OZONE:
EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS WITH RESPECT TO PROTECTION OF CHILDREN

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Prepared for
California Air Resources Board
California Office of Environmental Health Hazard Assessment

September 1, 2000

BACKGROUND:

The existing ambient standard for ozone (O_3) for the State of California is 0.09 ppm (180 $\mu g/m^3$) for a 1-hour averaging time. The standard was set in 1987. At the time, the Department of Health Services (DHS) concluded: "*A one-hour 0.08 ppm standard provides a small, but adequate margin of safety against acute effects...*", chronic effects in animals at 0.08 ppm "*...could be expected to occur in humans at somewhat higher concentrations...*" and that 0.08 ppm "*...would provide an adequate margin of safety against the occurrence of inflammation and therefore of chronic lung disease...*" (1). On review of all of the evidence, the State of California Air Resources Board (ARB) staff recommended a standard of 0.09 ppm averaged over 1-hour. The decision to maintain a one-hour averaging time was made for "historical reasons" (1).

In July, 1997, the U.S. Environmental Protection Agency promulgated an 8-hour standard of 0.08 ppm (157 $\mu g/m^3$). However, due to a U.S. Federal Court decision (2), the previous 1-hour standard of 0.12 ppm (235 $\mu g/m^3$) remains the operative standard. The rationale for the recommendation to switch to an 8 hour standard was based on an extensive summary of health effects that indicated "*...an array of health effects has been attributed to short-term (1 to 3 hours), prolonged (6-8 hours) and long-term (months to years) exposures to O_3*" (3). In its summary statement, the E.P.A. concluded that "*...longer exposure periods are of greater concern at lower O_3 concentrations...*" (3).

Principal Sources and Exposure Assessment:

The major source for O_3 exposure, for the vast majority of people, is from the outside air. Therefore, for practical purposes, understanding exposure patterns of infants and children to ambient O_3 is tied to an understanding of patterns of activities relative to the outdoors.

In an ARB study (4), children ages 11 and under spent nearly twice as much time outdoors per day (10% of a 24-hour period) versus only 5.1% for Californians ages 12 and over (Table 4.41; 4). Compared to a national sample, these young children spent more than 3-times as much time involved in sports and outdoor activities (Table 4.15 & p. 67; 4). For teenagers (ages 12-17), overall time differences compared to older adults was less striking (Table 3-5; 5). However, when time

spent in active sports and outdoor recreation was considered, teenagers spent more than twice as much time engaged in active sports and outdoor activities than did older persons (Table 3-8; 5).

In addition to the greater amounts of time spent outdoors, young children (≤10 years) have higher minute ventilation, expressed as L/minute/kg body weight, than do adults (Figure 1) (6). Thus, on a weight basis, the respiratory tract of young children can be expected to be exposed to a larger "dose" of O_3 for any given level of activity. Moreover, given the greater propensity of children to be outside and to engage in activities with ventilatory demands above the resting state (4; 5), it is to be expected over the short and long-term children will have greater exposures to ambient ozone that will adults.

Controlled Human Exposure Studies:

The 1987 ARB Staff Report on Health and Welfare Effects (1) supporting the current ambient air quality standard for ozone (0.9 ppm or 180 mcg/m^3 for 1 hour) stated the following: "*The major evidence directly related to the need for a one-hour ozone standard comes from brief exposures of human subjects in clinical studies. Evidence of ozone-induced dysfunction in humans is provided by research showing that alterations in pulmonary airflow tests (pulmonary function decrements) occur in healthy exercising adults and children exposed to ozone concentrations as low as 0.12 ppm for one or two hours. The subjects in these tests (sic) also experience respiratory symptoms. In similar studies at 0.10 ppm, such pulmonary function changes were not demonstrated although effects could occur at levels between 0.10 ppm and 0.12 ppm.*" Thus, 0.12 ppm was determined to be the lowest level of ozone for which adverse effects had been clearly demonstrated in humans. The Staff Report recommended that a standard of 0.09 ppm, averaged over 1 hour, would protect the public health from ozone exposure with an adequate margin of safety relative to the level at which acute pulmonary effects occur.

Controlled Exposure Studies in Children

Although controlled human exposure studies of the effects of ozone are rarely performed with children as subjects, several studies involving healthy and asthmatic adolescents have been published, including two since the last revision of the California ambient air quality standard. McDonnell *et al*. (7) reported small (mean=3.4%) decrements in forced expiratory volume in 1

second (FEV_1) in 23 boys (ages 8-11 years). Koenig *et al*. (8) exposed 22 adolescents (both genders, ages 14-19 years) to 0.12 ppm or 0.18 ppm ozone through a mouthpiece. Not all subjects were exposed to both concentrations. The exposure protocol was a 30-minute resting exposure followed by a 5-7 minute break for pulmonary function testing followed by a 10-minute exposure during moderate exercise. There were no significant decrements in FEV_1 with exposure to either concentration of ozone and no consistent differences between normal and asthmatic subjects. The same group of investigators (9) exposed another group of 12 non-asthmatic and 12 asthmatic adolescents (both genders, ages 12-17 years) to air or 0.12 ppm ozone for 1-hour with alternating 15-minute periods of rest and exercise. Healthy subjects had no significant decrements in pulmonary function after the ozone exposure, but there was a significant decrease in maximal expiratory flow at 50% of forced vital capacity (FEF_{25-75}) in the asthmatic subjects after ozone exposure compared to after filtered air.

The 1996 U.S. Environmental Protection Agency (EPA) criteria document on ozone reviews the studies described above and states that "the limited existing data do not identify adolescents as being either more or less responsive than adults" (10).

Controlled Exposure Studies in Adults – Pulmonary Function

Since the 1987 ARB review of the California ambient air quality standard for ozone, several controlled human exposure studies by U.S. EPA investigators have documented short-term decrements in pulmonary function in adult subjects with multi-hour exposures to concentrations of ozone below 0.12 ppm (11-13). In addition, one study also demonstrated evidence of acute airway epithelial injury and inflammation with such exposures (13). Folinsbee *et al*. (11) reported the results of a study of 10 male adults (ages 18-33 years) exposed to 0.12 ppm ozone for a total of 6.6 hours (moderate exercise for 50 minutes of each of 6 hours with a 35-minute lunch break after 3 hours). Hourly pulmonary function measurements showed that FEV_1 decreased in a roughly linear fashion throughout the exposure and had fallen by a mean of 13% by the end of exposure (three subjects had FEV_1 decrements of ≥25%). Symptoms of cough and chest discomfort were increased after ozone as compared to after filtered air. Airway responsiveness to methacholine (a measure of non-specific airway hyperresponsiveness to inhaled noxious stimuli) was also significantly increased (approximately doubled) after ozone exposure.

Using the same 6.6 hour protocol, these investigators (12) then compared the effects of three different ozone concentrations (0.08 ppm, 0.10 ppm, and 0.12 ppm) in a group of 22 males (ages 18-33 years). With 0.12 ppm, the responses were similar to those of the previous study. With the two lower concentrations, the responses to ozone were of lesser magnitude but still significant. The FEV_1 decrements after 0.08 ppm, 0.10 ppm, and 0.12 ppm exposures were 7%, 5%, and 13%, respectively (Figure 2). The methacholine responsiveness increased by 56%, 89%, and 121%, respectively. In yet another study using the 6.6-hour protocol by the same group of investigators (13), designed to look at airway injury and inflammatory responses in 38 males (mean age=25 years), there was a 8% decrease in FEV_1 after 0.08 ppm ozone and a 11% decrease after 0.10 ppm. In a paper summarizing the results of the 6.6-hour EPA exposures to these low-level concentrations of ozone, Folinsbee *et al*. (14) reported that 26% of subjects after 0.08 ppm, 31% after 0.10 ppm, and 46% after 0.12 ppm had decreases in FEV_1 >10%, with some decreases as great as 50%.

Given that children's pulmonary function responses to ozone are likely to be at least as great as those of young adults, it follows that a substantial proportion of healthy children will have symptoms and decrements in lung function with multi-hour exposures to ozone at concentrations allowable under the current California ambient air quality standard.

Repeated daily exposures to ozone have been shown to lead to attenuation of decrements in lung function and symptom responses in multiple controlled exposure studies. In two recent studies with 4 and 5 days of consecutive exposures to ozone, the cross-exposure decrement in FEV1 was greatest on the second day and greatly diminished by the fourth or fifth day (14a, 14b). Folinsbee at al. (14c) exposed 17 subjects to 0.12 ppm ozone for 6.6 hours on 5 consecutive days. While cross-exposure decrements in FEV1 declined progressively with each day of exposure, ozone-induced changes in methacholine responsiveness did not markedly attenuate across the 5 consecutive days of exposure. This result suggests that repeated exposure to ambient levels of ozone is not without hazard, despite the attenuation of symptom and spirometric responses.

There is considerable inter-subject variability in symptom and lung function responses to ozone, and some individuals do not respond at all to moderate levels of ozone in controlled exposure studies (14 d). The mechanism(s) underlying this variability in responsiveness to ozone is unknown.

The higher the effective dose of ozone, the greater the number of subjects that will have respiratory symptoms and decrements in lung function in controlled human exposure studies.

Controlled Exposure Studies in Adults – Airway Inflammation

Since the 1987 ARB review, the results of multiple controlled human exposure studies on the airway inflammatory effects of ozone have been reported (15-17). It is now clear that short-term exposure of humans to ozone can cause acute inflammation of the respiratory tract. To date, no controlled exposure study of ozone-induced inflammation has involved children. The study most relevant to the issue of whether the current California standard is adequately protective of the health of children was conducted by Devlin *et al*. (18). In this study, 18 males (ages 18-35 years) were exposed to 0.08 ppm ozone using the 6.6-hour EPA protocol described above. Ten of these subjects were also exposed to 0.10 ppm. Bronchoscopy to obtain bronchoalveolar lavage (BAL) fluid for cellular and biochemical analyses was performed 18 hours after the exposures. Significant increases in polymorphonuclear cells (PMNs), interleukin (IL-6), lactate dehydrogenase, prostaglandin E2 (PGE2), and α-1 antiprotease were found in BAL fluid after both concentrations of ozone. In addition, increased total protein and fibronectin levels were found in BAL fluid after 0.10 ppm and decreased phagocytosis of opsonized *Candida albicans* by alveolar macrophages recovered from BAL was observed after both concentrations of ozone. Although the mean changes in PMNs, IL-6, and PGE2 were not large, there were some subjects who had large responses. These data indicate that multi-hour exposures with exercise to concentrations of ozone allowable under the current California ambient air quality standard can cause acute airway injury and inflammation. The relationship between recurrent acute episodes of acute injury and inflammation in humans and the development of chronic respiratory disease is unknown, but given the potentially increased susceptibility of the developing respiratory tract of children to oxidant-induced injury, there is greater cause for concern about the long-term sequelae of such episodes.

Several recent studies have addressed the issue of whether repeated daily exposures to ozone on consecutive days leads to attenuation of airway injury/inflammation. Although 4-hour exposures to 0.2 ppm ozone during intermittent exercise for four consecutive days led to attenuation of the neutrophilic influx into BAL in two such studies (14a, 14b), evidence of persistent ozone-induced injury and/or inflammation was present after the 4-day exposures in both studies.

One controlled human exposure study that was designed to study the earliest events involved in ozone-induced inflammatory cell recruitment to the airways has some relevance to the margin of safety of the current California air quality standard. Krishna *et al*. (19) exposed 12 healthy adults (both genders, mean age=28 years) to 0.12 ppm ozone during intermittent light exercise. The subjects underwent bronchoscopy at 1.5 hours after exposure. While there were no significant differences seen in inflammatory cell numbers in either BAL fluid or bronchial biopsies between ozone and filtered air exposures, there was a significant increase in the percentage of bronchial mucosal blood vessels expressing P-selectin after ozone. P-selectin is an adhesion molecule that is involved in the margination and rolling of PMNs on blood vessel walls prior to transendothelial migration (diapedesis). This ozone-induced upregulation of P-selectin is early evidence of an inflammatory response following exposure to a concentration that is still regularly attained during the summer smog season in the Los Angeles basin.

As reviewed subsequently in this document, there are multiple epidemiological studies that have demonstrated an association between high ambient levels of ozone and exacerbations of asthma. The mechanism by which ozone induces asthma exacerbations is not entirely clear, but there have been several reports since 1987 of controlled human exposure studies in adults that have shed some light in this area. Two studies, Basha *et al*. (20) and Scannell *et al*. (21), showed enhanced inflammatory responses of asthmatic subjects as compared to healthy controls after a multi-hour exposure to 0.2 ppm ozone with moderate exercise. Another study by Molfino *et al*. (22) examined the effects of a 1-hour resting exposure to 0.12 ppm on the response to a subsequent ragweed or grass allergen challenge in seven allergic asthmatics (both genders, ages 21-64 years). The provocative concentration of allergen that caused a 15% decrease in FEV_1 was significantly lower after ozone than after filtered air, suggesting that allergen-specific airway responsiveness is increased after ozone exposure. The number of subjects studied was small and the findings could not be replicated in a study by another group of investigators (23). Nevertheless, several subsequent studies have demonstrated ozone-induced enhancement of the bronchoconstrictor response to allergen with higher doses of ozone. It is likely that there is at least a subset of allergic asthmatic individuals, including children, that will experience enhanced airway responses to allergen following high ambient ozone exposures.

Field Studies in Adults – Airway Inflammation

Although properly categorized as epidemiological rather than controlled human exposure research, two studies of ozone-associated airway inflammation in children involving ambient exposures to ozone are discussed here because of the use of nasal lavage, a technique that provides similar information to what is generated with BAL. Frischer *et al*. (24) performed multiple (five to eight) nasal lavages in 44 German children (both genders) during the 1991 summer ozone season (May to October). Comparing "high-ozone" (daily half-hour maximum ≥ 0.09 ppm) to "low-ozone" (daily half-hour maximum ≤ 0.07) days, significant increases in PMNs and eosinophilic cationic protein (ECP) in nasal lavage were observed on the high-ozone days. A follow-up study by the same group of investigators (25) during the 1994 summer ozone season (when the daily half-hour maximum exceeded 0.12 ppm on only one day) confirmed these findings in 170 school children (both genders, mean age=9 years).

Another study designed to investigate the inflammatory effects of ambient exposures to ozone was performed by Kinney *et al*. (26). In this study, 15 male subjects (ages 23-38 years) who jogged regularly on Governors Island in New York City underwent at least two bronchoscopies, one during the 1992 summer ozone season and one during the following winter; six subjects also had a third bronchoscopy during the 1993 summer ozone season. The maximum ozone concentration in summer 1992 was 0.11 ppm (mean=0.58); the maximum concentration in the following winter was 0.64 (mean=0.32); the maximum concentration in summer 1993 was 0.14 (mean=0.69). Lactate dehydrogenase (LDH), a marker of cell injury, was significantly higher in BAL during the 1992 summer than during the following winter. There were non-significant trends for increases in IL-8, a cytokine that is a potent chemoattractant for PMNs, and PGE2 during the 1992 summer. For the six subjects with a second summer bronchoscopy, IL-8 was significantly higher than compared to the previous winter. The results of this study also suggest that ambient exposure to concentrations allowable by the current California air quality standard can cause airway injury and inflammation.

Interactions

Since the 1987 ARB review, the results of several controlled human exposure studies on the combined effects of relatively low concentrations of ozone and one or more other pollutants have been reported. In addition to the fact that ozone is rarely the only pollutant of concern in a given air shed, the steeper dose-response for ambient ozone and lung function decrements observed in multiple field studies as compared to controlled laboratory studies has been thought to be due to the effects of co-pollutants in summer "acid haze" (27).

Koenig *et al*. (28) exposed 13 allergic asthmatic adolescents (both genders, ages 12-18 years) to three different exposure sequences (air for 45 min followed by 0.10 ppm sulfur dioxide for 15 min ; 0.12 ppm ozone for 1 hour; and 0.12 ppm ozone for 45 min followed by 0.10 ppm sulfur dioxide for 15 min). Only the ozone-sulfur dioxide sequence was associated with a significant decline in FEV_1 (-8%) across the exposure.

Koenig *et al*. (9) exposed 12 non-asthmatic and 12 asthmatic adolescents (both genders, ages 12-17 years) to four atmospheres (filtered air, 0.12 ppm ozone, 0.3 ppm nitrogen dioxide, and a mixture of the two pollutants) for 1 hour with intermittent moderate exercise. No decrements in pulmonary function were observed after any of the exposures. A similar study of asthmatic adolescents by the same investigators (29) involving four different exposure atmospheres (filtered air, 0.12 ppm ozone and 0.3 ppm nitrogen dioxide, 0.12 ppm ozone and 0.3 ppm nitrogen dioxide and 70 $\mu g/m^3$ sulfuric acid, and 0.12 ppm ozone and 0.3 ppm nitrogen dioxide and 0.05 ppm nitric acid vapor) again found no significant decrements in pulmonary function after any exposure.

Linn *et al*. (30) exposed 24 asthmatic adolescents (both genders, ages 11-18 years) to three atmospheres (filtered air, 0.2 ppm ozone and 0.3 ppm nitrogen dioxide, and 0.2 ppm ozone and 0.3 ppm nitrogen dioxide and 127 $\mu g/m^3$ sulfuric acid). Although there were no statistically significant mean differences among the exposures, a few subjects had relatively large decrements in FEV_1 after the exposure containing acid as compared to filtered air suggesting the possibility of susceptible sub-group. The same group of investigators (31) evaluated the pulmonary function and symptom responses of 41 children (both genders, ages 9-12 years, 26 with allergies or asthma) to a mixture of 0.10 ppm ozone, 0.10 ppm sulfur dioxide, and 100 μg/m3 sulfuric acid. There were no significant

decrements in pulmonary function after the exposure compared to after filtered air, but subjects with allergies and/or asthma had an exposure-related increase in respiratory symptoms.

Another interesting study by this group of investigators (32) involved exposure of 59 adolescents (both genders, ages 12-15 years) to smoggy Los Angeles air in a mobile laboratory during summer 1993. Ambient air during the exposures contained a mean ozone concentration of 0.144 ppm and a mean total suspended particulate concentration of 153 $\mu g/m^3$. Exposures were for 1 hour and 20 minutes with a 10-minute warm-up period, 1 hour of continuous moderate exercise, and a 10-minute post-exercise cool-down period. There was a significant decline in FEV_1 after the exposure to smoggy air as compared to after a filtered air control. Of note, unlike adults, the adolescents in this study did not report increased respiratory symptoms in association with decrements in FEV_1, suggesting that they are less aware of irritation and thus more at risk from ambient air pollution. Avol *et al*. (33) also studied 66 younger children (both genders, ages 8-11) using the same protocol and found a "similar reactivity to ambient oxidants" as for older children and adults. The ambient air during the exposures contained a mean ozone concentration of 0.113 ppm and a mean total suspended particulate concentration of 188 $\mu g/m^3$.

Epidemiological Studies of Acute and Chronic Health Effects:

The 1996 EPA criteria document for ozone provided an exhaustive review of the health effects of O_3 (10, vol. III). These will be summarized briefly, particularly those parts of the report that are relevant to children. Selected studies published since the release of the criteria document will be given a more detailed presentation.

The results of the EPA Criteria document are summarized in Table 1, which focuses particularly on those studies which include children exclusively or as part of a larger sample. Based on the types of data presented in Table 1, the EPA report came to a set of overall conclusions which are presented in Table 2. The summary statement from the Criteria Document did not provide a specific identification of children as particularly susceptible. However, the "Proposed Decision" document of November, 1996 (3) reported the results of an exposure assessment based on a variety of possible standards and identified the following as one of the "key observations" related to alternative standards: "*Children who are active outdoors... appear to be the at-risk population group*

examined with the highest percentage and number of individuals exposed to O_3 concentrations at and above which there is evidence of health effects, particularly for 8-hour average exposures at moderate O_3 concentrations ≥0.080 ppm." (3, Section IIB).

The remainder of the section on epidemiologic studies is devoted to studies published largely, but not exclusively, since the issuance of the "Decision" paper and which focus specifically on effects in children or present data on children in the context of general population surveys.

[THESE ARE ALL CHRONIC EFFECTS STUDIES, WHICH SHOULD FOLLOW ANY OTHER STUDIES ON ACUTE EFFECTS, WHICH IS WHAT THE EPA SUMMARY STATEMENT REFERRED TO.]From the point of view of relevance to the State of California, five recent publications are presented in some detail. Four of these are from the ARB/University of Southern California (USC) Children's Health Study (CHS) (34-37). Samples of 4th graders (9-10 years), 7th graders (12-13 years) and 10th graders (15-16 years) were enrolled from 12 southern California communities which were selected to maximize differences in ambient pollutant profiles between them (36). The initial sample size was 3,676 (36). The last study is one related to effects of long-term O_3 exposure carried out in a small sample of adolescents who were lifelong California residents (38)

A random sample of 10-12 year-old CHS subjects participated in a 2 season study of the effects O_3 on symptoms and lung function in healthy children and children with asthma or wheezing (34). Exposure assessment was based on ambient monitoring and personal passive sampler data. Exposure, symptoms and forced expiratory volumes and flows were assessed daily for 4 days for each child during mid-spring and mid-summer. Summary data for the distribution of ambient and personal ozone exposure were not given. Exposure to ozone was categorized as "low" and "high" for ambient data based on a cut-point of a 1-hour peak O_3 concentration above and below 100ppb. Personal monitoring data were valuated as "low" and "high" based on a lowest value for the "high" group that was at least 35% greater than the highest value of the low group. The results from this study are very difficult to interpret and not informative for several reasons: 1) All O_3 exposures are presented as dichotomous; 2) The principal lung function outcomes are presented as the difference between evening and morning function with no account taken of possible lagged effects on morning function (39)–a fact which makes the interpretation of any difference somewhat ambiguous; and 3) The estimation of ozone effects on symptoms in children with asthma appears counter-intuitive and

is likely due to increasing symptoms in the "healthy" group with increased O_3 concentrations. Therefore, no specific results are presented.

Data on the relationship between respiratory morbidity at baseline and air pollution have been reported for the CHS (36). Average daily 1-hour maximum and 24-hour average O_3 for the 12 communities in 1994 ranged between 41.3-97.5 ppb (mean=64.5 ppb) and 13.0-70.7 ppb (mean=34.9 ppb), respectively. A two-stage regression analysis provided estimates of the effect of community levels of ambient pollutants after adjustment for individual-level covariates. Average levels of NO_2 and acid (HNO_3+HCL) were associated with wheeze prevalence in males only–odds ratio (OR) and 95% confidence intervals (CI): 1.47 (CI, 1.08-2.02); 1.55 (CI, 1.09-2.21), respectively. No significant O_3 effects were observed. Similar results were obtained when the 1994 air pollution data were used.

Relationships between baseline lung function and air pollution also have been reported for CHS (37). Based on average 1986-1990 ambient pollutant data, significant O_3 effects were observed only for females. In single pollutant models, peak 1-hour daily ozone (5-year average of the 1 year daily averages) was associated with decrements in peak expiratory flow (PEFR) and maximum mid-expiratory flow (FEF_{25-75}) only. Somewhat larger effects for the same function measures were observed when the 1994 pollutant data were used. The only function measure on which 1-hour maximum O_3 had the largest effect was PEFR. Twenty-four hour O_3 was not related to any measure of lung function in either sex. For forced vital capacity (FVC),FEV_1 and PEFR, no 2-pollutant model fit the data better than single-pollutant models. For FEF_{25-75}, O_3 in combination with PM_{10} or NO_2 fit the data better than any single-pollutant model. When the data were stratified by time spent outdoors, the effects of O_3 on FEF_{25-75} were increased and those on PEFR decreased in girls. Effects were greater in girls with asthma compared to those without only for PEFR. All regression coefficients are presented in terms of the effect of an interquartile change in pollutant concentrations between communities (40 ppb in the case of 1-hour peak O_3). Unfortunately, insufficient data are given in the publications (36; 37) to estimate a percentage reduction in average PEFR and FEF_{25-75} in two typical girls each of whom resides in 2 communities with average 1-hour peak O_3 concentrations that differ by ~40 ppb and whose distribution of 1-hour and 24-average O_3 concentration do or do not exceed the current California standard for O_3.

The last of the four CHS publications focused on children in the sample who reported doctor-diagnosed asthma (35). In this study, O_3 concentrations were not associated with the occurrence of either bronchitis or phlegm. The strongest associations were seen with NO_2 in children with a history of asthma. No effects for either NO_2 or PM_{10} were observed in children who did not report a history of asthma.

Künzli and colleagues conducted a study of effects lifetime exposure to ambient O_3 on lung function in a group of 130 UC, Berkeley freshman, all of whom were life long residents of either the San Francisco Bay Area (SFBA) or the Los Angeles Basin (LAB) (38). Estimates of lifetime exposure to ambient O_3 were based on detailed residential histories, typical time activity patterns over the lives of the students and monthly average ambient O_3 based on the extant ARB monitoring network (inverse distance squared weighting). The reproducibility of the estimates of lifetime exposure were found to be comparable to that for laboratory and other health-related outcomes routinely used in epidemiologic studies (40). Relationships between lifetime exposure and lung function were not sensitive to any of the several O_3 metrics that were evaluated. The median lifetime 10 AM to 6 PM average O_3 concentrations based solely on residence-specific ambient monitoring data were 22.5 ppb (interquartile range: 17-28) and 51.5 ppb (IQR: 40-60) for the SFBA and LAB, respectively. Analyses demonstrated consistent and negative associations between lifetime exposure and measures of small airways function. No such relationships were found for FVC or $FEV_{1.}$ (Table 3) (38). The results were not altered by the inclusion of lifetime estimates of average 24-hourPM_{10} and NO_2 exposures. Of particular note is the fact the estimated coefficient based on the first 6 years of exposure is nearly identical to that for the total lifetime (up to 19 years). The relationship was found to be similar across both the SFBA and LAB (38, Figure 2). The authors estimated that a 20 ppb difference in average annual 8 hour exposure to O_3 over the first 19 years of life would result in a mean decrease of 14% (95% CI: -1% to -28%) in FEF_{75} compared to the population mean and a 7.2% (95% CI: +1% to -21%) for FEV_1.

The results of the above study are support by a study of similar design by Galizia and Kinney in 520 Yale freshman (41). Students who spent 10-years in residential locations with monthly average 1-hour peak O_3 concentrations greater >80 ppb (95th percentile of exposure distribution for study subjects) had 10% (95% CI: 1.3% to -21.3%) 13% (95% CI: -4.9% to -21.2%) reductions in FEF_{75} and FEF_{25-75}, respectively, compared to students in the lower 95% of the distribution. The reduction for FEV_1 was substantially smaller (-4.7%; 95% CI: 0.7% to -8.8%). Report of respiratory symptoms also was more common in adolescents from areas with O_3 > 80 ppb. Taken together this study and that of Künzli *et al*. (38) provide evidence that long-term exposure to increased concentrations ambient ozone may have detrimental effects on lung function. Moreover, they support studies on O_3 dosimetry in humans (10, Section 8.2.4.2) and animal toxicology data (42; 43) which predict that the maximum site of effect of O_3 in the human lung will be at the level of small airways (reflected by levels of FEF_{75} and to a lesser extent FEF_{25-75}).

[AS NOTED ABOVE – I WOULD MOVE ALL THE ACUTE EFFECTS STUDIES BEFORE THE CHS STUDIES, AS WELL AS YOURS AND KINNEY'S.]. Several recent studies provide some insight either into the shape of an O_3 exposure response function for population data. Castillejos and colleagues studied 40 children ages 7.5-11 years in Mexico City (44). Children with asthma or difficulty breathing with wheeze or FEV_1 < 80% predicted were excluded. Forced expiratory flows were assessed during 1-hour of treadmill exercise. Average hourly O_3 during the test but not $PM_{2.5}$ on the day of test was associated with decrements in FEV_1 and FEF_{25-75}, with the percentage decrements in the later measure being 2- 3 times greater than the former. Results were not affected by the symptom status of the children. Plots of the average 1-hour O_3 concentration during exercise versus % change in FEV_1 (Figure 3) suggest a threshold for effects at ~50 ppb. The authors interpreted this figure to indicate that "*...on average the response to O_3 is not detectable until a certain cumulative dose is attained....*". Another study conducted in the same group of children (39) measured morning and afternoon PEFR for approximately 1 month during each of three periods (winter: Jan. 23-Feb. 22, 1991; spring: April 22-May 27, 1991; fall: Oct. 11-Nov. 8, 1991). Hourly average O_3 was measured at the children's school as was 24-hour PM_{10} and $PM_{2.5}$. Early afternoon O_3 concentrations ranged between 17-319 ppb. A polynomial distributed lag model suggested a linear decline relation between 24-hour mean O_3 concentrations and morning peak flow (3.8% ↓ for each 25 ppb ↑ in 10 day exposure). The effect of O_3 on morning PEFR was independent of effects

of $PM_{2.5}$. In the case of afternoon PEFR, "*Exposures to O_3 briefer than 6 hours were not associated with reduced afternoon PEF*." Moreover, O_3 had a predominant effect over particles on afternoon PEFR.

A study of 941 primary school children (mean age 9.8±1.6 years) in Taiwan compared lung function across three different areas (45). One-hour peak O_3 ranged from 20-110 ppb. In multi-pollutant models (O_3, SO_2, CO, NO_2, PM_{10}), only O_3 (with 1-day lag) had an effect on both FVC and FEV_1. However, the O_3 effects did not appear to occur until 1-hour peaks exceeded ~60 ppb (Figure 4).

Two studies in adults also provide some useful data on the possible shape of the population O_3 response curve for lung function (46) and emergency department visits for asthma (47). Korrick, *et al*. studied 595 volunteers (age range 18-64 years, mean 35 years) who were performing a day hike on Mt. Washington, NH (46). Data on hourly O_3, 24-hour $PM_{2.5}$ and 24-hour strong aerosol acidity (sulfate equivalents) were available. Mean hourly O_3 (mean of base and summit 1-hour values) ranged between 21-74 ppb (mean 40 ppb). There was an inverse relation between hourly O_3 and FEV_1 (2.6% ↓ in FEV_1 per 50 ppb ↑ in O_3; 95% CI: 0.4-4.7%) which was not altered by adjustment for $PM_{2.5}$ and strong aerosol acidity. Decrements in subjects with self-reported asthma were approximately 3-fold greater. No effects were observed for PEFR or FEF_{25-75} with or without adjustment for $PM_{2.5}$ and acidity, although O_3 was associated with the frequency of >10% declines in FEF_{25-75}. Three methods were used to fit the O_3 FEV_1 exposure relationship. A threshold model with an inflection point near 40 ppb seemed to fit the data best (Figure 5).

Stieb and colleagues studied emergency department visits for asthma in St. John, New Brunswick, Canada from 1984-1992 (May-Sept. only) (47). Forty-nine percent of subjects were 15 years of age or younger. One-hour maximum O_3 ranged between 0-160 ppb (mean: 42 ppb; 95th %tile: 75 ppb), and a level of 80 ppb only was exceeded on 3.7% of study days. One-hour maximum O_3 was not highly correlated with SO_2, NO_2, SO_4^{2-} or TSP (all correlations ≤0.30). Only O_3 "exhibited a consistently positive association with asthma visit rates..."(47). Moreover, non-linear models revealed stronger associations both with 1-hour maximum and 24-hour average O_3. Only when values above the 75 ppb (95th %tile) were included was there an effect of 1-hour maximum O_3 on emergency department visits for asthma. The results were identical for subjects ages 0-15 and ≥15 years (Figure 6) (47) in terms of the shape of the response curve. However, at all O_3

concentrations, visits per day were higher in the older age group and, in regression models, were only significant in this latter group.

Finally, a daily time series study of women in Virginia which had data on multiple pollutants indicated that O_3 effects on declines in PEFR were not observed with 5-day average O_3 until values exceeded 35 ppb when 5-day average values were grouped as quartiles (48, see below and Table 4).

There are a number of studies which, although they do not necessarily permit any inference on the shape of the population O_3 response curve, do permit inferences on either the lower levels at which exposures to O_3 result in health effects and/or the contribution of O_3 to health effects relative to other ambient pollutants. These are summarized in Table 4. Only 2 of these studies were performed in the United States, and these were in the Eastern portion of the country.

The study of Neas *et al*. in Uniontown, PA is most relevant (Table 4) (49). In this daily time series study, O_3 was most strongly associated with daily cough episodes then any other of the other pollutants evaluated. Daily maximum 12- hour average O_3 never exceeded 80 ppb. Although O_3 also was strongly associated with decrements in PEFR, its effect was dependent on proper adjustment for temperature. In a 2- pollutant model with particle strong acid, the effect of O_3 on PEFR decrements was eliminated, despite only a modest correlation (r=0.48) between the 2 pollutants.

A times series study of non-smoking women in Virginia (Table 4) (48), while it did not include children, does, nonetheless, provide useful data.. O_3 exceeded the proposed EPA 8-hour standard of 80 ppb on only 2 days and PM concentrations were all below E.P.A. and WHO standards (Table 4). O_3 showed the strongest association of any pollutant with evening decrements in PEFR. Averages of 1-hour values seemed to have a larger effect than the maximum daily 8-hour average. When O_3 was expressed as quartiles of a 5-day moving average, effects appeared only at average O_3 concentrations >35 ppb (Figure 7) (48). Unfortunately, no multi-pollutant models were presented. However, correlations between O_3 and the other pollutants were modest (range 0.22 - 0.46, see Table 4).

Two studies conducted in Canada (50; 51) provide somewhat conflicting results. A study of berry pickers in British Columbia (Table 4), all of whom were ≤age 44 years, found associations of daily 1-hour maximum O_3 on decrements in FVC and FEV_1 that were independent of a number of other pollutants. One-hour maximum O_3 concentrations never exceeded 84 ppb (mean 44 ppb),

and the concentration of other pollutants was low. In contrast, a daily time series study of hospital admissions in Montreal (51) found associations between ambient O_3 with emergency room visits for respiratory illness only in people aged 64 and older. These associations were observed for only 1 of the 2 years studied. Mean 8-hour maximum concentrations averaged 29 ppb, and 1-hour maximum values averaged 33 ppb. To what extent the differences in the 2 studies relates to different endpoint and different pollutant mixtures cannot be determined.

The studies from European countries represent a mixture of designs, endpoints and ambient exposure profiles (Table 4). A study of daily hospital admission for asthma from 4 cities in the APHEA project (52) failed to show any associations with O_3 in children. However, a daily time series study of visits to a clinic in Santiago, Chile (53) did show an association between daily 1-hour maximum O_3 and respiratory visits for children between the ages of 2-14 years. No effects were seen for younger children. Effects of O_3 were independent of and greater than those for PM_{10} (the only other pollutant studied) in 2 pollutant models. A Dutch daily time series study of PEFR decrements and respiratory found associations between ambient O_3 and PEFR decrements and upper respiratory symptoms. The effects of black smoke on PEFR were greater (per IQR change) than those for O_3. No multi-pollutant models were presented.

Two of the European studies evaluated the effects of long-term pollutant exposures on respiratory health in children (Table 4) (54; 55). A 10 community Swiss study (54) in which average annual O_3 levels were very low and showed relatively little variation across communities, observed associations between annual O_3 concentrations and asthma and wheeze only in children without a family history of allergy and only when the communities with the highest and lowest O_3 concentrations were compared. A 9 community Austrian study (55) attributed both short-term and medium term decrements in forced expiratory volumes and flow to ambient O_3 concentrations that were independent of the other pollutants measured. An accompanying editorial suggested that the effects could not be ascribed solely to O_3 and might have an important component related to PM/NO_2 (56).

None of the epidemiologic studies that were reviewed provide any data on interactions between various pollutant mixtures on human health effects.

Conclusions:

Controlled Exposure Studies

Controlled human exposure studies of the effects of ozone involving children and adolescents have generally not shown greater decrements in pulmonary function than in adults. Children do appear to report less respiratory symptoms for a given magnitude of decrement in FEV1, suggesting that they are less likely to avoid high ambient exposures. Multi-hour exposures of adults during exercise to concentrations of ozone allowable under the current California air quality standard have been demonstrated to induce substantial pulmonary function decrements as well as airway inflammation. Persons with asthma appear to have enhanced airway inflammatory responses to ozone, and asthmatic responses to specific allergen appear to be enhanced by ozone. Field studies involving assessment of airway inflammation provide evidence of ozone-induced airway injury and inflammation from real-world exposures. Finally, controlled human exposure studies of ozone mixed with other pollutants have not tended to show greatly amplified effects over what exposure to ozone alone would be expected to have caused.

Epidemiologic Studies

Inspection of the data in figures 3-5 and 7 provides some basis on which to address the question of whether or not significant adverse health effects might be expected to occur in children. The various measures of lung function can be taken as a meaningful health outcome. Lowered lung function is associated with increased airway reactivity in children (57) and airways reactivity is associated with more rapid rates of lung function decline (58). Moreover, numerous studies in adults have indicated that level of lung function in adult life, especially FEV_1, is linked to the risk of respiratory illness and all-cause mortality (59-62). In 4 or the 5 sets of data quoted (Figures 3-5, 7), it appears that effects on measures lung function can be detected at levels below the current State standard of 90 ppb for a 1-hour maximum value. It is interesting to note that Schwartz (63) in a cross-sectional study of NHANES II data suggested that O_3 effects on FVC had a threshold at about 40 ppb. This value is not too different from that observed in several of the newer studies. Unfortunately, the California-specific, CHS studies cited do not provide useful data in this regard. Presumably the CHS will have relevant data in the future. However, the study of Künzli, *et al*. (38) and, to a lesser extent, that of Kinney, *et al.* (64) do provide evidence that long-term exposure at relatively low levels may have important effects on lung function. Finally, it should be noted that the issue that cannot be satisfactorily resolved is whether children indeed are at greater risk for

functional and or discrete health outcomes than are adults at any given level of ambient O_3. The data from Stieb and colleagues (47) are not supportive in this regard.

In contrast to the relative certainty about the levels at which O_3-related health effects may be seen, it is more difficult to be certain to what extent the observed effects are due to O_3 itself or O_3 in the context of the various pollutant mixtures in which it is found. No epidemiologic data on true interactions with other pollutants were found, and such data would be expected to be very difficult to obtain. The most compelling data cited are those from studies where a number of other pollutants have been studied in low concentration and where O_3-related effects are observed (50). Unfortunately, such data are few. Nonetheless, the number of studies which have identified important O_3-related health effects in the presence of other pollutants, either as the only association or the strongest association, clearly indicates that ambient O_3 concentrations are, at a minimum, an important marker for adverse health effects in children that are related to ambient air pollution.

Table 1:Summary of Ozone-Related Health Effects from Field and Epidemiologic Studies, 1996 U.S. E.P.A Criteria Document for Ozone

Type of Study	Outcome Measure	Range of O_3 Concentrations	Major Findings
"Camp Studies" of children ages 7-17*	FEV_1–regression slopes	1-hour peak: 100-160 ppb Minimum levels: 10-60 ppb	· Meta-analysis of 6 studies shows relationship between previous hour's O_3 concentration and FEV_1 of -0.50ml/ppb ±0.07 (27); · No evidence for response threshold
"Daily life" studies+ : repeated measurement of lung function in children mostly in elementary school ages	$FEV_{0.75}$;	· 1-hour peak: 3-63 ppb	· mean slope for $FEV_{0.75}$ -99ml/pbb ±0.36; no negative slopes for SO_4 or fine particles
	FVC, FEV_1 FEF_{25-75}	· 1-hour mean: 14-287 ppb	· only FVC with statistically signifiicant slope in relation to previous hour's O_3 in contrast to "Camp Studies"; however, signifcant slopes for FEV_1 and FEF_{25-75} with 24, 48 168 hour average O_3–suggest sub-acute effects
	FVC, FEV_1 FEF_{25-75} PEFR	· 1-hour peak: 3.5-103 ppb	· Significantly negative slopes for FVC, FEV_1, FEF_{25-75}; not affected by SO_2, NO_2, PM_{10}
	PEFR	· 1-hour peak: 0.0-66 ppb	· No association between O_3, SO_2, NO_2, and CoH with respiratory symptoms or PEFR

Type of Study	Outcome Measure	Range of O_3 Concentrations	Major Findings
Aggravation of existing respiratory disease†			
· asthmatic/non-asthmatic children	PEFR	· average 1-hour peak: 0.55±0.14 ppm; moving average 8-hour O_3: 0.46±0.13 ppm	· PEFR slopes: non-asthmatic children: -11.9L/min/0.1 ppm asthmatic children: -31.0L/min/0.1 ppm interaction between O_3. PM_{10}, temperature
· children attending camp for asthmatic children	PEFR, daily symptoms and treatment	· 1991 1-hour peaks: 0.154 ppm 1992 1-hour peaks: 0.063 ppm	· 1991 daily treatments correlated with daily O_3, SO_4 H^+, but not pollen; no associations in 1992 afternoon symptoms and PEFR variability correlated with O_3 and H^+
Daily Time series studies: 35 total studies reported; ¶	hospital admissions	wide range	difficult to isolate consistent effects for children; studies since 1992 show clear cut ozone associations with pneumonia and COPD in the elderly and with total respiratory admissions; early studies show effect for asthmatic admissions; difficult to draw conclusion specifically with regard to children

Type of Study	Outcome Measure	Range of O_3 Concentrations	Major Findings
Studies on effects of chronic exposure; 13 studies reported§	pathology allergic responses	(only 5/7 give ranges for studies with children)	
· 6 studies include children or restricted to children; 7th study restricted to teenagers and young adults	FEV_1, FVC, PEFR FEF_{25-75}	· median average 1-hour value: 0.03 ppm	· non-linear relation between average annual O_3 with threshold ~0.40 ppm; data consistent with effects on forced flows at concentrations <0.120 ppm; no control for other pollutants
		· 90th %tile average annual 1-hour peak: 0.34-0.50 ppm	· small decrements (<2%) in FEV_1 and FVC; results likely confounded by SO_4
		· average annual 1-hour peak: 0.024-0.031 ppm	· no effect on lung function, except for FEF_{25-75} in asthmatic children; results potentially confounded by SO_4
		· average ½-hour peak: 0.015-0.052 ppm	· increased asthma prevalence, no effects on forced volumes
		· 3 month average 1-hour peak: 0.100-0.200 ppm	· no effect on respiratory symptoms; effect on slope of Phase III of N_2 washout in all age groups, effect on forced volumes limited to subjects >14 years

* (Adapted from reference 10, vol. III—Table 7-15)
+ (Adapted from reference 10, vol. III—Table 7-18)
† (Adapted from reference 10, vol. III—Table 7-20)
¶ (Adapted from reference 10, vol. III—Tables 7-21 & 7-23)
§ (Adapted from reference 10, vol. III—Tables 7-25 & 7-26)

Table 2: Summary of U.S. E.P.A Conclusions Based on Data Summarized in Table 1 With Particular Reference to Children*

Effects of Short-Term Exposures to O_3

Respiratory Symptoms

- Association between O_3 exposure and presence of symptoms shown in human clinical, field and epidemiologic studies
  - Most common respiratory symptoms have higher incidence in young adults...and generally not reported in children
- Symptom responses follow a monotonic exposure-response relationship

Lung Function Responses

- Acute exposure to O_3 results in decreased forced expiratory volumes and flows
- Responses in healthy children are similar to those seen in adults

Exacerbation of Respiratory Disease

- Small decreases in forced expiratory volumes, increased respiratory symptoms and exacerbations of asthma occur with increasing ambient O_3, especially in children
- based on camp studies, estimate for pre-adolescent children exposed to 0.120 ppm, decrement is ~2.4%-3.0% FEV_1

- Increases in visits and hospitalization for respiratory disease seen with O_3 <0.12 ppm

Individuals and Populations Susceptible to Ozone+

Effects of Long-Term Ozone Exposures

- Findings suggest small, but consistent decrements in lung function
  - findings difficult to interpret due to uncontrolled effects of co-pollutants

***** (Adapted from reference 10, vol. III—Section 9)

+ No specific statement made with regard to children or adolescents; **NB**: McDonnell, *et al*. modeled ozone responses in chamber studies with subjects as young as 18 and found that decrements in FEV_1 in response to increasing O_3 decreased with age (65; 66).

Table 3:**Effective of Estimated Lifetime Exposure to Ambient Ozone on Various Measures of Lung Function***

Lifetime Average 10 AM - 6 PM O_3 Concentration+	1 Standard Deviation of Exposure Distribution in ppb (min/max concentration)	Parameter Estimates for Effect of 1 Standard Deviation Difference in Estimated Lifetime O_3 Exposure (±SE)†		
		FEV_1	FEF_{25-75}	FEF_{75}‡
Total Lifetime	14.8 (16/74)	-0.092 (0.089)	-0.331 (0.176)	-0.247 (0.122)
Age <6 years	18.1 (14/75)	-0.115 (0.091)	-0360 (0.180)	-0.260 (0.125)

***** (Adapted from reference 38, Table 5)

+ Based on inverse distance squared interpolation to residences

† None of the results for FEV_1 statistically significant; all results for FEF_{75} $0.05<p<0.10$; all results FEF_{25-75} statistically significant

‡ Forced expiratory flow after 75% of volume has been expired–measure of small airways

Table 4:**Selected Studies on Health Effects of Ozone Levels at Which Effects are Observed and Effects Relative to Other Pollutants**

Study Population	Outcome Measures	Ozone Concentrations	Other Pollutants	Results and Comments
83 4th and 5th grade children Uniontown, PA (49)	PEFR, symptoms	12-hour average; daytime mean=50 ppb; max.=88 ppb	SO_2, PM_{10}, $PM_{2.5}$, total SO_4, particle strong acid	· O_3 most strongly associated with evening cough in 1 pollutant models · O_3 and total SO_4 similar effect on PEFR ↓ and > than that for other pollutants (O_3 effect highly temperature dependent) · in 2-pollutant model with strong acid, O_3 effect on PEFR eliminated (correlation between O_3 & acid=.48) · widely variable individual-specific regressions
58 berry pickers ages 10-44, British Columbia, Canada (50)	forced expiratory flows	1-hour maximum range 13-84 ppb (mean=44)	aerosol acidity, $PM_{2.5}$, SO_4^{2-}, NO_3^-, NH_4^+ and elements Concentrations all low	· both FVC and FEV_1 negatively associated with daily max. O_3 · O_3 effect independent of other pollutants and strongest

Study Population	Outcome Measures	Ozone Concentrations	Other Pollutants	Results and Comments

Population of Montreal, Canada 1992-1993(51)	Emergency room visits for respiratory illness,	8 hour max.(1992): mean=29 ppb; max/90th %tile =65/43 ppb 1 hour max (1992): mean=33 ppb; max/90th %tile=79/49 ppb	PM_{10}, $PM_{2.5}$, SO_4 H^+ all PM_{10} <100 □/m^3; all $PM_{2.5}$ <71 □/m^3	· no relationships significant for 1992 data; focus on 1993 (generally lower pollutant concentrations) · only positive association-children <2 years and H^+ · authors raise ? of spurious result · O_3 effects confined to persons > age 64 years · O_3-acid correlations ~.46
Populations of 4 Western European Cities, 1986-92 (52)	Daily hospital admissions for asthma; stratified by age <15 years, 15-64 years	1-hour max: medians 27-72 ppb ranges 1-78, 7-283	NO_2, SO_2	· Over all cities, no effect for O_3 in children; suggestive effect in older people
Children 7-13 in Netherlands, 1995 (67)	PEFR, respiratory symptoms	8-hour max: range: 28-111 ppb (mean=67) 1-hour max: range 33-130 ppb (mean=77)	PM_{10}, black smoke, NO_2, grass pollen	· significant association between O_3 and ↓ PEFR with 2-day lag · association with upper resp. symptoms · black smoke effects on PEFR somewhat > O3 · no multi-pollutant models

Study Population	**Outcome Measures**	**Ozone Concentrations**	**Other Pollutants**	**Results and Comments**
Children ≤14 years attending	total and respiratory	1-hour max:	PM_{10}	· No O_3 effects for children

sentinel clinics in Santiago, Chile, 1992-93 (53)	visits	mean=56 ppb range=10-176 ppb IQR=31-77 ppb		< 2-years in single or 2 pollutant model · In single and 2-pollutant models, children 2-14 showed O_3 associations with upper and lower resp. visits; O_3 >> PM_{10}
473 non-smoking women in Virginia, 1995-96, 30% < age 27 years, summertime time series (48)	PEFR	1-hour: range=9-57 ppb mean=35 ppb daily max 8-hour mean: range=17-88 ppb, mean=54 ppb; proposed EPA. 8-hour standard of 80 ppb exceeded only on 2 days	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$ SO_4^{2-}, H^+, SO_2, NH_4^+ proposed EPA 24 hour $PM_{2.5}$ standard of 65 □/m^3 not exceeded on any day, nor was WHO 24-hr PM_{10} standard (110 □/m^3)	· modest association between 3-day average 1-hr O_3 and a.m. PEFR · strong association with evening PEFR, larger than all other pollutants except $PM_{10-2.5}$ · 3-day mean of 1-hr > max. 8-hour average · O_3 correlations with other pollutants ranged from 0.22 ($PM_{10-2.5}$) to 0.46 ($PM_{2.5}$) · Ozone effects apparent with 5-day average >35 ppb · no multi-pollutant models

Study Population	Outcome Measures	Ozone Concentrations	Other Pollutants	Results and Comments
Cross-section of children 6-15 years in 10 Swiss communities, 1992/1993 (54)	respiratory symptoms	1992 annual mean: range over 10 communities 9 ppb - 38 ppb # of hours/year >81 ppb: range 0-195 (7/10 <20 hours/yr)	PM_{10}, NO_2, SO_2	· Only association for O_3 was observed for wheeze and asthma in children from cities with lowest and highest O_3 concentrations compared · observed only in children without an allergic family history
1060 1st and 2nd grade children in 9 communities in Austria, 1994-1996 (55)	cross-sectional and longitudinal change in forced expiratory flows	1994-96 annual ½ hour mean: range 18-41 ppb; max. values 24 hr prior to lung function 51-59 ppb Spring, 34-40 ppb Fall	PM_{10}, SO_2, NO_2	· Short-term effects on FEV_1 and FEF_{25-75} (largest effects) · somewhat inconsistent by season · Adverse effects on longitudinal change for FEV_1 in 1994, 1995, but not 1996 · Adverse effects on longitudinal change in FEF_{25-75} only in 1995 · Unclear that effects are due solely to O_3 · question of effects related to PM_{10} and/or NO_2 (56)

Figures

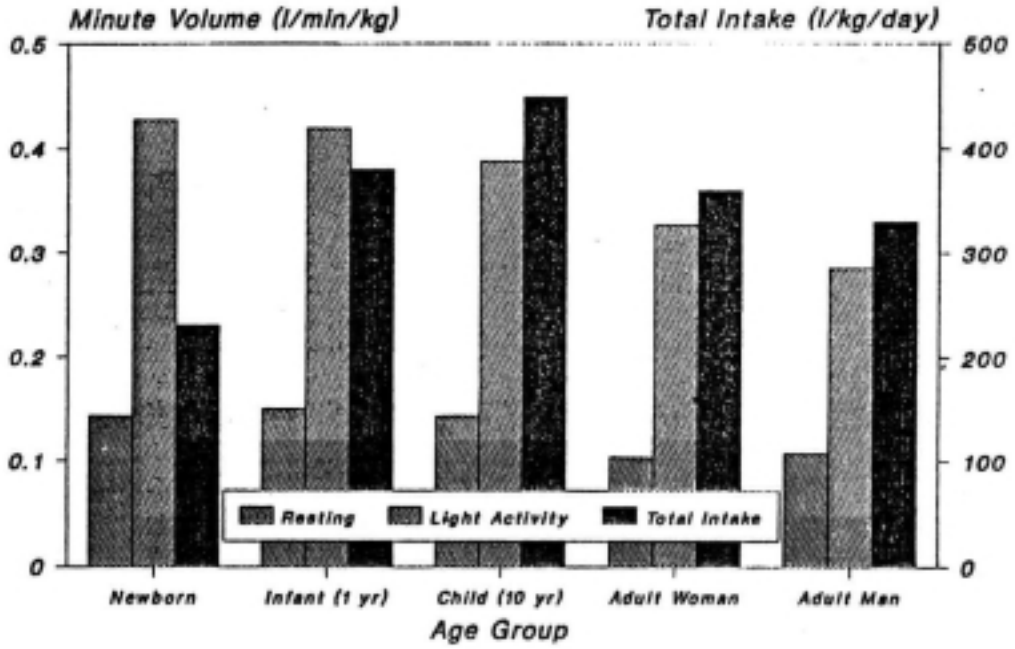

Figure 1: Minute ventilation as a function of age and level of physical activity (Reference 6)

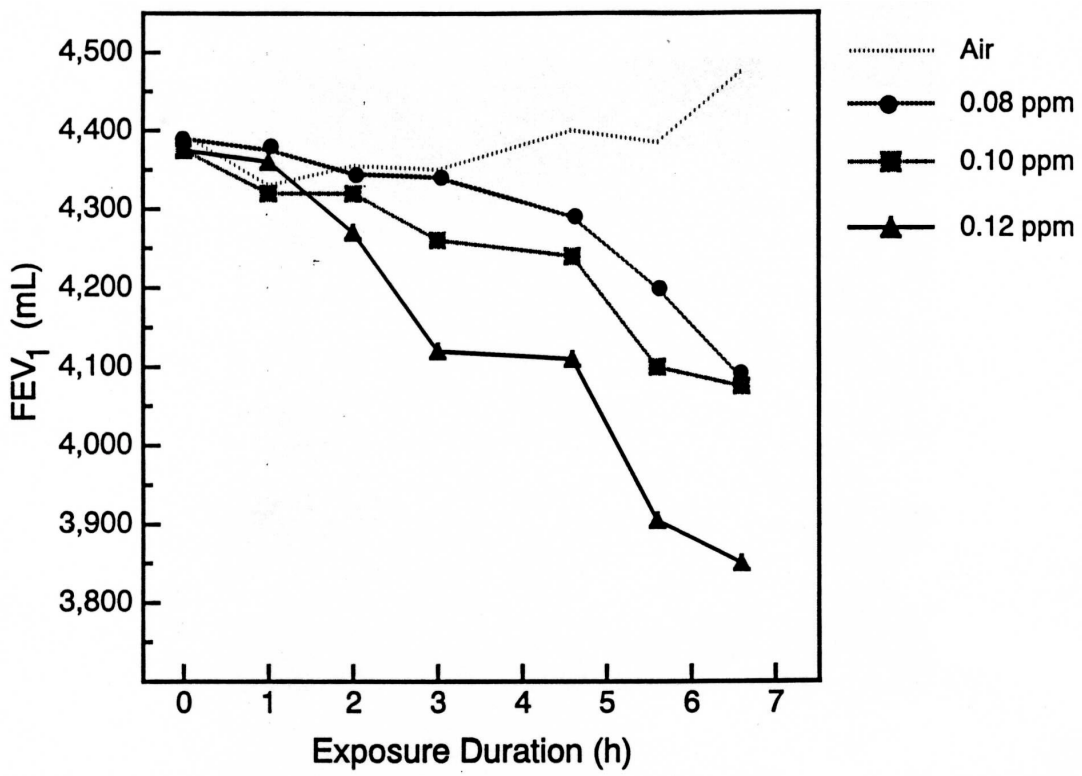

Figure 2: FEV_1 in relation to exposure at different O_3 concentrations. Total exposure duration was 6.6 hours (Reference 12)

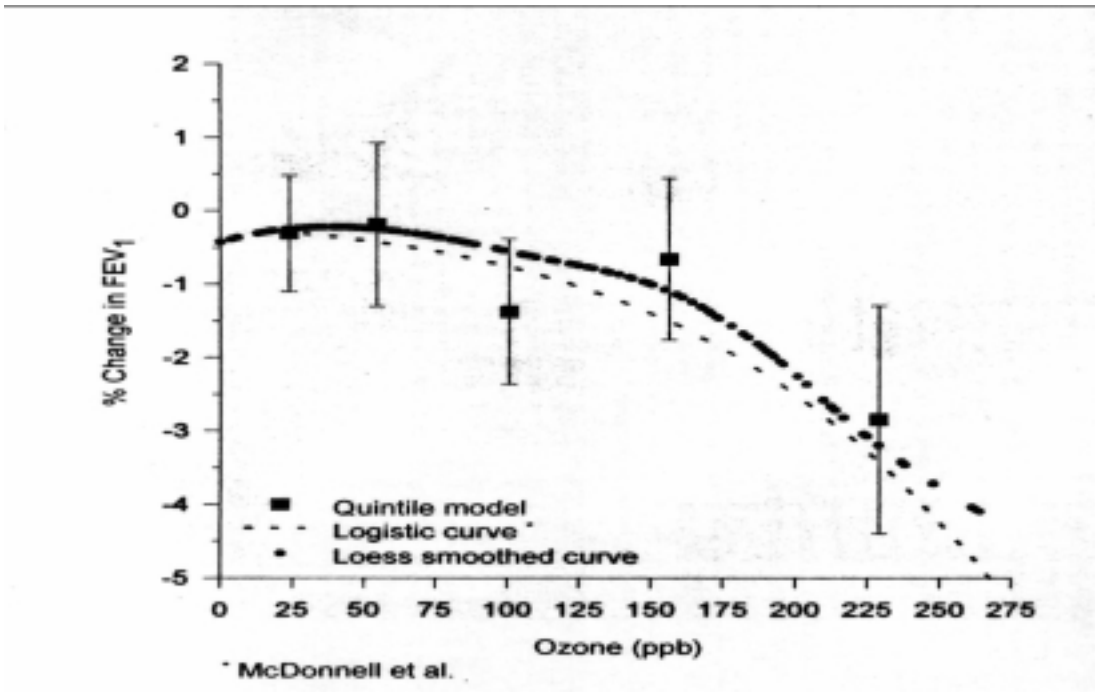

Figure 3: Percent change in FEV_1 based on 3 methods from (Reference 44). O_3 concentrations are averages of 1-hour maximum.

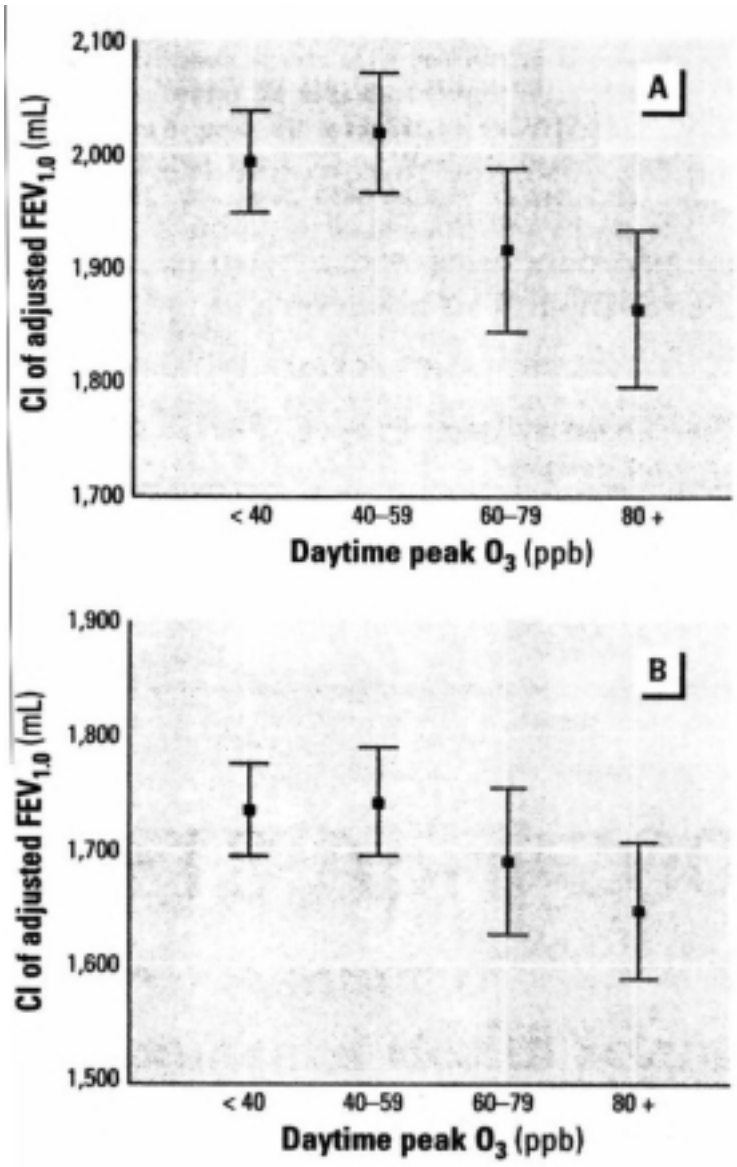

Figure 4: Relation between daily peak O_3 concentration and FVC and FEV_1 in 941 primary school children (Reference 45)

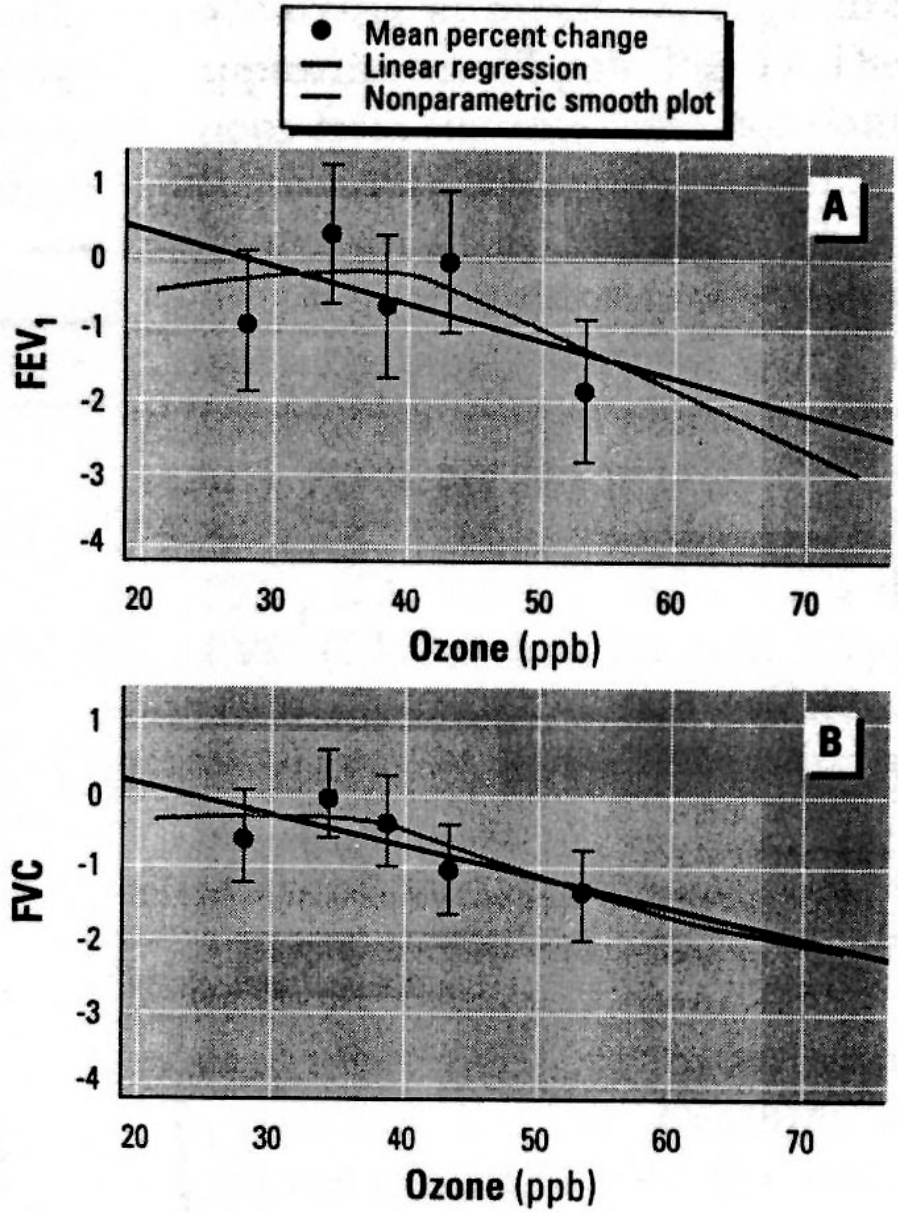

Figure 5: Relation between maximum 1-hour O_3 and FEV_1 and FVC in 595 hikers evaluated by 3 different models (Reference \(46)

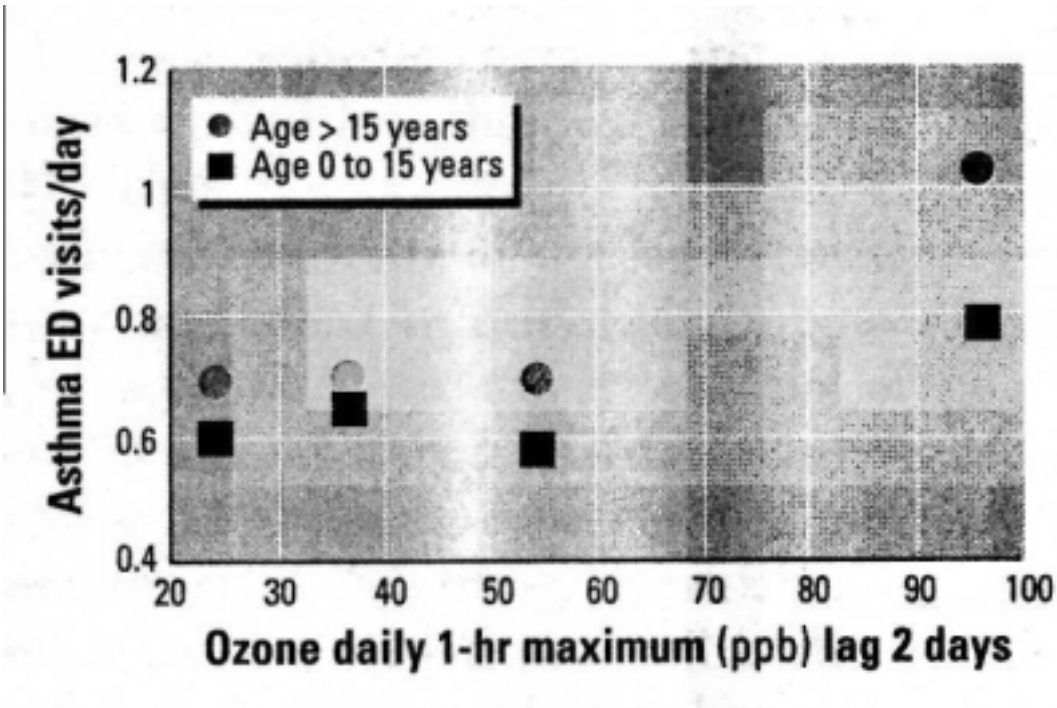

Figure 6: Relationship between emergency department visits for asthma and 1-hour maximum O_3 concentrations, stratified by age, St John, New Brunswick, Canada, 1984-1992 (Reference 47).

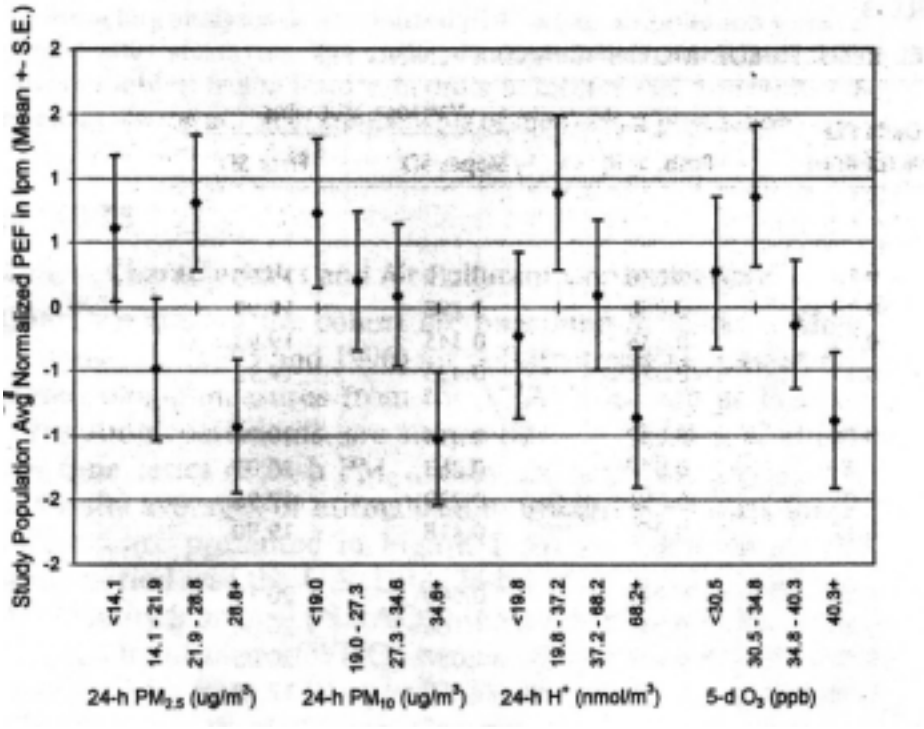

Figure 7: Normalized deviations in PEFR by method of Neas, *et al*. (49) in 473 non-smoking women in relation to quartiles of ambient pollutants (Reference 48). "5-d O_3" refers to a 5-day average of 1 hour O_3.

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