KEY HUMAN STUDIES DEMONSTRATING LUNG FUNCTION DECREMENTS NEAR THE CURRENT 1-HOUR NAAQS FOR OZONE

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Measurement Method[a,b]	Exposure Duration	Activity Level ($\dot{V}_E$)[c]	Percent Change in FEV_1[d]	Number, Sex, and Age of Subjects	Reference[e]
0 235	0.00 0.12	CHEM, UV	1 and 2 h of 6.6 h study	CE (40)	-0.2 (1 h) -1.2 (2 h) -2.6 (ns) -3.8 (ns)	10 male (18-33 years)	Folinsbee et al. (1988)
0 235	0.00 0.12	UV	1 h (mouthpiece)	R	-1.1 0.0 (ns)	4 male 6 female (13-18 years)	Koenig et al. (1985)
0 235 353	0.00 0.12 0.18	UV	40 min (mouthpiece)	IE (33) 30 min R + 10 min exercise	-1.0 +1.7 (ns) -0.3 (ns)	5 male 7 females (11-19 years)	Koenig et al. (1987)
0 235	0.00 0.12	UV	1 h (mouthpiece)	IE (33)	-2.4 -0.6 (ns)	5 male 8 females (12-17 years)	Koenig et al. (1988)
0 235	0.00 0.12	UV, UV	1 h (mouthpiece)	CE (86)	+2.4 -1.8 (ns)	10 male (19-29 years)	Schelegle and Adams (1986)
0 235	0.00 0.12	UV, UV	1 h	CE (89)	+4.1 -5.6 ($p < 0.02$) range: +10 to -29	15 male 2 female (24 ± 3 years)	Gong et al. (1986)
0 235 274	0.00 0.12 0.14	UV, UV	2 h	IE (68)	+1.0 +2.8 (ns) +1.6 (ns)	24 male (18-33 years)	Linn et al. (1986)
0 274	0.00 0.14[f]	UV, UV	1 h	CE (31)	-0.5 -4.2 ($p < 0.01$)	46 male 13 female (12-15 years)	Avol et al. (1985a,b)
0 294	0.00 0.15[f]	UV, UV	1 h	CE (53)	+0.6 -5.3 ($p < 0.05$)	42 male 8 female (26.4 ± 6.9 years)	Avol et al. (1984)

TABLE 3-2 (cont'd). KEY HUMAN STUDIES DEMONSTRATING LUNG FUNCTION DECREMENTS NEAR THE CURRENT 1-HOUR NAAQS FOR OZONE

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Measurement Method[a,b]	Exposure Duration	Activity Level ($\dot{V}_E$)[c]	Percent Change in FEV_1[d]	Number, Sex, and Age of Subjects	Reference[e]
0 294	0.00 0.15	UV, UV	2 h	IE (68)	+1.5 -0.5 (nd) range: +3 to -9	20 male (25.3 ± 4.1 years)	Kulle et al. (1985)
0 294	0.00 0.15	UV, UV	1 h (mouthpiece)	CE (55)	+0.6 -4.5 (ns) range: +3.5 to -30.6	10 female (22.9 ± 2.5 years)	Gibbons and Adams (1984)
0 314	0.00 0.16	UV, UV	1 h	CE (57)	+0.6 -6.1 ($p < 0.05$)	42 male 8 female (26.4 ± 6.9 years)	Avol et al. (1984)
0 314	0.00 0.16	UV, UV	2 h	IE (68)	+1.0 -2.3 ($p < 0.05$) range: +8.9 to -35.8	24 male (18-33 years)	Linn et al. (1986)
0 314	0.00 0.16[f]	UV, NBKI	1 h	CE (38)	-0.1 -0.8 (ns)	27 male 21 female (28 ± 8 years)	Linn et al. (1983), Avol et al. (1983)
0 333	0.00 0.17[f]	UV, NBKI	1 h	CE (42)	-0.4 -3.4 ($p < 0.006$)	45 male 15 female (30 ± 11 years)	Linn et al. (1983), Avol et al. (1983)
0 333	0.00 0.17[f]	UV, NBKI	2 h	IE (2 × R)	+0.6 -2.1 ($p < 0.05$)	14 male 20 female (29 ± 8 years)	Linn et al. (1980, 1983)
0 353	0.00 0.18	CHEM, UV	2 h	IC (65)	-1.0 -6.2 ($p = 0.008$) range: 0 to -23	20 male (23.3 ± 2.8 years)	McDonnell et al. (1983)
0 353	0.00 0.18	UV, UV	1 h (mouthpiece)	CE (86)	+2.4 -5.8 ($p < 0.05$)	10 male (19-29 years)	Schelegle and Adams (1986)

TABLE 3-2 (cont'd). KEY HUMAN STUDIES DEMONSTRATING LUNG FUNCTION DECREMENTS NEAR THE CURRENT 1-HOUR NAAQS FOR OZONE

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Measurement Method[a,b]	Exposure Duration	Activity Level ($\dot{V}_E$)[c]	Percent Change in FEV_1[d]	Number, Sex, and Age of Subjects	Reference[e]
0 392	0.0 0.2	UV, UV	2 h	IE (68)	+1.5 -3.1 (nd) range: +3 to -16	20 male (25.3 ± 4.1 years)	Kulle et al. (1985)
0 392	0.0 0.2	UV, UV	2 h	IE (30 for male, 18 for female subjects)	+0.3 -3.1 (ns) range: +6.0 to -16.6	8 male 13 female (18-31 years)	Gliner et al. (1983)
0 392	0.0 0.2	UV, UV	1 h	CE (90)	+4.1 -21.6 ($p < 0.001$) range: +10 to -46	15 male 2 female (24 ± 3 years)	Gong et al. (1986)
0 392	0.0 0.2	UV, UV	1 h	CE (77.5)	+1.7 -6.0 ($p < 0.05$)	10 male (24 ± 4 years)	Adams and Schelegle (1983)
0 392	0.0 0.2	UV, UV	1 h (mouthpiece)	CE (61.8)	-4.8 (ns)	8 male (22-46 years)	Adams et al. (1981)
0 392	0.0 0.2	UV, UV	75 min (mouthpiece)	CE (46)	-1.5 -8.0 (ns)	6 female (22-29 years)	Lauritzen and Adams (1985)
0 412	0.00 0.21	UV, UV	1 h	CE (89)	+1.9 -14.8 ($p < 0.05$)	6 male 1 female (18-27 years)	Folinsbee et al. (1984)
0 470	0.00 0.24	CHEM, UV	2 h	IE (65)	-1.0 -14.5 ($p < 0.005$) range: -1 to -36	20 male (22.9 ± 2.9 years)	McDonnell et al. (1983)
0 470	0.00 0.24	UV, UV	1 h	CE (60)	+0.6 -19.1 ($p < 0.05$)	42 male 8 female (26.4 ± 6.9 years)	Avol et al. (1984)

TABLE 3-2 (cont'd). KEY HUMAN STUDIES DEMONSTRATING LUNG FUNCTION DECREMENTS NEAR THE CURRENT 1-HOUR NAAQS FOR OZONE

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Measurement Method[a,b]	Exposure Duration	Activity Level ($\dot{V}_E$)[c]	Percent Change in FEV_1[d]	Number, Sex, and Age of Subjects	Reference[e]
0	0.00	UV, UV	1 h	CE (86)	+2.4	10 male	Schelegle and
470	0.24		(mouthpiece)		-10.5 ($p < 0.05$)	(19-29 years)	Adams (1986)
0	0.00	UV, UV	2 h	IE (68)	+1.5	20 male	Kulle et al. (1985)
490	0.25				-6.4 (nd)	(25.3 ±	
					range: +1 to -36	4.1 years)	

[a]Measurement method: UV = ultraviolet photometry, CHEM = gas phase chemiluminescence.
[b]Calibration method: UV = ultraviolet photometry, NBKI = neutral buffered potassium iodide.
[c]Minute ventilation ($\dot{V}_E$) reported in liters per minute or as a multiple of resting ventilation: IE = intermittent exercise, CE = continuous exercise, R = resting.
[d]Pre- to postexposure difference (percent) in the group mean of forced expiratory volume in 1 s (FEV_1); statistical significance based on difference between ozone (O_3) and filtered air (0.0 ppm O_3) exposures: ns = not significant, nd = not determined.
[e]See U.S. Environmental Protection Agency (1986).
[f]Measured in ambient air (mobile laboratory).
[g]"Suggested" significance based on Bonferroni inequality correction ($p < 0.006$).

O_3 concentration and exercise level were lower in the more recent study. No significant changes in respiratory function or symptoms were found in the group, probably because of the lower doses of O_3. Regression analyses of individual data, however, suggested that individuals receiving high doses of O_3 had effects that were comparable to those found in adolescents and young adults, although no definitive comparisons could be made because of differing ambient exposure levels and large intersubject variability in responsiveness to O_3. This finding is also consistent with the controlled exposure study by McDonnell et al. (1985a,b) indicating that the effects of O_3 on lung spirometry in children were very similar to those found in adults exposed under similar conditions, except that no significant increases in symptoms were found in children. Therefore, based on the available pulmonary function data, young children and adolescents do not appear to respond differently to O_3 than do adults.

A series of papers describing the effects of O_3 on subjects greater than 50 years of age appeared between 1986 and 1989 (Bedi et al., 1988; Bedi and Horvath, 1987; Drechsler-Parks et al., 1987, 1989; Reisenauer et al., 1988) (see Table 3-1).

Bedi and Horvath (1987) described the decrease in pulmonary function response in a single subject studied at age 32 and again at age 40. The major importance of this study is that it demonstrated a decline in response of considerable magnitude (ΔFEV_1 of -25% decreased to -5% over 8 years) that was observed longitudinally. This lends credence to the results of the cross-sectional studies indicating a decreased response in older subjects.

Drechsler-Parks et al. (1987) compared a group of older (age 51 to 76) subjects exposed to 0.45 ppm O_3 with a group of young adults studied under the same protocol (2-h intermittent exercise at 25 L/min). The older subjects had substantially smaller changes in function than the younger subjects, both male and female. Changes in FVC in the older subjects averaged -5.3% and in the young adults, -14.1%. Similar differences were observed for other functional measurements. Similar data for O_3 exposure are reported in a second paper by Drechsler-Parks et al. (1989).

Bedi et al. (1988) reported the results of a study in which older subjects were exposed to this same O_3 concentration (0.45 ppm) on three separate occasions. The responses were not reproducible from one exposure to the next. The group average did not change

appreciably between exposure series, indicating that even though the older subjects have more variable responses, they are less responsive to O_3, as a group, than younger subjects.

Reisenauer et al. (1988) also studied a group of older subjects, age 55 to 74 years. These O_3 exposures were conducted at 0.2 and 0.3 ppm O_3 using a light intermittent exercise regime. There were no significant changes in $FEV_{1.0}$. For the 0.3 ppm exposures, however, the female subjects (n = 10) had a slight rise (13%) in total respiratory resistance that was statistically significant.

The implication of these differences in responsiveness to O_3 in older subjects is unclear. Only standard spirometry tests have been used to evaluate responses. It is not known if changes in airway resistance or airway responsiveness to methacholine or histamine are similarly attenuated in older subjects. The possibility of inflammatory responses has not been studied in these older subjects.

Four additional publications (Eschenbacher et al., 1989; Kreit et al., 1989; Koenig et al., 1988; Koenig et al., 1987) report the results of controlled human exposure studies on the effects of O_3 on asthmatics (see Table 3-1). Also of interest is a new study of subjects with allergic rhinitis (McDonnell et al., 1987).

Kreit et al. (1989) studied nine asthmatics exposed to 0.4 ppm O_3 for 2 h while performing intermittent exercise with a ventilation of about 53 L/min. All subjects had a history of physician-diagnosed asthma and were sensitive to methacholine. Medications were withheld for at least 12 h prior to exposure. Nine nonasthmatic subjects were also studied under the same protocol. Both groups of subjects had significant decreases in FVC, FEV_1, FEV_1/FVC, forced expiratory flow at 25 to 75% of FVC (FEF_{25-75}), and inspiratory capacity after O_3 exposure. The changes in FEV_1, FEV_1/FVC, and FEF_{25-75} were more negative in the asthmatics than in the normals (e.g., Δ% FEV_1 was -13.4% in normals and -23.1% in asthmatics). Specific airway resistance (SR_{aw}) was not significantly increased in normals but was in asthmatics after O_3 exposure. A significant increase in SR_{aw} also occurred after air exposure in the asthmatics. The change in SR_{aw} after O_3 was more than twice that after exercise in air (ΔSR_{aw}-air = +3.82, ΔSR_{aw}-ozone = +8.02 cm H_2O/L/s). Both groups experienced a similar relative increase in methacholine responsiveness after O_3 exposure, expressed as a decrease in the provocative methacholine concentration that

causes a 100% increase in baseline SR_{aw}. It is important to note that these subjects underwent methacholine challenge both 90 min before and 90 min after exposure.

It is not clear to what extent the preexposure challenge may have confounded the results, particularly because the nonasthmatics received a substantially larger dose of methacholine than the asthmatics. Normal subjects appeared to have a depressed FEF_{25-75} prior to exposure (≈12% decrease after methacholine challenge). There were no differences in O_3-induced symptom responses between normals and asthmatics.

A second report of this study (Eschenbacher et al., 1989) additionally included a description of the effects of indomethacin pretreatment in O_3-exposed normal subjects. The data for adult asthmatics were those reported by Kreit et al. (1989). Indomethacin pretreatment in normals caused a marked decrease in O_3-induced spirometry changes ($\Delta FEV_1 - O_3 = -21.5\%$; $\Delta FEV_1 - O_3$ + indomethacin $= -10.6\%$). However, there was also a surprising, but substantial, placebo effect, suggesting a possible behavioral component in O_3 response. Indomethacin, an inhibitor of cyclooxygenase pathways of arachidonic acid metabolism, had no effect on the increase in airway responsiveness caused by O_3. Indomethacin appears to primarily block the "restrictive" (i.e., decreased FVC) effect of O_3 and does not alter the bronchoconstrictive or airway reactivity responses. Of additional interest was the observation that "normal" subjects in the indomethacin study had an FEV_1 decrease, after an identical protocol, which was not unlike the response of the asthmatics, thus raising the question of the normality of the subjects or the possible confounding effect of a preexposure methacholine challenge. Further research is, therefore, needed to fully understand any potential differences in O_3 responsiveness between asthmatic and healthy adult subjects.

The responses of adolescent asthmatics to 0.12 ppm and 0.18 ppm O_3 were tested by Koenig et al. (1987). The mouthpiece exposure sequence consisted of 30 min rest followed by 10 min exercise (minute ventilation [$\dot{V}_E$] = 33 L/min). In addition to the 10 asthmatics, 10 healthy adolescents were also studied. There was a significant increase in total respiratory resistance (forced oscillation method) in both normals and asthmatics exposed to 0.18 ppm O_3. There were no significant changes in FEV_1 in either subject group. At 0.12 ppm O_3, there were no significant differences that could be attributed to O_3 in either asthmatics or normals.

Koenig et al. (1988) have also studied adolescent asthmatics (n = 10) and healthy adolescents (n = 10) exposed to either air, 0.12 ppm O_3, 0.3 ppm nitrogen dioxide (NO_2), or the combination of O_3 plus NO_2. The mouthpiece exposures lasted 60 min and included two 15-min exercise periods during which ventilation averaged about 35 L/min. Medications were discontinued at least 4 h prior to exposure. In the asthmatics, an 11% decrease in $FEF_{50\%}$ was observed after 0.12 ppm O_3 exposure. One of the subjects had an exceptionally large decrease in $FEF_{50\%}$ of −60%, which occurred approximately 20 min after the end of exposure. This same subject did not have a large change in $FEF_{50\%}$ when exposed to O_3 plus NO_2, suggesting that the response of this individual to O_3 may have been anomalous. There were no other responses attributed to O_3 in this study, either in normal or asthmatic subjects. The authors tentatively suggested that adolescent asthmatics may be slightly more responsive to these low levels of O_3. However, replication of these observations will be required before this suggestion can be substantiated.

McDonnell et al. (1987) studied 26 subjects with allergic rhinitis to determine if the presence of allergies was a predisposing factor for O_3 sensitivity. These allergic subjects had airway responses to histamine that were similar to a comparable group of nonallergic subjects. Exposure to 0.18 ppm O_3 for 2 h with heavy intermittent exercise caused increased responsiveness to histamine and a decrease in several spirometric variables. The only apparent difference between the allergic subjects and previously exposed nonallergic subjects was a significant increase in airway resistance in the allergic subjects. These data on allergic and asthmatic subjects suggest that both of these groups have a greater rise in airway resistance after O_3 exposure than do normal subjects. The relative order of airway responsiveness to O_3 is normal < allergic < asthmatic.

Between 1987 and 1989, a series of reports were presented or published concerning a study of apparent seasonal variation in O_3 responsiveness in residents of Los Angeles (Avol et al., 1988; Hackney and Linn, 1989; Hackney et al., 1989; Linn et al., 1988) (see Table 3-1). The definitive report of this study is the journal publication by Linn et al. (1988). From a large number of subjects tested for O_3 responsiveness, 12 responsive and 13 nonresponsive subjects were selected to participate in further testing. Characteristics of the subjects are presented below:

	Gender	Age	Health Status	Mean ΔFEV_1
Nonresponders	8M/5F	5 > 30	All Normal	+1%
Responders	5M/7F	2 > 30	4 Normal 6 Atopic 2 Asthmatic	−12.4%

In all tests, subjects were exposed to 0.18 ppm O_3 during 2 h of intermittent heavy exercise (ventilation = 35 L/min/m^2 body surface area [BSA]) at 35 °C and 35% relative humidity (RH). These 25 subjects participated in two more pairs of exposure to O_3 and clean air. The initial tests were conducted in late spring (1986) and the followup tests occurred in late summer/early fall (1986) and again in winter (early 1987). A subsequent follow-up test with a smaller number of subjects (17 of the 25) occurred in spring (1987). The differences between responsive and nonresponsive subjects, which were of course significant at the time of the first test, were no longer significant at the first two follow-up studies in late summer and winter. This suggested the possibility that ambient oxidant exposure during the summer months produced an "adaptation" response that persisted for several months. This suggestion was further strengthened when a reduced number of subjects were exposed to O_3 again, one year later. At this time, the responsive subjects appeared to regain their sensitivity to O_3 exposure. The mean absolute changes in FEV_1 for the four exposures in the responsive subjects were −385, −17, +16, −347 mL respectively for the spring, fall, winter, and spring tests respectively. Corresponding changes for the nonresponders were +28, +90, +34, +81 mL. Because the experimental design was not optimal, these results need to viewed with caution and, as the authors state, "It is not clear that these results can be generalized." Nevertheless, these findings clearly suggest that results of experimental O_3 exposures of residents of high oxidant areas must be viewed with caution if frequent ambient exposure was a possibility during the period of experimental exposure.

Additional information presented by Hackney et al. (1989) indicated that 8 of the 12 responders were reactive to methacholine and had a history of respiratory allergies. In addition, 10 of the 12 responders had a history of some symptomatic complaints when exposed to "smog". The authors suggested that allergy or atopy may be a risk factor for excess response to O_3 although other studies have indicated that increased airway reactivity is not predictive of O_3 responsiveness. They further speculated that nonresponders could be at

increased risk for chronic health effects of cumulative ambient O_3 exposure because they would be less likely to avoid such exposures because of their lack of symptomatic complaints.

Controlled human exposure studies reviewed earlier in the 1986 U.S. EPA criteria document have suggested that some impairment of exercise performance may be associated with O_3 exposure. Subjective statements made by individuals engaged in these controlled studies indicate that the perception of pain occurring with deep breathing may be an important factor that limits performance of continuous heavy exercise at O_3 concentrations $\geq$ 0.18 ppm. Studies by Gong et al. (1986) and by Schelegle and Adams (1986) substantiate these earlier findings, whereas a third study by Linder et al. (1988) suggests that small decrements in maximal exercise performance may occur at O_3 concentrations $<$0.18 ppm (see Table 3-1).

Gong et al. (1986) found that maximal performance tested after exposure of endurance athletes continuously exercising at heavy work loads ($\dot{V}_E$ = 89 L/min) for 1 h in a hot environment was impaired in 0.20 ppm O_3. This level of O_3 exposure also reduced pulmonary function and enhanced respiratory symptoms and airway responsiveness to histamine. Maximal performance was not impaired after exposure in 0.12 ppm O_3, despite small but significant group mean decrements (5.6%) in FEV_1. Similarly, Schelegle and Adams (1986) found that exercise performance, as determined by completion of the exposure protocol, was impaired following exposure of endurance athletes who were continuously exercising at heavy work loads ($\dot{V}_E$ = 87 L/min) for 1 h at O_3 concentrations $\geq$0.18 ppm, but not at 0.12 ppm. Significant decrements in pulmonary function and increased respiratory symptoms also occurred at $\geq$0.18 ppm O_3.

The effect of O_3 inhalation on performance of maximum exercise tests was also studied by a group of Swiss investigators (Linder et al., 1988). Twenty-four subjects (12M, 12F) were studied while performing maximal incremental exercise tests. The maximum exposure duration was 28 min and the minimum was 16 min. The tests were performed in clean air, 0.07 ppm O_3, and 0.13 ppm O_3 in an environmental chamber (24 °C; 50% RH). Small, but significant (t-test), increases (2%) in $FEV_{1.0}$ were observed after clean air exposure. Except for women exposed to 0.13 ppm (-1.4%), no changes in FEV_1 were observed with O_3 exposure. Performance on the maximum exercise test was decreased 11% in women and 7% in men at 0.13 ppm and 5% and 4%, respectively, at 0.07 ppm ($p < 0.05$, t-test). During the tests conducted at 0.13 ppm, there was also a small decrease (2.5 to 5%) in

anaerobic threshold, defined as the workload at which the venous lactate concentration exceeded 4 mM. It is not clear to what extent the exercise performance test results may reflect behavioral responses to the odor of O_3.

There are a number of questions that may be raised about the paper by Linder et al. (1988). From the graphical presentation of the data on FEV_1, it appears that no significant changes would be detected by an appropriate statistical analysis (i.e., an analysis of variance appropriate for repeated measures, rather than multiple t-tests). The authors did not indicate whether appropriate precautions were taken to randomize or "blind" the exposures. Furthermore, no information is provided about the selection criteria for subjects. Because the effects were reported for very low exposure concentrations and brief exposure durations (maximum 28 min) and because they appear to be out of line with previous studies of exercise performance during O_3 exposure, it is important to determine if these observations can be verified.

The data currently available indicate that reduction in exercise performance may occur in many well-conditioned athletes after performing continuous heavy exercise for 1 h at O_3 concentrations ≥ 0.18 ppm. These athletes are capable of sustaining very high exercise $\dot{V}_E$ (i.e., >80 L/min) for 1 h. Any performance decrements occurring at O_3 concentrations <0.18 ppm are less certain and need to be verified. It must be noted, however, that other environmental conditions, such as increased ambient temperature and/or relative humidity, may independently affect subjective symptoms and may independently impair exercise performance. Therefore, it may be difficult to differentiate work performance effects caused by O_3 from physiological or behavioral effects caused by other conditions in the environment.

Studies utilizing longer exposure durations, particularly at lower levels of exercise, were not previously reviewed in the 1986 U.S. EPA criteria document. Among the newer studies, two (Folinsbee et al., 1988; Horstman et al., 1989, 1988) address the effects of O_3 exposures for durations >2 h (see Table 3-1). The first of these was designed to determine the effects of prolonged exposure to the present level of the 1-h NAAQS for O_3 (0.12 ppm) on 10 young adult subjects that are representative of individuals who spend most of the day outdoors exercising at moderate intensities (e.g., adults performing heavy labor). Subjects were exposed to either 0.0 or 0.12 ppm O_3 for a total of 6.6 h. During the exposure, the subjects exercised for six periods of 50 min each; each exercise period was followed by

10 min of spirometry testing and rest. An additional 35 min for lunch was interposed between the third and fourth exercise period. The ventilation during the exercise averaged about 41.5 L/min and heart rate ranged from 108 to 124 beats/min.

Prolonged exposure to 0.12 ppm O_3 resulted in progressively larger changes in respiratory function and symptoms with time. By the end of 6.6 h of exposure, group mean changes were as follows: FEV_1 had decreased 13.0%, FVC had decreased 8.3%, and $FEF_{25-75\%}$ had decreased 17.4%. On forced inspiratory tests, forced inspiratory vital capacity and forced inspiratory volume in 0.5s were decreased 12.6 and 20.7%, respectively. Respiratory symptoms of cough and pain on deep inspiration increased with the increasing duration of O_3 exposure. There was also a marked increase (about twofold) in airway responsiveness to methacholine following O_3 exposure. No changes were observed with clean air exposure. The changes in lung function reported at the end of exposure were similar in magnitude to those previously observed in healthy subjects performing at heavy levels of exercise ($\dot{V}_E \geq 60$ L/min) in much higher O_3 concentrations (>0.2 ppm) for shorter durations (i.e., ≤ 2 h).

The need for additional concentration-response information led to a subsequent study using the same O_3 exposure protocol. Twenty subjects were exposed for 6.6 h to four O_3 concentrations (0.0, 0.08, 0.10, and 0.12 ppm) in random order. The results of this study were reported, in part, at the 1988 U.S.-Dutch symposium (Horstman et al., 1989) and at the 1988 Annual Air Pollution Control Association Meeting (Horstman et al., 1988). The ventilation in this study was slightly lower than in the first study, averaging 38.9 L/min. The $FEV_{1.0}$ decreased by 7, 7, and 12.3% at 0.08, 0.10, and 0.12 ppm, respectively. The airway resistance response to methacholine was increased by factors of 1.56, 1.89, and 2.21, respectively. There was also a significant increase in the symptom of pain upon deep breath, a typical symptom of acute O_3 exposure.

The study by Folinsbee et al. (1988) is the first clinical study to demonstrate increased airway reactivity to inhaled bronchoconstrictors in subjects exposed to low O_3 concentrations for prolonged periods of time. Other studies reported in the recent literature have identified these effects in humans exposed to O_3 for shorter durations (see Table 3-1). The study by McDonnell et al. (1987) described an increase in airway reactivity to histamine in 26 healthy subjects with allergic rhinitis who were exposed to 0.18 ppm O_3 for 2 h while undergoing

heavy ($\dot{V}_E$ = 64 L/min) intermittent exercise. Seltzer et al. (1986), in a study of 10 healthy individuals exposed for 2 h to air and to either 0.4 or 0.6 ppm O_3 while undergoing moderate intermittent exercise, observed an increase in the number of neutrophils in bronchoalveolar lavage (BAL) fluid 3 h after O_3 exposure. Furthermore, they observed an increase in airway reactivity to methacholine following O_3 exposure and their data were suggestive of an association between the degree of inflammation and the increase in airway reactivity.

A series of reports by Koren et al. (1989a,b; 1988a,b) described the inflammatory and biochemical changes in the airways consequent to O_3 exposure (see Table 3-1). In these studies, subjects were exposed to 0.40 ppm for 2 h while performing intermittent exercise (15 min exercise, 15 min rest) at a ventilation of 70 L/min (35 L/min/m^2 BSA) (i.e., the same protocol as used by McDonnell et al., 1983). The main purpose of these studies was to examine cellular and biochemical responses in the airways of ozone exposed subjects. To accomplish this, BAL was performed about 18 h after the O_3 exposure. Standard lung function tests were also performed before and after exposure. A mean decrease in FEV_1 of 960 mL after O_3 exposure was reported. An eightfold increase in polymorphonuclear leukocytes (PMNs) was observed after O_3 exposure, confirming the observations of Seltzer et al. (1986). A twofold increase in protein, albumin, and immunoglobulin G were indicative of increased epithelial permeability as previously suggested by the technetium-labeled diethylene triamine pentacetic acid (DTPA) clearance studies of Kehrl et al. (1987). In addition to confirmation of these previous findings, Koren et al. (1989b) provided evidence of stimulation of fibrogenic processes including increases in fibronectin (6.4×), tissue factor (2.1×), Factor VII (1.8×), and urokinase plasminogen activator (3.6×). There was a twofold increase in the level of prostaglandin E_2 and a similar elevation of the complement component C3a. Levels of the leukotrienes LTC_4 and LTB_4 were not affected. Koren et al. (1989a) reported that an inflammatory response, as indicated by increased levels of PMNs, was also observed in BAL fluid from subjects exposed to 0.1 ppm O_3 for 6.6 h (same protocol as Folinsbee et al., 1988).

Further evidence supporting the hypothesis that cyclooxygenase products of arachidonic acid metabolism (prostaglandins, thromboxane) may play a role in O_3-induced spirometry changes comes from a study by Schelegle et al. (1987). These investigators demonstrated a significant attenuation of decrements in FVC and $FEV_{1.0}$ when subjects were treated with the

cyclooxygenase inhibitor indomethacin prior to O_3 exposure. Subjects were exposed to 0.35 ppm for 1 h of continuous exercise (60 L/min); $FEV_{1.0}$ decreased 26.3% on the no-drug day, but only 10.6% after indomethacin pretreatment.

The above studies indicate that the inflammatory process caused by O_3 exposure is promptly initiated (Seltzer et al., 1986) and persists for at least 18 h (Koren et al., 1989b). The time course of this inflammatory response and the O_3 exposures necessary to initiate it, however, have not yet been fully elucidated. Furthermore, these studies demonstrate that cells and enzymes capable of causing damage to pulmonary tissues were increased and the proteins that play a role in the fibrotic and fibrinolytic processes were elevated as a result of O_3 exposure.

Graham et al. (1988) showed an increase in PMNs in nasal lavage fluid collected from subjects exposed to 0.50 ppm for 4 h at rest. There was a 3.5-fold increase in nasal PMNs immediately after exposure and this increased further (6.5-fold) by the following day (i.e., 20 h later). This study suggests that a nasal inflammatory response may serve as a qualitative indicator of an inflammatory response in the lung.

Kehrl et al. (1987) observed an increased rate at which inhaled technetium-labeled DTPA diffused from the airway and alveoli into the bloodstream in eight healthy subjects who endured heavy exercise for 2 h in 0.4 ppm O_3. Kehrl et al. (1989) reported results from an additional 16 subjects studied in the same manner. For the combined group of 24 subjects exposed for 2 h to 0.40 ppm O_3, the average rate of clearance of technetium-labeled DTPA was 1.08%/min. This clearance rate was some 60% faster than that observed after air exposure. The average O_3-induced decrement in FVC in these subjects was −10%. This study confirms that clearance of technetium-labeled DTPA is accelerated after O_3 exposure and, in conjunction with the Koren et al. (1988a,b; 1989a,b) observations, strongly suggests that this accelerated clearance is due, in part, to an increased epithelial permeability within the lung. These changes in permeability are most likely associated with acute inflammation and could potentially allow better access of inhaled antigens and other substances to the submucosa. Results from studies of these endpoints at lower O_3 levels have not been reported.

These observations by Koren, Kehrl, and co-workers have raised the question of whether acute inflammation occurs following exposure to low levels of O_3 for prolonged

periods of time (>2 h). Results from studies determining if these newly identified O_3 effects are occurring at low O_3 concentrations (i.e., ≤0.12 ppm) remain to be more fully reported and evaluated. This information will improve our understanding of the nature of inflammatory responses, including the biochemical and molecular changes in the lung, that occur in O_3-exposed subjects.

Another series of papers by Gerrity and co-workers (Gerrity, 1987; Gerrity et al., 1988; Gerrity and McDonnell, 1989) examining O_3 uptake in the respiratory tract have important implications for modeling the health effects of O_3 exposure in humans and for extrapolating data from animals to humans (see Table 3-1).

Gerrity et al. (1988) studied 18 healthy young males to determine the fractional uptake of O_3 by the upper respiratory tract (URT), excluding the larynx, and by the lower respiratory tract (LRT), including the larynx. In order to measure O_3 concentrations during the breathing cycle, a chemiluminescent O_3 analyzer was modified to increase its response time. Gas was sampled at the level of the posterior larynx from a tube inserted through the nose. Mean inspired and mean expired (alveolar) values of pharyngeal O_3 concentration were used to compute the fractional uptake of O_3 in the URT and LRT. The investigators studied the effects of changes in O_3 concentration (0.1, 0.2, 0.4 ppm), breathing frequency (12 and 24 breaths per minute) and mode of breathing (nasal, oral, oronasal). The differences between the various treatment conditions were small; the average URT uptake was about 40% and average LRT uptake was about 91% (of the O_3 that reached the larynx), resulting in an average total respiratory tract uptake of approximately 95%. (In other words, of the O_3 entering the URT, about 40% was removed. Of the remaining 60% that reached the trachea, 91% was removed. Total uptake is therefore $40\% + (0.91 \times 60\%) = 95\%$.) Increased frequency of breathing caused a decreased fractional removal of O_3 in both URT and LRT, presumably because of decreased residence time in the airway and increased flow rate. The lowest fractional removal of O_3 in the URT occurred during nasal breathing. The differences between nasal and oral or oronasal breathing, however, were very small. The lack of significant differences between nasal and oral breathing on O_3-induced changes in lung function and respiratory symptoms was recently reported by Hynes et al. (1988), also suggesting that the mode of inhalation may not affect O_3 uptake as much as previously expected.

In a second paper, Gerrity and McDonnell (1989) reported the influence of the O_3-induced change in breathing pattern on the O_3 uptake efficiency. Subjects were exposed to 0.4 ppm O_3 during continuous 60 min exercise at a ventilation of about 40 L/min. At the end of the exposure, there was a 25% reduction in spontaneous tidal volume and a 45% increase in breathing frequency. Associated lung function changes included a 13% reduction in FVC and an 18% reduction in FEV_1. The change in breathing pattern was accompanied by a 9% reduction in the LRT O_3 uptake efficiency (fractional LRT uptake decreased from 68% to 62%). Total O_3 uptake (about 80%) was only reduced about 4% because there was a slight increase in O_3 uptake in the URT. The reduction in LRT O_3 uptake was correlated with the decrease in tidal volume, suggesting that an increased depth of inspiration increases the dose delivered to the LRT. The O_3 uptake "efficiencies" reported in these two papers are not strictly comparable because the methods used to make the calculations of O_3 uptake were different in each paper. The authors suggested that the reduction in tidal volume may act as a protective mechanism for the lower airways, but that the loss of this response with repeated exposures may permit increased O_3 delivery to the lower respiratory tract.

Gerrity (1987) described a model of nasopharyngeal uptake of O_3 using data from various animal species, including humans. The conclusion reached in this analysis was that nasopharyngeal O_3 uptake decreases with increasing flow but that there was also a considerable species variation in uptake (see Section 3.1.3.3 and Table 3-6).

The above observations of Gerrity and co-workers have important implications for interpretation of heavy exercise studies. Increased tidal volume increased LRT O_3 delivery, but there may be a limit beyond which increases in tidal volume will not cause increased LRT O_3 delivery. Further modeling studies will hopefully address whether such a limit exists in the physiological range of human ventilation.

Available data on respiratory tract uptake efficiency in humans appears to fit the predicted model, making it possible to develop dose-response information from the wealth of controlled human exposure studies that have already been published. The current likelihood of making animal-to-human extrapolations based on this information and on the comparison of respiratory tract uptake of O_3 across different mammalian species is discussed later in Section 3.1.3.3.

3.1.2 Field and Epidemiological Studies

Field and epidemiological studies reviewed earlier in the 1986 Criteria Document (U.S. Environmental Protection Agency, 1986) reported a variety of results concerning associations between exposures to ambient O_3 and various measures of respiratory effects. The results of many of these studies were found to be directionally consistent with the findings of controlled human exposure studies, especially those providing reasonably good evidence for associations between ambient O_3 exposures and acute pulmonary function decrements. Results of other epidemiology studies evaluating other health endpoints, e.g. exacerbation of asthma or other chronic lung diseases, were found to be more difficult to interpret due to methodological limitations, but some of these latter studies tended to point toward possible increases in symptom aggravation or changes in lung function of asthmatic subjects being associated with increased total oxidant levels, ambient O_3 concentrations, or interactions between ambient O_3 levels and temperature. However, no consistent pattern of findings for aggravation of symptoms or lung function changes emerged for patients with other types of chronic lung disease. Newer field and epidemiology studies (summarized in Table 3-3), as with the older literature, continue to provide somewhat mixed results across various health endpoints measured—with most progress having been made with regard to provision of further information concerning exposure dynamics related to the induction of pulmonary function decrements by short-term ambient O_3 exposures.

Included among the newer studies published since 1986 are reports by Raizenne and coworkers on several aspects of field studies of children in two summer camps in Ontario (Raizenne et al., 1987; 1989), one at Lake Couchiching (LC) about 100 km north of Toronto, Ontario, and one at a Girl Guide camp on the north shore of Lake Erie. In the LC study (Raizenne et al., 1987), the strongest association between lung function and environmental variables was found in nonasthmatics, with FVC decrements correlated ($p < 0.01$) with 24-h lag functions for average $SO_4^=$, partilces ≤ 2.5 μm ($PM_{2.5}$), and temperature. The association of peak expiratory flow rate (PEFR) with unlagged 1-h O_3 was statistically significant and the average slope of the regression line was -2.7 (mL/s/ppb). Temperature was significantly associated with all lung indices in nonasthmatics but not in asthmatics. The average slope of PEFR for temperature in nonasthmatics was -21.7, a much stronger association of PEFR with temperature than with O_3. Coefficients of variation

TABLE 3-3. FIELD AND EPIDEMIOLOGIC STUDIES ON EFFECTS OF OZONE (O_3)[a]

Study Description	Pollutants/Environmental Variables	Results and Comments	References
Effects of pollutants and other environmental variables on symptoms and lung function were examined in children attending a summer camp at Lake Couchiching (LC), about 100 km N of Toronto, Ontario. LC study was 6/30-7/8/83; n = 52, 23 nonasthmatic (11 males, 12 females) and 29 asthmatics (16 males, 13 females), avg. age 12.1 year. Symptom questionnaire and function tests given twice daily to each child between 7:30-9:30 a.m. and 4:30-6:30 p.m. Children's activity levels not estimated.	Hourly O_3 ranged from ≈10 to 110 ppb. SO_2, NO_x, O_3, $SO_4^=$, H_2SO_4, pH, PM_{10}, $PM_{2.5}$, RH, T, barometric pressure, wind speed and direction were also meaured.	Strongest association between lung function and environmental variables was in nonasthmatics, with FVC decrements significantly correlated ($p < 0.01$) with lagged avg. SO_4, $PM_{2.5}$, and T. Unlagged PEFR significantly correlated with 1-h O_3. Also, significant association of T with all lung function indices in nonasthmatics, but not in asthmatics. Coefficient of variation stable aeross morning and evening tests.	Raizenne et al. (1987)
(a) Effects of pollutants and other environmental variables on lung function were examined in girls attending one of three 2-week Girl Guide camp sessions on north shore of Lake Erie. Cohort (n = 104) screened by methacholine challenge (MC) and skin prick tests for 10 common respiratory allergens; 5 asthmatics withdrawn from the study (n = 99). Lung function tests administered twice daily. Children's activity levels not estimated.	1-h O_3 ranged from <10 to 143 ppb; max. 1-h O_3 > 100 ppb on 14 days of total study (6 weeks). For other pollutants and variables measured, see Raizenne et al. (1987) because same protocol used here as in that study.	(a) Associations between aerometric data and lung function measurements were not reported by pollutant in this reference. Aggregate analysis for full study not reported. Lung function changes reported for 5 episode days only. $FEV_{1.0}$ decrements statistically significant on 2 episode days for methacholine nonresponsive subjects.	Raizenne et al. (1989)
(b) Subset of 12 girls (7 MC+, 5 MC-) studied pre- and postexercise on 1 low pollution (control) day and 1 peak pollution day (episode, O_3 1-h > 139 ppb, $SO_4^=$ > 80 $\mu g/m^3$).		(b) Group mean FVC increased postexercise in the n = 12 subset by 40 mL, 71 mL in MC- and 17 mL in MC+. Pollution effect not statistically significant	
Time-activity pattern analysis approach of Mage (1985) used to evaluate likely cumulative (6 h) O_3 and H_2SO_4 exposures/doses experienced by children in above Lake Erie Girl Guide camp study, summer 1986. See Raizenne et al. (1987, 1989) for protocol and related information.	Continuous 1-h O_3, SO_2, NO_2, and acid aerosols (as H_2SO_4); 1-h O_3 range = 40-143 ppb; max. 12-h acid particle concentration = 28 $\mu g/m^3$ in one episode; FP-SO_4 = 100 $\mu g/m^3$ for peak hour.	Dosimetry model was developed for relating heart rate (from a 12-min, graded cycle ergometer test) to ventilation and then to O_3 and H_2SO_4 dose. Also, 5 randomly selected children wore portable heart-rate monitors, providing data for use in the dosimetric model. Application of the dosimetry model thus developed and used to estimate individual 6-h cumulative doses for O_3 and H_2SO_4 expsoures on one control and one episode day indicated negative trend in lung function (PEFR) as cumulative dose increased for both O_3 and H_2SO_4, although slopes for each did not differ significantly from zero ($p > .10$).	Raizenne and Spengler (1989)

TABLE 3-3 (cont'd). FIELD AND EPIDEMIOLOGIC STUDIES ON EFFECTS OF OZONE (O_3)[a]

Study Description	Pollutants/Environmental Variables	Results and Comments	References
Effects of pollutants and other environmental variables on respiratory functions in 91 children (53 boys, 38 girls; ages 8-15) attending 2 to 4 weeks of summer camp at Fairview Lake, NJ. Subsets were n = 37 for all 4 weeks, n = 34 for first 2 weeks only, n = 20 for last 2 weeks only. Symptom questionnaire; FVC, $FEV_{1.0}$, MMEF by spirometry; and PEFR by mini-Wright flow meter were measured once/test day (most of days in camp) sometime between 11:00 a.m. and 6:30 p.m. All children had validated spirometric data for ≥7 days of their 2-or 4-week camp stay. Activity levels of the children were not estimated. Respiratory health status determined by parental questionnaire only. Children slept in screened-in shelters but otherwise were exposed to ambient air 24 h/day.	Max. 1-h O_3 ranged from 40 to ≈100 ppb, with max. 1-h > 80 ppb on 9 of 27 days of O_3 recorded. O_3, SO_4, H_2SO_4, PM_{15}, $PM_{2.5}$, T, humidity, and wind speed and direction measured. Levels not reported for SO_2, pH, NO_3, NH_4.	Average regression slopes for respiratory function vs. max. 1-h O_3 concentration reported for the full cohort, for boys and girls separately and for subsets in attendance for all 4 weeks and for respective 2-week sessions. Average regression slopes (±S.E.) were -1.03 ± 0.24 and -1.42 ± 0.17 mL/ppb for FVC and $FEV_{1.0}$, respectively; and 6.78 ± 0.73 and -2.48 ± 0.26 mL/sec/ppb for PEFR and MMEF, respectively. Residuals from 1-h O_3 vs. respiratory indices were calculated for no. hours from 9:00 a.m. until function measurement; cumulative daily O_3 exposure (sum of 1-h O_3 concentrations from 9:00 a.m. until function measurement); avg. $[H^+]$ on day of test; avg. PM_{15} on day of test; T in hour preceding tests; RH in hour preceding tests; and heat stress index (temperature-humidity index, THI). $PM_{2.5}$ residual and lagged variables not tested. Most slopes of regression significant at $p < 0.05$ (differences from zero). Not clear if slopes for data subsets significantly different from each other (e.g., function vs. O_3 < 60 ppb and function vs. O_3 < 80 ppb). No formal analysis performed for possible concentration threshold.	Spektor et al. (1988a)
Effects of O_3 on respiratory function and symptoms examined in 30 nonsmoking adults (2 of 10 females non-Caucasian) exercising almost daily outdoors (Tuxedo, NY) for 15 to 55 min (avg. ca. 30 min), July to early August, 1985. Pre- and postexercise lung function measured and questionnaire answered postexercise. Pulse rate, calibrated to $\dot{V}_E$ indoors, taken postexercise. Exercise regimen self-selected. Dosimetry estimated and linear regressions done for: pulmonary function changes vs. (1) mean exercise and O_3 concentration; and (2) postexercise function and O_3 concentration. Persistence of effects tested by linear regressions. Subjects screened only by questionnaire; 2 with previous history of asthma but asymptomatic.	1-h O_3 concentration range 21-124 ppb; average not given in text (>60 ppb); max. THI =78°; max. acidic aerosol (as H_2SO_4) = 9 $\mu g/m^3$ during study. SO_2, NO_x, PM_{15}, $PM_{2.5}$, $SO_4^=$, NO_3, NH_4^+, and T and RH measured but not reported; only correlation of O_3 concn. with O_3 dose, THI reported; H^+, NH_4^+, and $SO_4^=$ concentration not reported; Aeroallergens not measured.	Significant ($p < 0.01$) decrements in FVC, $FEV_{1.0}$, PEFR, FEF_{25-75}, and $FEV_{1.0}$/FVC associated with O_3. No persistence of effects seen. No symptoms reported by subjects. Mean decrements showed unexpected inverse relationship with calculated $\dot{V}_E$ levels, as indicated by regressing pulmonary function changes and postexercise function against inhaled ozone during exercise. $\dot{V}_E$ ranges given, but not group or subset means. Subjects not screened for atopy. Exercise done in Sterling Forest, wooded research park, on paved roads or trails.	Specktor et al. (1988b)

TABLE 3-3 (cont'd). FIELD AND EPIDEMIOLOGIC STUDIES ON EFFECTS OF OZONE (O_3)[a]

Study Description	Pollutants/Environmental Variables	Results and Comments	References
Lung function measured by spirometry for 154 children ages 10-12 yrs (90 males; 64 females) in Kingston and Harriman, TN. Spirometry done between 10 a.m. and 1 p.m. on up to six days at least 1 week apart during Feb. to April 1981. Child-specific OLS models of FVC, $FEV_{0.75}$, MMEF, and $V_{75\%}$ fit on 1-h O_3 max. and 24-h FP and FP-$SO_4^=$. Means ± SD of distributions of estimated child-specific slopes computed and tested for significance by *t*-test.	Max. O_3 (1-h) concentrations ranged from 3 to 63 ppb. Other ambient pollutants measured: NO_2, TSP, IP, RSP, FP, SO_2 and FP-$SO_4^=$.	Significantly negative mean slopes on O_3 for all lung function variables. Among regressions on FP and FP-$SO_4^=$, only one statistically significant mean slope (i.e., pos. mean slope of MMEF on FP). Results insensitive to outlier audits and inconclusive for sensitivity variation. Association between fitted slopes and individual characteristics not significant. Author noted: Exposure assessment limited by outdoors-only monitoring; lack of time-activity data; period of seasonal change spanned by study; possible confounding by T or pollen; and very low O_3 concentrations raise plausibility questions.	Kinney (1986)
Review and analysis that evaluates consistency of pulmonary/respiratory function results among 5 epidemiologic studies and compares results of 4 of the 5 with data from controlled (chamber) studies as modeled by Hazucha (Hazucha, 1987; U.S. Environmental Protection Agency, 1986). Epidemiologic studies included panel study of school children, two summer day camp studies, one residential summer camp study (Kinney, 1986; Lippmann et al., 1983; Lippmann and Lioy, 1985; Bock et al., 1985; Lioy et al., 1985; Spengler et al., 1985; and Ozkaynak et al., 1985). Subjects were children and/or adolescents (ages 7-16).	See individual references for pollutants and other environmental variables measured.	Results of 4 of 5 epidemiologic studies documented in 1986 U.S. EPA O_3 Criteria Document or in this summary (see text and this table for Kinney, 1986). Transformation (assuming linearity) of data from Hazucha's quadratic model of controlled human exposure studies data compared with coefficients reported in the epidemiologic studies. Coefficients of pulmonary function decrements in epidemiologic studies larger than those reported in controlled studies. Authors postulate cumulative effects over multihour exposures known or thought to occur among cohorts of the 4 epidemiologic studies may account for larger decrements in lung function found with ambient exposures.	Kinney et al. (1988)
Time-activity analysis approach developed by Mage et al. (1985) used to estimate possible prolonged O_3 exposure for a hypothetical camper experiencing typical daily activity schedule in relation to pattern of hourly O_3 concentrations measured in Mendham, NJ, summer camp study previously reported by Bock et al. (1985) and Lioy et al. (1985). See Ch. 11 of 1986 Criteria Document (U.S. Environmental Protection Agency, 1986), for description of Mendham summer camp study.	See Bock et al. (1985) and Lioy et al. (1985) in U.S. Environmental Protection Agency (1986)	Time-activity analysis indicated that campers in Mendham study likely participated in high exercise activities (sports, swimming, etc.) during hours (10 a.m. - 8 p.m.) of high O_3 concentration (≥0.10 - 0.12 ppm). Estimation of total O_3 dosages received during 4-day O_3 episode period led authors to state that it is possible to hypothesize that the residual ozone effect on pulmonary function (i.e. earlier-reported lagged O_3 exposure effects on PEFR) was probably due to the accumulated dose of ozone rather than the peak (1 h) concentration.	Lioy and Dyba (1989)

TABLE 3-3 (cont'd). FIELD AND EPIDEMIOLOGIC STUDIES ON EFFECTS OF OZONE (O_3)[a]

Study Description	Pollutants/Environmental Variables	Results and Comments	References
Follow-up study (Sept., 1980-April, 1981) of pollutant-respiratory symptom relationships in subsets of children from 1979 Chestnut Ridge cross-sectional study of >4,000 elementary school children. Subsamples selected from six schools in study area with consistently higher levels of air pollution during previous 4 years. Subsamples (3) stratified by reported symptoms. One or more of following measures taken for 144 children: diaries, symptom questionnaire, spirometry. Telephone follow-up each 2 weeks on diaries; spirometry done at school; pollutants (including O_3) measured at 1 monitor (data from 17 monitors for SO_2 generally reflected in data at single monitor). Diary panel study covered 8 mo; successive PEFR spirometry studies of 9 weeks each done in respective groups of the three subsamples.	Means and range of max. daily 1-h values: O_3 mean = 32.4 $\mu g/m^3$, range = 0-129 $\mu g/m^3$; SO_2 mean = 51.2 $\mu g/m^3$, range = 18-176 $\mu g/m^3$; NO_2 mean = 40.5 $\mu g/m^3$, range = 12-79 $\mu g/m^3$; CoH mean = 0.38 CoH units, range = 0.1-1.3 CoH units; T mean = 1.3 °F, range = -22° to +22 °F.	Relationships of maximum hourly SO_2, NO_2, O_3, and CoH and min. T for each 24-h period to daily upper and lower respiratory illness, wheeze, and PEFR were evaluated using multiple regression models adjusted for illness occurrence or levels of PEFR on preceding day. No air pollutant was strongly associated with respiratory illness or with PEFR. Authors concluded that this study can best be interpreted as showing no acute effects of studied pollutants on respiratory symptoms or PEFR in children at levels lower than the current NAAQS, but also noted that conclusion must be tempered by relatively low levels of pollutants encountered and possibility of exposure misclassification.	Vedal et al. (1987)
Follow-up examination in 1980-1981 of cohorts of school children studied in six cities of U.S. Reexamination of between- and within-city results from earlier report (Ware et al., 1986). Respiratory symptom questionnaires completed by parents; spirometry done at school to obtain $FEV_{1.0}$, $FEV_{0.75}$, FVC, MMEF. Symptoms (cough, bronchitis, child illness, wheeze, asthma) fit to multiple logistic model.	Continuous measurements (hourly values) of SO_2, NO_2, O_3, meteorological variables (18 h/day). Three daily values of mean particle mass for $PM_{2.5}$, PM_{15}, TSP; 1 daily value for FP (<2.5 μm), $SO_4^=$. Monthly means of each pollutant calculated from daily means and an estimate of air pollution exposure in the previous year was calculated for each child in given city by averaging the monthly means for 12 mo proceeding the month of the spirometric examination. Except for O_3, all pollutant levels high pos. correlated; O_3 lowest in cities with high levels of other pollutants.	All particle measures (TSP, $PM_{2.5}$, PM_{15}) associated with substantial increases in respiratory illness reporting rates; only PM_{15} associations statistically significant. SO_2 (also correlated with particle measures) showed much weaker association with respiratory symptoms than association with particle measures. Weak association of NO_2 with symptoms. Negative association of O_3 with cough and chest illness, but annual O_3 positively associated with asthma and hay fever (in contrast to neg. assoc. of latter symptoms with all other pollutants). No sig. assoc. of pulmonary function levels with any of the pollutants, leading authors to conclude that increased rates of illness not associated with permanent loss of pulmonary function in preadolescent years.	Dockery et al. (1989)
Effects of pollutants and other environmental variables in summer (Jul.-Aug.) and winter (Jan.-Feb.) on three categories of hospital admissions examined: total respiratory, total respiratory excluding asthma, and nonrespiratory admissions to 79 acute-care hospitals serving ≈5.9 million people in southern Ontario, Canada. Data for 1974 and 1976-1982 examined. Pollutant data collected from 17 stations along 280-mile corridor between Windsor and Peterborough.	Mean of 1-h O_3 daily max: summer, 48.8-68.7 ppb; winter, 19.8-27.3 ppb. Range (avg. for 1974-1983) of 1-h daily max O_3 in Aug., 1-199 ppb. O_3, NO_2, SO_2, $SO_4^=$, CoH, T, RH measured.	Significant correlations found in summer between O_3, SO_2, and T versus deviations from the mean respiratory admissions, with and without asthma, for the same day of week in the same season and year. Stepwise multiple regression analysis based on each year separately indicates that $SO_4^=$ and T accounted for about 5% of the variance from the mean in respiratory or asthma admissions in summer. Testing of the 8-h maximum O_3 statistic in place of the 1-h O_3 statistic did not increase the correlation coefficient with respiratory admissions. (In winter, asthma admissions were correlated with T only.)	Bates and Sizto (1987)

TABLE 3-3 (con't). FIELD AND EPIDEMIOLOGIC STUDIES ON EFFECTS OF OZONE (O_3)[a]

Study Description	Pollutants/Environmental Variables	Results and Comments	References
Extension of previous work on relationship between pollutants and hospital admissions; extended to include month of June for 1979 to 1985 and July and August of 1983. See Bates and Sizto (1987) above.	1-h O_3, SO_2, NO_2, $SO_4^=$, CoH measured 24-h/day each 6/day; T also measured.	Analyses of O_3-associated hospital admissions for June 1983, in which O_3 levels were highest of all months and years analyzed, showed no excess of respiratory admissions in that month. Temperature explained less variance than $SO_4^=$, but T plus $SO_4^=$ accounted for 3%; and with O_3 plus T and $SO_4^=$, variance was about 5.6%. Authors conclude there are reasons against attributing the association either to O_3 or to $SO_4^=$ and postulate that O_3 and $SO_4^=$ are co-pollutants or surrogates of causative factor. PM_{15} and $PM_{2.5}$, H^+, and aeroallergens not measured.	Bates and Sizto (1989)
Effects of pollutants and other environmental variables on respiratory symptoms and PEFR evaluated in 11-mo population study of asthmatics living in high-O_3 area (Glendora) of Los Angeles County, CA. Detailed questionnaires given at outset on medical/occupational histories and personal factors, including general activity patterns; psychological tests (Asthma Symptom Checklist, State-Trait Anxiety Inventory, etc.) also given, once during good air period and once on smoggy day. Lung function (spirometry) and bronchodilator responses measured at outset in all subjects. Daily diaries (checked 2×/week), mini-Wright flow meters (calibrated 2×/week), and Nebulizer Chronology attached to metered-dose broncho-inhaler used to record symptoms, day and night PEFR, and medication use, respectively. Symptom questionnaire given 2×/week. Multiple regression analyses for overall group; then subsets (two groups of "responders") analyzed separately and compared with rest of cohort.	Air pollutant measurements for April to November 1983 used in statistical analyses. Daily maximum of NO_x, NO_2, SO_2, CO, THC less than CA standards or NAAQS. $SO_4^=$ > 25 $\mu g/m^3$ on 4 day; TSP > 100 $\mu g/m^3$ on 78% of days with data. Daily maximum 1-h average O_3 concentrations (from continuous monitoring) = 0.01-0.11 ppm on 102 days; 0.12-0.19 ppm on 65 days; 0.2-0.34 ppm on 60 days; and 0.35-0.38 ppm on 3 days. Acroallergens sampled: spores, pollens, grasses, molds, miscellaneous debris; all generally low except for group of common molds (rusts, smuts, mushrooms) present in thousands/m^2 on sampler.	Eight of 91 subjects completing study (of 109 recruited) showed no variability in asthma status during the 230-day study. Respiratory status of final study population (n = 83) as a whole not related, either clinically or statistically, to maximum 1-h average O_3 from <0.12-0.38 ppm; no significant effect of O_3 on Days t, t-1, t-2, t-3 for any respiratory variable even when adjusting for medication use, symptoms, and PEFR on Day t-1. Subset analyses showed association of O_3 with symptoms and with day and night PEFR in subjects in top quartile for respiratory measures, but association did not follow a consistent relationship with ambient O_3 concentrations. $\dot{V}_E$ levels during outdoor time not estimated. Outcomes not related, time outdoors versus indoors or to outdoor time on "clean" versus "smoggy" days. Subsets ("responders") differed from rest of cohort mainly in scores (Asthma Symptom Checklist) on factors for fatigue, hyperventilation, rapid breathing. Aeroallergens from trees showed significant (and clinically relevant) relationships to respiratory variables.	Gong (1987)
Reanalysis of daily diary study of student nurses working and living at schools in Los Angeles (Hammer et al., 1974). This paper reexamines the nurses' data using logistic regression models and time-series methods to account for serial correlation in symptom rates on successive days (see U.S. Environmental Protection Agency, 1986, for details of Hammer et al., 1974).	Total oxidant, CO, and SO_2 measured; total oxidant concentrations reached episodic levels.	Associations found between total oxidants and cough and eye irritation, confirming part of findings of original study. Association with cough only at oxidant concentrations above ca. 20 pphm. Previously reported associations between oxidants and chest discomfort and headache (Hammer et al., 1974) not confirmed.	Schwartz et al. (1988)

[a]NO_2 = nitrogen dioxide, SO_2 = sulfur dioxide, $SO_4^=$ = sulfate, CoH = coefficient of haze, T = temperature, RH = relative humidity, PM_{15} = particles ≤15 μm, $PM_{2.5}$ = particles ≤2.5 μm, H^+ = hydrogen ion, $FEV_{1.0}$ = forced expiratory volume in 1 s, $FEV_{0.75}$ = forced expiratory volume in 0.75 s, FVC = forced vital capacity, MMEF = maximum mid-expiratory flow rate, TSP = total suspended particulate, FP = fine particles, PEFR = peak expiratory flow rate, NO_x = nitrogen oxide, CO = carbon monoxide, THC = total hydrocarbon, NAAQS = National Ambient Air Quality Standards, $\dot{V}_E$ = minute ventilation, H_2SO_4 = sulfuric acid, PM_{10} = particles ≤10 μm, PEF = peak expiratory flow, MC+ = methacholine positive, MC− = methacholine negative, FP−SO_4 = fine sulfate particles, NO_3 = nitrate, NH_4 = ammonium, THI = temperature-humidity index, FEF_{25-75} = forced expiratory flow.

(CV%) were stable across the daily morning and evening tests of pulmonary function. Although asthmatics had somewhat larger CV%, no statistical differences in CV% for a.m. versus p.m. tests were seen in either group. Activity or exercise levels were not estimated, nor was amount of indoor (as on rainy days) versus outdoor activity estimated (i.e., actual exposure as well as proportion of higher versus lower exercise levels).

Raizenne et al. (1989) also presented preliminary data from a study of the effects of air pollution on girls aged 8 to 14 who attended one of three consecutive 2-week sessions of the Girl Guide camp on Lake Erie (June 29 through August 9, 1986). The health status of each camper participating in the study (112 of 145) was characterized by questionnaires completed by parents, by bronchial challenge with methacholine (positive responses were classified as Mch+ and negative responses were classified as Mch−), and by skin-prick tests for atopy. The influence of air pollution episodes on lung function was examined by comparing lung function responses for each girl on episode days with mean responses on "control" days (the latter defined as days with a 1-h O_3 maximum of ≤90 ppb; $SO_4^=$ ≤ 15 $\mu g/m^3$; and sulfuric acid, H_2SO_4, ≤10 $\mu g/m^3$). Also, lung function on the morning following an O_3 episode versus the average function on control days was examined.

Maximum decrements of 3.5% and 7% for $FEV_{1.0}$ and PEFR, respectively, were reported to be associated with four distinct air pollution episodes in which O_3, H^+, and $SO_4^=$ were all elevated. Only $FEV_{1.0}$ changes were statistically significant and only on 2 episode days (one each in Camp Sessions 1 and 2). For each camp session, the mean values for FVC, $FEV_{1.0}$, and maximum mid-expiratory flow rate (MMEF) exhibited a U-shaped pattern over time; larger first-day decrements were followed by a subsequent, more gradual return to baseline. This pattern was not observed for PEFR. The largest $FEV_{1.0}$ and PEFR decrements were observed in methacholine responsive (Mch+) children the morning after (July 26) the highest O_3 level measured (July 25) during the study. In Mch− children, however, the $FEV_{1.0}$ change was positive and the PEFR change was negative, both on July 25 and July 26. In Camp Session 3, improvement in both $FEV_{1.0}$ and PEFR were noted. The authors postulated the exposure of campers in Session 3 to a regional episode prior to their arrival in camp, with recovery occurring while at camp. No hypothesis was put forward to explain the positive $FEV_{1.0}$ change in Mch− children on the day of the highest peak O_3 level and on the day following. The lack of an aggregate analysis and the presence

of largely unexplained temporal trends in pulmonary function make interpretation of these study results difficult. This report of the study does not provide strong evidence for the effects of O_3 or of air pollution episodes on pulmonary function.

On July 25, when the 1-h O_3 level was elevated (143 ppb), 12 subjects performed pre- and postexercise spirometry (exercise level and resulting $\dot{V}_E$ not estimated). For this subset of subjects, postexercise FVC and $FEV_{1.0}$ were observed to increase on control day tests and to decrease on the episode day (results on the episode day were compared with the mean pulmonary function test results for all control days). The function changes did not attain statistical significance, however (Raizenne et al., 1989).

During the study of girls attending the Lake Erie residential camp, investigators (Raizenne and Spengler, 1989) examined the use of heart rate as a surrogate for pulmonary ventilation during daily activities. A dosimetric model was developed using heart-rate data from a standardized exercise test and from portable heart-rate recording devices. Individual exposure estimates were developed, based on time-activity data, and were related to changes in lung function observed in the children. For both O_3 and H_2SO_4, the slopes of function (i.e., peak expiratory flow rate, PEFR) versus pollutant did not differ from zero when the data were adjusted for dosimetry. Adjusted data for $FEV_{1.0}$ were not reported.

From a field study they conducted in 1984 at a YMCA summer camp (Fairview Lake) in northwestern New Jersey, Spektor et al. (1988a) have reported associations between O_3 and variations in respiratory functions for 91 children attending camp for at least 2 weeks. Average slopes for the regressions between O_3 concentrations and functions were significantly negative ($p < 0.05$) for FVC, $FEV_{1.0}$, MMEF, and PEFR for all children and for boys and girls separately. Comparable data were obtained for cohort subsets (2-week campers). When data were truncated at a heat stress index (temperature-humidity index, THI) of 78 °F, the average slopes for girls were reduced by half for the data sets restricted to THI <78 °F, eliminating significant differences in $FEV_{1.0}$ changes between girls and boys. Little or no comparable effect of a heat stress component was seen in boys. Activity levels were not estimated, so that the $\dot{V}_E$ component of the responses was not estimated for individual children or for cohort subsets.

As reported by the authors, multiple regression analyses indicated that the O_3 concentration in the hour preceding spirometry, the cumulative daily O_3 exposure during

the hours between 9:00 a.m. and the function measurement, ambient temperature, and humidity were the most explanatory environmental variables for daily variations in pulmonary function, with the 1-h O_3 concentration having the strongest influence. The authors calculated predicted average functional decrements from the average slopes of the base data set (Table 3-1, Spektor et al., 1988a), assuming the exposure-response curve to be linear, of FVC, 4.9%; FEV, 7.7%; PEFR, 17%; and MMEF, 11% for O_3 at the current standard of 120 ppb. Of the 91 children studied, 33 (36%) had individually statistically significant $FEV_{1.0}$ responses, with an average coefficient in that subset of −2.97 mL/ppb, or about a 16% decrement—again assuming linearity—at 120 ppb O_3. The values for the 2-week subsets are generally consistent directionally with O_3 concentrations in the respective 2-week periods and the total period. Likewise, slopes for data truncated at <60 ppb and <80 ppb O_3 show general directional consistency with the O_3 concentration data, except for FEF_{25-75}.

Several considerations should be noted. Ozone and temperature are statistically correlated in this study ($r = 0.37$), with evidence of effects of heat stress on O_3-associated decrements in function. If the respiratory effects depend nonlinearly on interactions between temperature (or THI) and O_3, this may confound interpretation of the effects of O_3. Data were truncated at 60 and 80 ppb and the conclusion was drawn that O_3-associated effects occurred at <60 ppb. A formal test for threshold would seem to be in order. The differing number of pulmonary function test days does not appear to have been adequately accounted for in the pooled analysis. The results of this well-conducted study would be strengthened, however, by additional analyses. As reported, calculated decrements at the level of the current standard should be interpreted cautiously.

Spektor et al. (1988b) conducted a field study of the effects of O_3 in ambient air on pulmonary function in 30 healthy adult nonsmokers (20 males, all Caucasian; 10 females, 2 non-Caucasian) exercising outdoors each work day (between 11:30 a.m. and 6:30 p.m., June 27-August 2, 1985, except for July 4 and 5) in Sterling Forest research park in Tuxedo, New York. A respiratory questionnaire was administered before exercise and spirometry was performed before and after exercise. The outdoor exercise regimen was selected by the subject. Following each exercise stint, the subject measured his own pulse rate. Ventilation ($\dot{V}_E$) for each exercise period was estimated from the subject-reported heart-rate data,

calibrated from heart-rate data recorded from indoor treadmill exercise at a pace similar to the outdoor exercise level.

For each subject, on each exercise day, pre- and postexercise function measurements were taken, and changes in function were determined for FVC, $FEV_{1.0}$, ($FEV_{1.0}$/FVC), PEFR, and FEF_{25-75}. Subject-specific exposures were estimated from duration of exercise, mean O_3 concentration during the exercise period, $\dot{V}_E$, and the tidal O_3 inhaled during exercise. Pollutants and environmental variables measured were O_3, SO_2, nitrogen oxides, ambient aerosols (PM_{15} and $PM_{2.5}$), aerosol acidity and other fine-particle ions, temperature, humidity, and wind speed and direction. Pulmonary function variables were regressed on mean O_3 concentration during exercise for each subject, as well as against the O_3 concentration during exercise on the preceding day. Interactions of other environmental variables with O_3 were tested.

All pulmonary function indices showed significant ($p < 0.01$) O_3-associated decrements. No clear effects from other variables on the effects of O_3 were seen. Mean decrements were reported as smaller in 10 subjects with $\dot{V}_E > 100$ L/min than those in 10 subjects with $\dot{V}_E$ of 60 to 100 L/min or those in 10 subjects with $\dot{V}_E < 60$ L/min. The decrements were reported to be about twice as large as those seen in 1- to 2-h chamber studies in which $\dot{V}_E$ levels were comparable. No association was found between preexercise lung function and mean O_3 concentration during exercise on the preceding day (no evidence of persistence of O_3 effects). No symptomatic responses were reported. Analysis of lung function changes for ventilations of 50 to 80 L/min was reported by the authors to indicate that the influence of $\dot{V}_E$ on lung function decrements peaks at about 80 L/min.

This study substantiates the effects of O_3 on pulmonary function in populations engaging in continuous exercise outdoors for short periods of time (15 to ca. 60 min; average duration of ca. 30 min). The study further suggests that pulmonary function decrements observed with ambient exposures to O_3 at 0.12 ppm or somewhat lower may be larger than those seen with comparable O_3 exposure concentrations and exercise conditions in controlled human exposure chamber studies, possibly due to potentiation of O_3 effects by other ambient cofactors.

In a study by Kinney, the effects of air pollutants on lung function were measured by spirometry in children (ages 10-12, 90 male and 64 female) in Kingston and Harriman, TN,

with spirometry done at least six times, ≥1 week apart, from February through April 1981 (Kinney, 1986; cited in Kinney et al., 1988). Ozone and other pollutants were monitored at a single site in central Harriman. Temperature and aeroallergens were not measured. Values for FVC, $FEV_{0.75}$, MMEF, and $\dot{V}_{75\%}$ were regressed (ordinary least squares model) on the 1-h maximum O_3 concentrations and on the 24-h-average fine particles (FP) and FP-$SO_4^=$ concentrations. Ozone concentrations ranged from 3 to 63 ppb during the study. Concentrations of other pollutants (SO_2, NO_2, total suspended particulate (TSP), inhalable particles (IP), respirable suspended particles (RSP), and FP) were not reported. Slopes of all four lung function-O_3 regressions were significantly negative. A positive mean slope of MMEF on fine particle concentrations was reported. As noted in Kinney et al. (1988), outdoor-only monitoring and lack of time-activity data compromise the specification of true exposures; and the low O_3 concentrations present during the study detract from plausibility.

Kinney et al. (1988) later published an interpretive evaluation of five epidemiological studies of the effects on lung function of acute exposures to O_3. In that review, they compared the coefficients of O_3-associated lung function declines reported in those epidemiology studies with modeled exposure-response relationships for such effects derived from a synthesis by Hazucha (1987) of results from controlled human exposure studies. Hazucha (1987) modeled the effects of exercise-related ventilation rates ($\dot{V}_E$) in potentiating the effects of O_3 on pulmonary function, using pooled data from 2-h chamber studies of healthy young adults exercising intermittently. Kinney et al. (1988) reexpressed the data of Hazucha (1987) in units consistent with the epidemiologic study results (assuming a linear relationship between lung function decline and concentrations up to 100 ppb and using baseline functions obtained in Kinney, 1986). The resulting coefficients were reported as being larger than those from controlled studies, especially for FVC (which was about five times the mean FVC coefficients from the controlled studies). Kinney et al. (1988) concluded that the "effective" exposures in the epidemiologic studies were cumulative over longer periods (from 8 to 12 h versus the 2-h exposures used to generate the controlled exposure data analyzed by Hazucha).

The Kinney et al. (1988) analysis provides further results suggesting that possibly larger lung function decrements occur with ambient O_3 exposures than those seen in controlled human exposure studies. However, caution is warranted given several considerations. For

one, no justification was given for the use of the linear model and the transformation of data from Hazucha (1987), who had used a quadratic model. At concentrations ≤100 ppb, a linear model would tend to overestimate lung function decrements if the quadratic model is actually more appropriate, whereas at higher O_3 concentrations the linear model would underestimate lung function decline in comparison to a quadratic model. Unfortunately, although the upper end of the range of O_3 concentrations measured in the epidemiologic studies reviewed partially overlaps the lower end of the range used in the controlled studies modeled by Hazucha, the mean concentrations in the respective epidemiologic studies from which data were used were <100 ppb—thereby not allowing for a direct comparison of the magnitudes of the effects seen with ambient versus controlled exposures across a fuller range of exposures of interest (e.g., 0.05 to 0.15 ppm O_3). Also complicating the comparison are possible differences in exposure durations—leading, in fact, to the postulation by Kinney et al. that the effective O_3 exposures (including lower ambient O_3 levels) were likely to have been more prolonged (8 to 12 h) in the epidemiology studies than the exposure duration (2-h) used in the controlled exposure studies.

Lioy and Dyba (1989) also reported a new analysis of previous data suggestive of prolonged O_3 exposures being the effective exposures in an earlier field study conducted in Mendham, NJ, as reported on by Bock et al. (1985) and Lioy et al. (1985). In this case, Lioy and Zyba used a time-activity pattern analysis for a hypothetical typical camper that would have experienced a usual daily activity schedule analogous to children participating in the Mendham summer camp study. They found that the time-activity analysis indicated a likelihood that periods of increased exercise for the camper would have likely occurred over prolonged periods of time (several hours) during which ambient ozone levels were elevated (i.e., above 0.10 to 0.12 ppm). Evaluation of the total estimated O_3 dosages likely experienced on successive days of a 4-day O_3 episode further led them to hypothesize that the accumulated, multihour doses from prolonged daily exposures to ambient O_3 may have been most important in producing the pulmonary function decrements earlier reported for the Mendham study, rather than next day residual effects being due to peak O_3 concentrations.

Vedal et al. (1987) reported data from an 8-mo panel study of symptoms and concurrent but successive 9-week PEFR studies in asthmatic and nonasthmatic school children living in the Chestnut Ridge area of western Pennsylvania. Neither respiratory symptoms nor PEFR

was strongly associated with any of the environmental variables, which included peak 1-h O_3, NO_2, SO_2, and CoH, and daily temperature. Level of PEFR on the previous day was the strongest predictor of daily PEFR. True exposures to O_3 and other pollutants may have been misspecified, because data were obtained from only one monitor for the whole area, except for SO_2, for which an average of values from 17 monitors was used; and individual exposures and activity levels were not estimated. Further, levels of O_3 during this school-year study were very low, with the daily maximum 1-h levels ranging from 0 to 129 ppb, with a mean of 32.4 ppb.

Results for the 1980-1981 school year have been recently reported by Dockery et al. (1989) from an ongoing study of the effects of ambient air pollution on respiratory health in children living in six cities in the United States: Watertown, MA; Kingston-Harriman, TN; Steubenville, OH; Portage, WI; a geographically defined portion of St. Louis, MO; and Topeka, KS. Previous results showed that the reported prevalence of chronic cough, bronchitis, and chest illness increased by about a factor of two across the range of TSP and SO_2 concentrations measured in the six cities. Lung function was determined at school by spirometry, and a respiratory illness and symptom questionnaire was completed by each child's parents. Pollutants measured included TSP and particles ≤ 15 μm (PM_{15}) and $PM_{2.5}$, O_3, NO_2, and SO_2. Continous measurements (hourly values) of SO_2, NO_2, O_3, and meteorological variables, as well as daily values for various particle measures (e.g., TSP, PM_{15}, $PM_{2.5}$, etc.), were taken. Monthly means for each pollutant were calculated from daily means, and an estimate of air pollution exposure during the previous year was obtained for each child by averaging the monthly means for a given city for the 12 mo preceeding the child's spirometry test. All pollutant concentrations were highly positively correlated with each other in all cities, except for O_3, which was highest in those cities with low levels of the other pollutants. The pulmonary function parameters measured were FVC, $FEV_{1.0}$, $FEV_{0.75}$, and MMEF. Five respiratory illness or symptom categories were also considered: bronchitis, cough, chest illness, wheeze, and asthma.

As in previously reported results from earlier years of this study, chronic cough, bronchitis, and chest illness were positively associated with all three measures of particulate pollution—TSP, PM_{15}, and $PM_{2.5}$—but only associations with PM_{15} were statistically significant. Sulfur dioxide, which showed correlation with the particulate measures, was

much more weakly associated than particles with the respiratory symptoms. The association of NO_2 with respiratory symptoms was also weak. There were negative associations of O_3 with cough and chest illness, but annual O_3 showed a strong positive association with asthma and hay fever (in contrast to negative associations of these symptoms with all other measured air pollutants). No association was found between air pollutant levels and the pulmonary function measures, including $FEV_{0.75}$ and MMEF, which are more sensitive measures of small airway impairment than $FEV_{1.0}$ and FVC. This led the authors to conclude that the increased rates of illness observed for some pollutants were not likely associated with permanent loss of pulmonary function—at least in preadolescent years.

Bates and Sizto (1987) have reanalyzed earlier data (Bates and Sizto, 1983; Bates, 1985) and extended their analyses to more recent data (now covering 1974 and 1976-1983) for examining correlations between environmental variables and hospital admissions for 79 acute-care hospitals in southern Ontario, Canada. Pollutant concentration data for O_3, NO_2, sulfur dioxide (SO_2), coefficient of haze (CoH), and sulfate ($SO_4^=$) were collected at 17 sampling stations located across a 280-mile corridor between the Windsor and Peterborough areas of Southern Ontario. Correlations were examined for relationships among environmental variables and between environmental variables and three categories of hospital admissions for winter (January-February) and summer (July-August), i.e. for total respiratory admissions (TRA), TRA minus asthma (TRA—A), and nonrespiratory admissions, separately.

The authors concluded that an association exists in southern Ontario between O_3 and TRA and TRA—A in summer, but they note that these results are not in agreement with those of Richards et al. (1981), who found no associations between O_3 and admissions to children's hospitals or emergency room visits in Los Angeles, where O_3 levels are higher than those in southern Ontario. They concluded, as well, that aerosol $SO_4^=$ levels explain the highest percentage variance in TRA from pollution in summer, but are not correlated with TRA in winter. They also concluded that O_3 and $SO_4^=$ may be surrogates for one or more other species that travel with them in summer but not in winter, such as hydrogen ions (H^+) in the fine-particle range. Lastly, it should be noted that Bates and Sizto (1987) specifically tested the maximal 8-h O_3 average for correlation with TRA. The Pearson correlation coefficient was not affected by substitution of the 8-h value in place of the mean of the hourly

O_3 maxima previously used. The correlation between the 1-h and 8-h O_3 maxima across all monitoring stations was 0.986.

Using the same methodology, Bates and Sizto (1989) examined aerometric and hospital admissions data for June, July, and August 1983 and for June in the years 1979 through 1985 because June 1983 was observed to have O_3 levels higher than those in any July or August previously examined. Analyses showed no excess respiratory admissions in June 1983. Furthermore, in years for which excess hospital admissions were observed in June (1982 and 1985), increased admissions were in the categories of "acute bronchitis" and "asthma," but not in other respiratory categories, a finding inconsistent with O_3-associated excess admissions reported earlier. The authors concluded that these findings cast doubt "on the primacy of O_3 as the cause" of increased admissions, and that there are reasons against attributing excess admissions either to O_3 or $SO_4^=$.

Although asthmatics are not unequivocally more sensitive to O_3 than nonasthmatics, neither have they been shown to be less sensitive (U.S. Environmental Protection Agency, 1986). Therefore, the findings of an epidemiologic study of asthmatics reported by Gong (1987) are of particular interest. Gong (1987) studied the relationship between air quality and the respiratory status of 83 asthmatics living in a high-oxidant area of Los Angeles County. The study covered February to December 1983, but data analyses were limited to a 230-day period (April 15-November 30) because of staggered entry of subjects into the study and the high frequency of missing or incomplete data encountered in the earlier part of the study period.

Regression and correlation analyses between O_3 and average symptom scores, asthma medication index (AMI), and day and night PEFR across subjects showed weak, nonsignificant relationships. These daily outcome variables were compared for days with maximum 1-h-average O_3 in three ranges: <0.12 ppm, 0.12-0.19 ppm, and >0.20 ppm; "no statistical or clinical significance was detected." Individual exposures and activity patterns were not estimated in these two analyses. Multiple regression analyses also indicated the lack of a significant overall relationship between O_3 (and other independent variables) and respiratory status, despite the use of lagged variables and the inclusion of other pollutants, meteorological variables, aeroallergens, and AMI. Total suspended particulates directly affected PEFR, but the relationship was not consistent in the analysis. Aeroallergens showed

significantly negative relationships to respiratory variables, but only the effect of trees was considered clinically relevant. Temperature and humidity showed no significant effect on the respiratory variables in this study.

Although there was no significant overall effect of O_3 on respiratory variables in the 83 asthmatic subjects, multiple regression analysis of subjects whose O_3 coefficients on various days were in the top quartile for dependent variables (respiratory measures) showed significant and consistent effects of O_3 on day t and the previous day $(t-1)$. Multiple regression testing of subsets for associations of symptom score or day or night PEFR on the same day's O_3 and the previous day's value of the same responses showed highly significant O_3 coefficients for all three respiratory measures.

The clinical significance of responses in symptom scores and day and night PEFR was evaluated for all subjects by individual regression analyses. No subject had evidence of significant worsening of symptoms attributable to O_3 during the study. Adult subjects with high scores in fatigue, hyperventilation, dyspnea, congestion, and rapid breathing in the Asthma Symptom Checklist had more negative slope coefficients for O_3 than subjects with low-to-moderate scores on the checklist. "Responders" (statistically identified by multiple regression analysis) scored consistently higher in the the factors representing fatigue, hyperventilation, and rapid breathing. The higher scores of these responders, however, "were apparently not associated with differences in ambient ozone concentrations since the test scores were similar during relatively low (first test) and high (second test) ozone days. The significance of the psychological results is unclear at this time and will be the subject of further analyses" (Gong, 1987).

Lastly, it should be noted that a reanalysis by Schwartz et al. (1988) of the Los Angeles epidemiology study of student nurses earlier reported by Hammer et al. (1974) confirmed the Hammer et al. results showing oxidants to be significantly associated with eye discomfort and cough. However, earlier reported associations between oxidants and headache or chest discomfort were not confirmed. The relationship of oxidants to eye irritation has been previously reported by others and appears to be related to peroxyacetal nitrate (PAN) rather than O_3. Cough has been shown, however, to be a respiratory symptom related to O_3, and the present reanalysis (using logistic regression models and time-series analyses controlling for autocorrelation effects) confirmed the presence of an apparent threshold for "cough"

earlier found by the "hockey-stick" function analysis done by Hammer et al. (1974). The upward flexure point in the dose-response curve occurs near the value reported by Hammer et al. (ca. 20 pphm total oxidants)—a value likely including O_3 levels well above the current 1-h O_3 NAAQS of 0.12 ppm.

3.1.3 Laboratory Animal Studies

The more recently published reports on the animal toxicology of O_3 were evaluated according to their overall relevance to the issues of O_3 toxicology described below. A report not clearly applicable or unique in its contribution was not considered. Hence, studies that added little or no data or insight to the issues being addressed, or that corroborated or tended to duplicate the content of other studies contained in the Ozone Criteria Document (U.S. Environmental Protection Agency, 1986) were eliminated in order to summarize the newer pertinent data as briefly as possible. Additional literature has been selected for review here that contained information on (1) the effects of multihour and multiday exposures to O_3, (2) the potential health effects of chronic O_3 exposure, and (3) the conceptual and empirical linkages between animal and human O_3 toxicology (i.e., extrapolation). Information on a less-specific, but nevertheless important, aspect of O_3 toxicity (e.g., "adaptation") is given here as well.

3.1.3.1 Effects of Multihour Exposures

Three studies on the effects in animals of multihour exposures to O_3 (Table 3-4) have been reported (Van Bree et al., 1989; Rombout et al., 1989; Costa et al., 1989). Results of these studies point to the fact that concentration (C) dominates duration of exposure (T) in eliciting a toxic response to the lung as determined by lavagable plasma protein on the lung surface. All three studies suggest that exposure C and T can be modeled mathematically and clearly demonstrate the dominance of C in eliciting effects. Although the effect of T on response is clearly C dependent, the influence of T is apparent at all levels, with some indication that C and T interact in a synergistic manner in the low C-long T exposures. Although further work on this last point is needed, it appears that the C $\times$ T approach only holds for a given C and cannot be applied in a general fashion.

TABLE 3-4. EXPERIMENTAL ANIMAL STUDIES ON THE RELATIVE INFLUENCE OF OZONE (O_3) CONCENTRATION AND DURATION OF EXPOSURE[a]

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Exposure Duration and Protocol	Species	Observed Effects	Conclusions	Reference
250 500 750 1,500 4,000	0.13 0.26 0.38 0.77 2.0	0, 1, 2, 4, or 8 h; 1-54 h	Wistar rats	Concentration, duration, and time of day of exposure affected response of lavage fluid protein levels. Duration of exposures less than half as significant as time of exposure. Concentration dominated.	The time of exposure day is important in studying oxidant toxicity. The primary determinants are concentration and time followed by duration. A quadratic polynomial could model the response.	Rombout et al. (1989)
784	0.4	12 h; 1-3, 7 days	Wistar rats	Acute inflammation resulted from O_3 exposure as indicated by lavage fluid protein and tissue antioxidant enzymes. Exposures of 1-3 days did not alter the peak or recovery profiles of lavage fluid protein or PMNs.	Oxidant stress is evident at the lung tissue level. Effects of O_3 beyond 1 day do not appear to be cumulative. Recovery from exposure is unaltered from 1-3 days of exposure.	Van Bree et al. (1989)
196 392 784 1,568 2,352	0.1 0.2 0.4 0.8 1.2	1-8 h	F-344 male rats	Matrix study design showed dominance of C over T in protein response.	A polynomial model described data and suggested C × T interaction (synergism) at decreased C and increased T. The C × T = k could only be applied at constant C.	Costa et al. (1988, 1989)
980 1,568	0.5 0.8	2 or 7 h with CO_2 hyperventilation		Lung function variables showed T effects but were dominated by C. Linearity held for FVC, as seen in humans, but did not hold for other variables.	C dominates T. Functional changes do not correlate with permeability to protein. Rat model mimics human data and can be appropriately applied.	

[a]PMNs = polymorphonuclear leukocytes, C = concentration, T = exposure duration, CO_2 = carbon dioxide, FVC = forced vital capacity.

Costa et al. (1989) have attempted to address whether the apparent cumulative loss of lung function seen with O_3 exposure in human subjects also occurs in experimental laboratory animals. As reported in humans by Folinsbee et al. (1988), FVC fell in a linear fashion with estimated cumulative exposure, which incorporated ventilation, but only at lower concentrations (≤0.5 ppm for up to 7 h). At 0.8 ppm, the effect of T on the C response dramatically increased, as was seen in their matrix studies of C × T relationships and in similar studies by Van Bree et al. (1989). Hence, the impact of T is C dependent. It should be noted, however, that the apparent cumulative toxicity of O_3 may be endpoint dependent as well and that the simple loss of lung volume, FVC or FEV_1, may demonstrate such a relationship (linearity) more clearly than more interdependent measures such as DL_{CO} and N_2 washout.

3.1.3.2 Effects of Multiday Exposures

An animal model has been developed (Costa et al., 1988) that exhibits the same pattern of attenuated response to intermittent short-term O_3 (a phenomenon known as "adaptation") as has been described in humans. More specifically, repeated 2-h exposures of rats for up to 5 days resulted in adaptation or attenuation of the O_3-induced functional deficits, with sustained but not worsening protein accumulation occurring in the lavage. However, the histopathology of these animals appeared to worsen and evolve from an acute to a more chronic inflammatory pattern. Recovery or exposure points beyond 5 days were not conducted. Antioxidant levels of the lung tissues showed a slight upward trend during this period, but their role in the pattern of response is unclear. This model demonstrates that morphological and biochemical changes continue even while lung dysfunction attenuates with repeated O_3 exposure, suggesting that the use of lung function tests alone to assess injury can result in misinterpretation of risk to health with repeated exposures to O_3. Whatever the precise mechanisms and attenuation events, however, animal studies have demonstrated that chronic exposures cause effects, some of which are irreverisible.

The protein and PMN response to repeated 12 h nocturnal exposures for up to 3 days as an analogue of an O_3 "episode" appeared to be governed by the initial exposure only (Van Bree et al., 1989). In other words, the degree of response and recovery time were unaltered by additional exposures during the 2- or 3-day period.

3.1.3.3 Effects of Chronic Exposure to Ozone

Several recent reports on O_3 effects in laboratory animals have focused on the structural alterations of the distal lung associated with prolonged, repeated exposures (see Table 3-5). In both the adult and neonate rat (Barry et al., 1988; Grose et al., 1989; Huang et al., 1988; Gross and White, 1987) and the monkey (Tyler et al., 1988; Hyde et al., 1989), high ($\geq$0.25 ppm) ambient levels of O_3 appear to similarly affect the junctional airways of the distal bronchioles and the proximal alveoli. Shifts in cell population occur that result in more cuboidal cells interfacing the airway lumen, effectively presenting less cell surface to the air, and presumably reducing individual cell dose (Crapo et al., 1985; Barry et al., 1985, 1988; Sherwin and Richters, 1985). Interstitial inflammation predominates over time, resulting in thickened septal areas that do not completely recover during several weeks of postexposure clean air (Huang et al., 1988; Barr et al., 1988; Moffatt et al., 1987). These findings are largely consistent with the reports of enhanced collagen deposition and reduced turnover with very high ambient levels of O_3 (0.57 to 0.8 ppm) in monkeys (Reiser et al., 1987) and rats (Hacker et al., 1986; Pickrell et al., 1987), but appear discrepant with collagen analyses in chronically exposed rats at very low O_3 concentrations (Filipowicz and McCauley, 1986; Wright et al., 1988), unless exposure is intermittent (Tyler et al., 1988).

A preliminary report from the U.S. EPA's chronic O_3 study (Grose et al., 1989) showed that repeated daily exposure of rats to a daily episodic profile of O_3 (22 h, 0.06-ppm background with a 0.25-ppm peak; equivalent to a square wave that averaged 0.19 ppm over 9 h) for 12 mo resulted in small, but significant, decrements in lung function that were consistent with early signs of focal fibrogenesis in the proximal bronchoalveolar junction (see Chang et al., 1991). Augmentation of lavagable protein levels and tissue fractions of ascorbate- and glutathione-related enzymes after 12 mo of O_3 exposure were indicative of the continued oxidant challenge. Further results of these studies through to 18 mo of exposure and with recovery periods will be published. The functional implications of these alterations in distal airway architecture have been explored in one higher level O_3 study (0.5 ppm) in which airflow mechanics were reversibly altered (Gross and White, 1987). Changes in lavagable enzymes in rats (Grose et al., 1989) and lipids in monkeys (Rao et al., 1985a,b) after prolonged exposures are consistent with shifting cell populations and/or inflammation,

TABLE 3-5. CHRONIC OZONE (O_3) EFFECTS IN EXPERIMENTAL ANIMALS

Ozone Concentration $\mu g/m^3$	Ozone Concentration ppm	Exposure Duration and Protocol	Species[a]	Observed Effects[b]	Conclusions	Reference
1,862	0.95	8 h/day for 90 days	Male Sprague-Dawley rats	Inflammation in proximal acinus; decrease in terminal bronchial lumen diameter without change in volume, while respiratory bronchiole volume increased 3.4×.	Respiratory bronchioles are formed from centriacinar alveolar ducts. The focal lesion induced by O_3 within the acinus appears to shift distally with respiratory bronchiolization.	Barr et al. (1988)
235 1,470	0.12 0.25	12 h/day for 6 weeks	F-344 rats: neonates vs. adults	Damage to proximal alveolar tissues. Shift in cell population to more, smaller, cuboidal cells. Epithelial thickness increased, interstitial macrophages doubled.	Enhanced Type I cell turnover, interstitial inflammation was concentration dependent; no age-related differences.	Barry et al. (1985) Crapo et al. (1985)
490	0.25	12 h/day for 6 weeks	Male F-344 rats: neonates vs. adults	Decreased ciliated surface of Clara cells and number of brush cells per square millimeter of terminal bronchiolar basement membrane.	Structure of the terminal bronchiolar cells is significantly altered; no age-related differences.	Barry et al. (1988)
245 490 980	0.125 0.25 0.50	21 h/day for 3 to 12 mo	F-344 male rats	No consistent increase in lung collagen or total protein content. Significant increase in ^3H protein incorporation into collagen and total protein in rats exposed to 0.25 ppm for ≥3 mo or to 0.125 ppm for ≥9 mo.	Prolonged exposure to O_3 increases the turnover rate of lung collagen and total protein content.	Filipowicz and McCauley (1986)

TABLE 3-5 (cont'd). CHRONIC OZONE (O_3) EFFECTS IN EXPERIMENTAL ANIMALS

Ozone Concentration $\mu g/m^3$	Ozone Concentration ppm	Exposure Duration and Protocol	Species[a]	Observed Effects[b]	Conclusions	Reference
118 490	0.06 0.25	0.06 ppm for 13 h/day; slow 9-h peak of 0.25 ppm, 5 days/week; for 12 mo	F-344 male rats	Decrements in lung volume and N_2 washout consistent with restrictive lung lesions. Antioxidant enzymes were increased and lavage fluid protein was elevated.	Lung lesion resulting from O_3 exposures is evident and appears to be restrictive in nature, suggesting possible fibrogenesis.	Grose et al. (1989)
1,372	0.70	20 h/day for 28 days; postexposure of 4 to 9 weeks	F-344 male rats	Decreased lung volumes, decreased DL_{CO}, and altered airflow mechanics after exposure. A 4-week recovery allowed most parameters to return to normal. Some flow decrement remained through 9 weeks. Some interstitial collagen remained after each mild inflammation.	Airflow dysfunction may be related to thickening of alveolar ductal regions. Continuous recovery post-exposure was not apparent for some of the flow-related variables.	Gross and White (1986)
980	0.5	20 h/day for 52 weeks; 12 week postexposure recovery; kills at 6 and 12 mo	F-344 male rats	Increased in FRC and RV and 6 and 12 mo; DL_{CO} decreased over same period. The 3-mo recovery period resulted in reversibility of the functional lesion. Inflammation was mildly correlated with function and reversed.	Chronic O_3 exposure in rats induces a mild lesion which is reversible.	Gross and White (1987)
1,568	0.8	3 days	Male Sprague-Dawley rats, 24 to 365 days old	Increased collagen synthesis with greatest changes occurring at >60 days of age.	Increased collagen synthesis following O_3 exposure may be age dependent.	Hacker et al. (1986)

TABLE 3-5 (cont'd). CHRONIC OZONE (O_3) EFFECTS IN EXPERIMENTAL ANIMALS

Ozone Concentration $\mu g/m^3$	Ozone Concentration ppm	Exposure Duration and Protocol	Species[a]	Observed Effects[b]	Conclusions	Reference
294	0.15	8 h/day for 6 or 90 days	Bonnet monkeys	Qualitative changes in secretory products in nasal epithelium caused by 6 days of exposure; also quantitative changes: increase in stained mucosubstance after O_3 exposure for 6 days; after 90 days, there was significantly less than after 6 days; nasopharyngeal region only minimally affected and only at 6 days.	O_3 causes quantitative changes in stored secretory products in anterior nasal cavity epithelium.	Harkema et al. (1987a)
294 588	0.15 0.30	8 h/day for 6 or 90 days	Macaque monkeys	Injury and cell changes in transitional and respiratory epithelium of nose. Shortened cilia, cell necrosis, secretory cell hyperplasia and inflammation at 6 days. Goblet cell hyperplasia by Day 90.	Ambient O_3 can cause nasal cell injury and changes after both short and long term exposures.	Harkema et al. (1987b)
118 490	0.06 0.25	0.06 ppm for 13 h/day; slow 9-h peak of 0.5 ppm, 5 days/week; 1, 3 weeks and 3 mo; recovery for 6 weeks	F-344 male rats	Shift from acute inflammatory phase to more chronic character. Increased cell volumes of Type I and especially Type II cells and interstitial thickening subsided by 6 weeks postexposure.	Interstitial inflammation may remain and lead to chronic matrix damage.	Huang et al. (1988)

TABLE 3-5 (cont'd). CHRONIC OZONE (O_3) EFFECTS IN EXPERIMENTAL ANIMALS

Ozone Concentration $\mu g/m^3$	Ozone Concentration ppm	Exposure Duration and Protocol	Species[a]	Observed Effects[b]	Conclusions	Reference
294 588	0.15 0.30	8 h/day; 6 or 90 days	Macaque monkeys	Respiratory bronchiolitis at 6 days, persisting to 90 days of exposure; nonciliated bronchiolar cells were hypertrophied and increased in number.	Persistent epithelial injury in respiratory bronchioles at O_3 concentrations as low as 0.15 ppm.	Hyde et al. (1989)
784 1,254	0.40 0.64	8 h/day for 90 days	Bonnet monkeys	Changes focused in respiratory bronchioles: (1) thicker walls, narrower lumens; (2) more cuboidal cells, fewer squamous cells; (3) thicker interstitium; (4) more cellular organelles associated with protein synthesis.	Concentration-dependent reactive peribronchiolar inflammation; apparent "adaptive" shift in cell populations.	Moffatt et al. (1987)
1,117 2,156	0.57 1.10	19 h/day for 11 days; 1-60 days postexposure	F-344 female rats	At Day 12, concentration dependent inflammation, Type II cell hyperplasia. Increased elastolytic/ collagenlysis. Reduced intracellular collagenlysis. At 60 days, increased total collagen and modest alveolar ductal fibrosis.	Proteolysis and altered collagen turnover results in increased lung collagen after high O_3 levels.	Pickrell et al. (1987)
294 588 294	0.15 0.30 0.15	8 h/day for 90 days 8 h/day for 21 days	Bonnet monkeys	18:2 and 20:4 fatty acids in BAL increased $\approx 2\times$ in O_3-exposed monkeys; cholesteryl ester levels decreased and phosphatidylcholine increased with 90-day exposures. Lung PUFA levels decreased at 0.15 and 0.30 ppm, whereas plasma LCAT activity increased at 0.3 ppm.	Changes in lung lipids may be related to O_3 and protection from oxidation by O_3.	Rao et al. (1985a,b)

TABLE 3-5 (cont'd). CHRONIC OZONE (O_3) EFFECTS IN EXPERIMENTAL ANIMALS

Ozone Concentration $\mu g/m^3$	Ozone Concentration ppm	Exposure Duration and Protocol	Species[a]	Observed Effects[b]	Conclusions	Reference
1,196	0.61	8 h/day for 1 year	Cynomolgus monkeys	Increased lung collagen with altered crosslinking. Reducible crosslinks returned to control levels by 6 mo post; however, the nonreducible hydroxypyridinium remained elevated.	The collagen synthesized during exposure was abnormal, and once deposited remained irreversible.	Reiser et al. (1987)
588	0.3	7 h/day, 5 days/week for 6 weeks	Swiss-Webster male mice	Greater increase in Type II cell area ($p = 0.08$) than number (n.s.).	Damage to Type I cells with Type II cell hyperplasia and possible alteration of lung connective tissue.	Sherwin and Richters (1985)
490	0.25	8 h/day; alternating O_3/Air each of 18 mo (intermittent group) vs. 18 mo continuous exposure	Cynomolgus monkeys	Both groups: respiratory bronchiolitis, increased number of respiratory bronchioles, alterations in lung growth. Continuous group: Increased number of inflammatory cells (mostly macrophages) in lumen and interstitium. Intermittent group: Increase in total lung collagen, chest wall compliance (suggestive of delay in lung maturation), and inspiratory capacity.	Episodic exposures had continued injury during nonexposure periods, indicating higher risk than anticipated.	Tyler et al. (1988)
235 490 980	0.12 0.25 0.50	21 h/day for 6, 12, and 18 mo	F-344 male rats	No increase in total lung collagen. No significant increase in ^3H protein incorporation into collagen and total protein in O_3 exposed rats.	Prolonged exposure to O_3 did not alter age-related changes in collagen synthesis rates or collagen content of the lung.	Wright et al. (1988)

[a]F-344 = Fischer-344

[b]^3H = tritiated thymidine, N_2 = nitrogen, DL_{CO} = diffusing capacity for carbon monoxide, FRC = functional residual capacity, RV = residual volume, BAL = bronchoalveolar lavage, PUFA = polyunsaturated fatty acids, LCAT = plasma lecithin cholesterol acyltransferase, n.s. = not significant.

but remain nonspecific effects that still need to be linked with progressive injury or defensive adjustments to the O_3 challenge.

Ozone also has a significant impact on nasal epithelium and mucosal lining (Harkema et al., 1987a,b). The health significance of this finding is uncertain, but is consistent with the deposition data on O_3 from both animal and human studies. Hence, though O_3 is relatively insoluble in water, the nose appears to provide some degree of scrubbing, and thus, provides protection to the deeper lung. Species differences in this capability are an important extrapolation question (see below).

3.1.3.4 Animal-to-Human Extrapolation

The more recently published studies cover two aspects of extrapolation: (1) models and their validation and (2) species comparisons.

The Miller model (Miller et al., 1987a,b; Overton et al., 1987; Miller and Overton, 1989) of lower respiratory tract deposition of O_3 has been enhanced with the incorporation of both ventilatory parameters and empirically derived anatomical data (see Table 3-6). Use of the model with input parameters from several rodents and humans indicates preferential deposition, and presumably associated injury, in the bronchoalveolar junction, which is consistent with empirical findings in laboratory animals. The model agrees well with the total and partitioned uptake values determined in human studies (Gerrity et al., 1988), though it fits less well with the rodent uptake data (Wiester et al., 1988). Although the reasons for this are not as yet clear, the overall consistency of the predicted deposition distribution within the lung and the approximate equality of dose rate/surface area increase confidence in the model (Gerrity and Wiester, 1987).

Both human and animal uptake studies of O_3 have been conducted (see Tables 3-1 and 3-6). Although humans (Gerrity et al., 1988) appear to retain a somewhat greater fraction of the inhaled O_3 than do rodents (Wiester et al., 1988), the biological significance of this difference is uncertain at this time, especially considering the slight differences in technique. Santrock et al. (1989) have shown that with continued exposure, products of O_3, as indicated by an oxygen-18 (^{18}O) label, accumulate in the lungs of mice with continued exposure. The difference in total uptake between humans and laboratory rodents may result in part from differences in nasopharyngeal removal of O_3 (40% in humans, 17% in rats; as reported by

TABLE 3-6. STUDIES RELEVANT TO POTENTIAL ANIMAL-TO-HUMAN EXTRAPOLATIONS

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Exposure Duration and Protocol	Species[a]	Observed Effects[b]	Conclusions	Reference
	None		Rats Hamsters Baboons Humans	There were significant differences in lung levels of CAT, GSH S-trans, and GSH-Px; rats had greater deviation from the other 4 species.	Hamster is best model for human antioxidant enzymes.	Bryan and Jenkinson (1987)
588 784	0.3 0.4	0.3 ppm for 1 h (rat) 0.4 ppm (human)	F-344 male rats Male humans	Total uptake in rats was approximately 44% of that inspired. Human uptake was 96%, with 36% uptake in the nasopharynx. Estimated doses to lung surface of each species were about the same assuming nasal uptake in the rat of 20%.	Conclusions suggest that tissue dosing of lungs in rats and humans may not be as different as might appear on the basis of total uptake.	Gerrity and Wiester (1987)
	None	Model	—	A mathematical model was used to quantitatively assess the impact of physiochemical (solubility, reactivity, diffusivity radial air phase transport) and physiological variables (lung size, ventilation rate) on the distribution of O_3 dose to the respiratory tract.	Liquid phase reactivity and surface liquid thickness contribute most to the O_3 tissue absorption rate and, therefore, to the determination of local tissue dose and its regional distribution.	Hanna et al. (1989)
1,960	1.0	1 h	Rabbits Rats Mice	Enrichment of ^{18}O in respiratory tracts of animals exposed to $^{18}O_3$; more in lining layer than whole tissue.	Tracing ^{18}O in tissues and tissue subfractions following $^{18}O_3$ exposure is feasible and practical.	Hatch and Aissa (1987)
392-3,920	0.2-2.0	4 h	Swiss albino mice Sprague-Dawley rats N.Z. white rabbits Golden hamsters	BAL protein increases after O_3 were most marked in guinea pigs ($\geq$0.2 ppm). Mice, rats, and hamsters at $\geq$1.0 ppm. Rabbits at 2.0 ppm. Not body weight/size dependent and not comparable in order of sensitivity to $COCl_2$.	There are species differences in susceptibility to O_3. Mechanisms not clear but antioxidants are not inversely correlated.	Hatch et al. (1986)

TABLE 3-6 (cont'd). STUDIES RELEVANT TO POTENTIAL ANIMAL-TO-HUMAN EXTRAPOLATIONS

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Exposure Duration and Protocol	Species[a]	Observed Effects[b]	Conclusions	Reference
1,960	1.0	2 h ($^{18}O_3$) animals preexposed 1 year to cycled 0.25 ppm O_3 5 days/week	F-344 male rats	Total respiratory uptake was determined by fractional uptake from inhaled gas. Deposition distribution in the nose, trachea, and lung were determined for ^{18}O distribution in those tissues. Total uptake was 54%; distribution was nasopharynx 44%, trachea 7%, lung 49%. No exposure group differences.	Approximately 44% of the inhaled O_3 was scrubbed by the nose of rats. Most of the remainder deposited in the pulmonary region. Chronic O_3 exposure did not affect uptake.	Hatch et al. (1989)
392-3,920	0.2-2.0	Model	Rats Guinea pigs Rabbits Human data	Model applied to human FEV_1 data and to BAL protein values for several rodents to compare tissue dose-based response.	Guinea pigs appear most sensitive to O_3 on tissue dose basis. Humans appear to receive higher dose to elicit effect, which creates potential conflicts in interpretation.	Miller et al. (1987a,b) Miller and Overton (1989)
	None	Model	Composite rat and guinea pig data	Theoretical model incorporates variety of factors associated with deposition in lower respiratory tract.	Major target for tissue dose is bronchiolar alveolar junction. Appears to be common across species and correlates with pathology.	Overton et al. (1987)
1,960	1.0	Up to 1 h; 24 h post	Mice	$^{18}O_3$ used to track O_3 deposition; products accumulated linearly over 1 h of exposure and were removed exponentially during the 24 h after exposure.	^{18}O is a useful marker for O_3 exposure, accumulating linearly with time ($\leq$1 h) at a single O_3 concentration. Reaction products are removed during recovery.	Santrock et al. (1989)
	None		Rabbits Guinea pigs Rats Hamsters Mice Humans Pigs Sheep	There were significant differences in lung levels of ascorbic acid, α-tocopherol, and nonprotein-SH among the various species.		Slade et al. (1985)

TABLE 3-6 (cont'd). STUDIES RELEVANT TO POTENTIAL ANIMAL-TO-HUMAN EXTRAPOLATIONS

O_3 Concentration $\mu g/m^3$	O_3 Concentration ppm	Exposure Duration and Protocol	Species[a]	Observed Effects[b]	Conclusions	Reference
588 1,176 1,960	0.3 0.6 1.0	1 h	Sprague-Dawley rats, male	Total respiratory uptake of O_3 on a fractional basis was about 40%. The value did not change with exposure concentration or over the normal range of tidal breathing.	Fractional uptake of O_3 in rats is about 40% of that concentration inhaled ≤1.0 ppm. Although this uptake did not change, actual dose was concentration dependent.	Wiester et al. (1987)
588 1,176	0.3 0.6	1 h	F-344, Sprague-Dawley, and Long-Evans rats. Hartley guinea pigs.	Total respiratory uptake was about 42% for all species. Guinea pigs had uptake slightly but not significantly higher than the rats.	Fractional uptake of O_3 in rodents is about 42% and appears not to be species dependent.	Wiester et al. (1988)

[a]F-344 = Fischer-344, N.Z. = New Zealand.
[b]CAT = catalase, GSH = glutathione, O_3 = ozone, ^{18}O = radiolabeled oxygen, $^{18}O_3$ = radiolabeled ozone, BAL = bronchelveolar lavage, $COCl_2$ = phosgene, FEV_1 = forced expiratory volume in 1 s, SH = sulfhydryl.

Hatch et al., 1989), resulting in shifts in regional doses in the two species (surface area differences and other factors are incorporated). Significant biological variations in lung tissue concentrations of several antioxidants have also been reported (Bryan and Jenkinson, 1987; Slade et al., 1985). How these antioxidants act individually or collectively as a defense against exogenous oxidants is not clear, especially considering that five animal species tested for O_3 toxicity in concentration-response studies using BAL protein did not show corresponding variations in their susceptibilities (Hatch et al., 1986). Thus, target tissue dosimetry data, such as that being pursued with ^{18}O are needed, along with additional species sensitivity data to refine this issue. Nevertheless, the ability of the mathematical model to discern relative species sensitivities is encouraging, despite its evolutionary state (Miller and Overton, 1989). Further work is still needed, however, to clarify various input components of the model, such as the roles of reactive surface fluid components and regional ventilation, for example, thereby ensuring its continued refinement and applicability to the extrapolation issue (Hanna et al., 1989).

3.2 SUMMARY AND CONCLUSIONS: HEALTH EFFECTS DATA

Concisely summarized below are the key findings and conclusions that emerge from the above review of the most pertinent, key O_3 health effects studies published in the 1986 to early 1989 period after completion of the 1986 U.S. EPA Ozone Criteria Document.

The newer studies reviewed from the 1986-1989 period provide further information related to evaluation of several key issues pertinent to decision making regarding potential revision of the primary O_3 NAAQS. Such issues include: (1) clarification of exposure dynamics (i.e., characterization of effective exposure patterns-concentrations, durations, etc.) determining the induction of acute effects (pulmonary function decrements, respiratory symptoms, lung inflammation, etc.) associated with short-term O_3 exposures; (2) evaluation of potential increased (or decreased) susceptibility of various population groups earlier hypothesized as possibly being at differential risk for O_3-induced health effects; (3) evaluation of the potential for induction of chronic lung damage/disease by repeated short-term and/or more chronic O_3 exposures; and (4) additional clarification of O_3 dosimetry aspects of

importance in better understanding observed human exposure effects and to enhance capabilities to carry out both qualitative and quantitative animal-to-human extrapolations.

3.2.1 Exposure Dynamics for Short-Term Ozone Exposure Effects

Newer data from 1- and 2-h controlled human exposure studies (Avol et al., 1987; Linn et al., 1986) add to earlier existing concentration-response data indicating that lung function decrements occur in children and young adults exposed for 1 to 2 h to low O_3 concentrations ranging from 0.12 to 0.16 ppm while performing moderate to heavy exercise. Explanations for variations across studies in reported lowest-observed-effects-levels among individuals and among cohorts include: subject characteristics, exposure histories of subjects, exercise levels, and possible but presently unidentified differences in actual controlled exposure conditions.

Data from two other newer studies (Gong et al., 1986; Schelegle and Adams, 1986) also substantiate earlier findings that statistically significant reductions in maximal exercise performance may occur in well-conditioned athletes after performing continuous heavy exercise ($\dot{V}_E > 80$ L/min) for 1 h at O_3 concentrations ≥ 0.18 ppm, but not at 0.12 ppm. Data from a third study (Linder et al., 1988) suggest that small decrements in maximal exercise performance may occur at O_3 concentrations < 0.18 ppm, but limitations and questions concerning this study require further verification of the results. Environmental conditions such as high ambient temperature and/or relative humidity may affect subjective symptoms and may independently impair exercise performance such that differentiation between O_3-induced effects and effects of other environmental conditions may be difficult.

In addition, newly emerging controlled human exposure studies of prolonged exposure (for up to 6.6 h) to low O_3 concentrations ranging from 0.08 to 0.12 ppm report progressively larger pulmonary function decrements and increased respiratory symptoms with increasing duration of exposure at moderate exercise levels ($\dot{V}_E = 40$ L/min) (Folinsbee et al., 1988; Horstman et al., 1988, 1989). The effects are similar in magnitude to those previously reported for healthy subjects performing heavy exercise ($\dot{V}_E > 60$ L/min) in high ozone concentrations (≥ 0.2 ppm) for shorter durations (≈ 2 h).

In addition to the above, new data also demonstrate increased lung inflammatory and biochemical changes from exposures to moderately high levels (0.40 ppm) of O_3 for 2 h with intermittent exercise ($\dot{V}_E = 70$ L/min), as determined from BAL 18-h post-O_3-exposure

(Koren et al., 1989a,b; 1988a,b). Cells and enzymes capable of causing damage to pulmonary tissues, along with proteins involved in fibrotic and fibrinolytic processes, were increased at 18-h postexposure. Also, evidence of increased epithelial permeability from the air to blood compartments (as determined by clearance of technetium-labeled DPTA) was observed (Kehrl et al., 1987). Koren et al. (1989a) further reported elevated PMNs, also as determined by BAL, in subjects exposed for 6.6 h to 0.1 ppm O_3.

Three newer studies on the effects in laboratory animals of multihour O_3 exposures provide information on relationships between concentration (C) and duration (T, time) of exposure. Rombout et al. (1989), Van Bree et al. (1989), and Costa et al. (1988) report that C dominates T in eliciting O_3-induced changes in lavagable protein and antioxidant enzyme levels. Preliminary modeling efforts describing these data suggest that C $\times$ T interaction (synergism) occurs at decreased C and increased T; however, C $\times$ T relationships can only be applied at a given C and cannot be applied in general. The time of day of exposure is also an important determinant of oxidant toxicity because nocturnal exposures cause greater responses than do diurnal exposures, possibly due to dosimetric differences because rats exercise more at night. These results suggest that the primary determinants of acute O_3 lung toxicity may, therefore, be exposure concentration and time of day of exposure, followed by the duration of exposure.

Also, certain other newer information suggests that interpretation of the results of controlled human O_3 exposures should take into account whether frequent ambient exposure was a possibility during the period of study (Avol et al., 1988; Hackney and Linn, 1989; Hackney et al., 1989; Linn et al., 1988). This information also suggests that further work is still needed to resolve the implications of attenuation of pulmonary function responses to O_3. Subjects grouped according to their responses in the early spring to 0.18 ppm O_3 for 2 h with intermittent exercise were tested the following fall, winter, and again the next spring. Although "nonresponders" showed little seasonal variation in their response to O_3, "responders" showed attenuated responses in the fall, persistence of attenuation into the winter, and a return to their initial lung function responses to O_3 by the following spring. Many of the responders were reactive to methacholine and had histories of respiratory allergies and/or symptomatic complaints when previously exposed to smog.

Newer field and epidemiological studies have employed numerous refinements over some of the older studies, in the form of (a) better estimates of exposure, not just to O_3 but also to other pollutants and other environmental variables that can confound or otherwise influence the outcome (e.g., Bates and Sizto, 1987; Spektor et al., 1988a,b; Raizenne et al., 1987); (b) use of serial measurements of pulmonary function for determining correlations with pollutants and other environmental variables (e.g., Raizenne et al., 1987, 1989; Spektor et al., 1988a,b); and (c) better biomedical characterization of cohorts (e.g., Raizenne et al., 1987, 1989; Gong, 1987). Despite their refinements, however, newer field and epidemiologic studies have produced mixed results regarding the possible role of O_3 versus the roles of other agents or factors in eliciting the functional decrements and/or rates of respiratory symptoms or respiratory disease observed. Although functional decrements and respiratory symptoms have been shown in a number of studies to be statistically associated with O_3, other studies have shown them to be wholly attributable to particles (e.g., Dockery et al., 1989), partially attributable to particles (e.g., Kinney, 1986), or partially attributable to other environmental factors such as ambient temperature or humidity (e.g., Spektor et al., 1988a) or even aeroallergens (e.g., Dockery et al., 1989; Gong, 1987).

Data reported from some of the newer field and epidemiologic studies (e.g., Raizenne et al., 1987, 1989; Spektor et al., 1988a,b; Kinney et al., 1988) show pulmonary function decrements that are as large or larger than those observed in human controlled (chamber) studies. Investigators have variously interpreted these larger decrements as likely being due to: (a) cumulative effects of O_3 occurring as the result of multihour exposures; (b) interactive effects with other pollutants (additive or synergistic effects); (c) interactive or possibly independent effects of other environmental factors (e.g., temperature); (d) possible misspecification of true exposures, either because of inadequate knowledge of dosimetry or other types of inadequacies in exposure characterization; and/or (e) possible persistence of effects from one day to the next.

Although permitting easier comparison of epidemiologic findings with chamber-study data, the method of reporting raises several questions that need to be further evaluated. For example, data on functional decrements have been reported as $-$mL/ppb O_3 for measures such as $FEV_{1.0}$ and FVC and as $-$mL/sec/ppb for measures such as PEFR and MMEF. Expression of data in this form assumes that (a) O_3-induced changes in respiratory function

are linear across all concentrations encountered in these studies (from zero up through episodic levels); and (b) the relationships among C, T, and $\dot{V}_E$ do not change with variations in these respective components of exposure. These assumptions are open to question, especially considering results from newer animal C × T studies. For example, the relationships between respiratory function changes and the respective components of exposure —C, T, and $\dot{V}_E$—have not been tested at concentrations <0.08 ppm in chamber studies; and data obtained in chamber studies at the lowest concentration used (0.08 ppm) have not been modeled to determine whether changes in the influence of respective components are monotonic across ranges of C, T, or $\dot{V}_E$. Furthermore, questions of nonlinearities in the respective effects of C, T, and $\dot{V}_E$ on O_3-induced pulmonary function changes are far from resolved. Also, Kinney et al. (1988), transformed data from controlled (chamber) studies modeled by Hazucha (Hazucha, 1987; U.S. Environmental Protection Agency, 1986) and compared them with data from five epidemiologic studies. The transformation assumed the applicability of a linear model even though Hazucha had fit data from controlled (chamber) studies to a quadratic model in describing changes in pulmonary function as a function of $\dot{V}_E$. Mean concentrations in the five epidemiologic studies were lower than the lowest concentration used in the controlled studies modeled.

As for respiratory symptoms, the newer field and epidemiologic studies have reported lack of association of various respiratory symptoms with O_3 more often than they have reported demonstration of such an association with the typically low O_3 levels studied. Studies reporting no significant increases in symptoms following short (1-h to multihour) daily exposures (over multiple days to multiple months) to ambient air containing O_3 include: (a) studies of children attending day or residential camps (Raizenne et al., 1987, 1989; Spektor et al., 1988a), (b) at least two panel studies (Dockery et al., 1989; Vedal et al., 1987), and (c) a study of adults exercising outdoors nearly every day (Spektor et al., 1988b). Another study (Schwartz et al., 1988), reanalyzing data from the Hammer et al. (1974) panel study of nurses in Los Angeles and using currently more widely accepted statistical approaches, did show that cough was associated with total oxidants, but only at relatively high levels (where O_3 concentrations were likely well above 0.12 ppm).

3.2.2 Evaluation of Differential Susceptability of Potential Special Risk Groups

Newer data published in the 1986-1989 period provides further data useful in evaluating possible differential sensitivity in two of several subpopulation groups of interest: (1) the elderly and (2) asthmatics. With regard to the first group, in controlled human exposure studies, older subjects (≥50 years old) appear to have smaller changes in lung function than younger subjects when exposed to similar O_3 concentrations (Bedi et al., 1988; Bedi and Horvath, 1987; Drechsler-Parks et al., 1987, 1989; Reisenauer et al., 1988). There were no significant differences between the responses of men and women to O_3 exposure for FEV_1 and FVC, although women had a significant increase in total respiratory resistance (Reisenauer et al., 1988). Because women had slightly lower mean exercise $\dot{V}_E$ during the studies, the data suggest that women may be somewhat more responsive to O_3 than men (Drechsler-Parks et al., 1987; Reisenauer et al., 1988). The responses to O_3 may be less reproducible, however, in older than in younger adults (Bedi et al., 1988). These results suggest a possible dropoff in responsiveness to O_3-induced pulmonary function changes sometime in late middle-age.

As for asthmatics, in other new studies of adults with and without asthma (Kreit et al., 1989; Eschenbacher et al., 1989), both groups experienced similar responses to 0.4-ppm O_3 exposure, as indicated by decrements in standard spirometric pulmonary function tests and airway responsiveness to methacholine. Specific airway resistance was not increased in nonasthmatics, but in asthmatics nearly twice the increase in SR_{aw} was seen after exercise in O_3 versus air exposures. No symptom differences were observed between adult asthmatics and nonasthmatics. Preexposure challenge with methacholine may have confounded the results, however. Responses were also similar for adolescent asthmatics and nonasthmatics exposed to 0.12 and 0.18 ppm O_3 (Koenig et al., 1987, 1988), although a small but significant increase in $FEF_{50\%}$ was observed in asthmatics after 0.12 ppm O_3 exposure. In the adult nonasthmatics studied by Eschenbacher et al. (1989), indomethacin pretreatment blocked the restrictive but not the airway reactivity component of the effects of O_3; a placebo effect was also observed in these nonasthmatics. A study by McDonnell et al. (1987) indicates that adults with allergic rhinitis show similar airway responsiveness to histamine after exposure to 0.18 ppm O_3 as a comparable group of nonallergic subjects. The only

difference was a significant increase in airway resistance in the allergic subjects. The newer data on allergic and asthmatic subjects suggest that both of these groups have a greater increase in airway resistance after O_3 exposure than do healthy subjects. The apparent order of airway responsiveness to O_3 from these studies is normal < allergic < asthmatic subjects. Further research will be required, however, before this hypothesis can be substantiated.

Results from a few of the newer epidemiology studies are also suggestive of possible increases in asthma or allergic responses among some individuals. For example, Dockery et al. reported a positive association of annual O_3 exposures to increases in asthma and hay fever symptoms in schoolchildren, but not with other respiratory symptoms or pulmonary function decrements. Also, in a panel study more specifically on asthmatics, Gong (1987) reported that, although respiratory symptoms occurred during the study, they did not correlate significantly with O_3; and no worsening of symptoms attributable to O_3 occurred in overall group statistical analyses. However, other multiple regression analyses of responses of those asthmatics in the top quartile for respiratory measures did show relationships between the respiratory measures and O_3, but these associations showed no clear concentration-response pattern (Gong, 1987).

3.2.3 Ozone Impacts on Lung Structure/Chronic Disease Processes

Several studies, by Koren et al. (1988a,b; 1989a,b) and Kehrl et al. (1987), were noted earlier as showing increased lung inflammatory responses and other biochemical changes capable of causing damage to pulmonary tissue, as well as increased lung epithelial permeability, with 2-h exposures of humans to 0.4 ppm O_3 and elevated PMNs in BAL fluids following 6.6-h exposure to low O_3 levels (0.1 ppm). These results increase concern regarding possible induction of chronic lung damage by O_3 exposures and lead to questions about effective exposure dynamics possibly related to such effects.

Costa et al. (1988) have demonstrated that laboratory animals exhibit a similar pattern of attenuated pulmonary function changes in response to repeated short-term O_3 exposure as previously described in humans. Both morphological and biochemical changes, however, occur while lung dysfunction attenuates with repeated O_3 exposure. These results add to concern that the attenuation phenomenon for short-term pulmonary function changes may not be beneficial, but rather may increase the potential for more serious chronic lung damage.

They also suggest that the use of lung function tests alone to assess O_3-induced lung injury may result in misinterpretation of data concerning health risks associated with multiday O_3 exposures. More research is needed, therefore, to improve our knowledge of relationships between acute and chronic lung injury.

Other new studies in monkeys and rodents provide further support for earlier findings that prolonged, repeated exposure to high concentrations of O_3 (≥0.4 ppm) lead to the development of peribronchiolar inflammation (Barr et al., 1988; Moffatt et al., 1987), increased lung collagen content (Reiser et al., 1987; Pickrell et al., 1987; Hacker et al., 1986), and lung function changes (Gross and White, 1986, 1987). Even at lower O_3 concentrations (0.12 to 0.30 ppm), a lesion is still evident at the junction of the conducting airways and the gas exchange regions of the lung, characterized by cell population shifts along with interstitial inflammation and thickening (Huang et al., 1988; Crapo et al., 1985; Barry et al., 1985, 1988; Sherwin and Richters, 1985), but without increased lung collagen content in rats (Wright et al., 1988; Filipowicz and McCauley, 1986).

In a chronic exposure study (0.25 ppm, 8 h/day, 18 mo), one group of monkeys was exposed to O_3 for each day of the 18 mo, whereas another group was exposed to O_3 every other month, with the intervening month being an air exposure (Tyler et al., 1988). Thus, on a C × T basis, the intermittent group received half the amount of O_3 exposure. Both groups of monkeys had morphometric changes, such as respiratory bronchiolitis, but only the intermittent groups had an increase in total lung collagen and pulmonary function changes. This suggests that under these experimental conditions, intermittent exposure could enhance the potential for the development of fibrogenic processes and indicates that to understand the health effects of O_3, it is critical to better understand the effects ambient exposure patterns. Preliminary information (Grose et al., 1989) from an exposure that mimics an urban O_3 pattern (0.19 ppm average concentration of O_3 over 9 h) of rats for 12 mo indicates that significant decrements in lung function also occur at these lower O_3 concentrations that are consistent with early signs of focal fibrogenesis in the centriacinar region of the lung. Increased lavagable lipids in monkeys (Rao et al., 1985a,b) found after prolonged exposure to ambient levels of O_3 (0.15 to 0.30 ppm) are also consistent with the shifting cell populations and/or inflammation reported at these concentrations. Multiple exposures to ambient levels of O_3 (0.15 and 0.30 ppm, 8 h/day for 6 or 90 days) also cause injury and cellular changes in

transitional and respiratory epithelium of the nose of nonhuman primates (Harkema et al., 1987a,b; Hyde et al., 1989).

3.2.4 Ozone Dosimetry Aspects

Newer studies related to the dosimetry of O_3 show that differences in mode of breathing do not produce appreciable differences in fractional uptake of O_3 in the respective regions of the human respiratory tract. Increased frequency of breathing results in a decreased fractional removal of O_3 in both the URT and the LRT, possibly as the result of decreased residence time in the airways and increased flow rate. The lowest fractional removal of O_3 in the URT occurred during nasal breathing, so that shifts from nasal to oronasal breathing resulting from exercise would somewhat offset increases in delivered dose caused by increased breathing frequency (Gerrity et al., 1988). Ozone-induced changes in tidal volume during 60-min, continuous-exercise ($\dot{V}_E$ = 40 L/min) exposures to 0.4 ppm resulted in a slight reduction in total O_3 uptake (4%) and a larger reduction in LRT O_3 uptake (9%). Thus, the typical O_3-induced reduction in tidal volume may partially protect the lower airways, with possible loss of that protection with recovery of normal tidal volume that occurs during multiday exposure (Gerrity and McDonnell, 1989). Increased flow rates appear to reduce nasopharyngeal uptake (Gerrity, 1987). Additional modeling is need, however, to determine the effects of heavy exercise on regional dosimetry, especially on O_3 uptake in the LRT. Additional data are still needed in other areas important to animal-to-human extrapolation, namely, relative species sensitivities.

Mathematical dosimetry models indicate preferential deposition of O_3 in the bronchoalveolar junction of several species of laboratory animals and in humans that is consistent with laboratory animal data on the site of the O_3 morphological lesion (Miller and Overton, 1989; Miller et al., 1987a,b; Overton et al., 1987). Humans appear to retain a greater fraction (95%) of inhaled O_3 than do rats (50%), but tissue dose rates/surface area in each species may not be that different if nasopharyngeal partitioning is considered (Wiester et al., 1987, 1988; Gerrity and Wiester, 1987; Gerrity, 1987). Target dosimetry data, such as that being conducted with $[18]O_3$ (Hatch et al., 1989; Santrock et al., 1989; Aissa and Hatch, 1988; Hatch and Aissa, 1987) are needed, along with species sensitivity data (Bryan and Jenkinson, 1987; Hatch et al., 1986; Slade et al., 1985) to better refine this issue.

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